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Impact of Critical Illness on Subsequent Cancer Care and Outcomes, in Patients With Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is the third most common form of cancer in Scotland, with one in six patients with CRC being treated in critical care within two years of their diagnosis, and estimates for overall five-year survival in Scotland being less than 50%. The impact of critical illness on subsequent CRC care quality and outcomes remains poorly understood. This thesis uses novel linkage of available national datasets to critical care admission records to describe a cohort of >40,000 Scottish patients with CRC, investigating how critical illness impacts adherence to cancer care quality performance indicators (QPIs), receipt and quality of adjuvant systemic anti-cancer therapy (SACT), and five-year overall survival. Using a Bayesian statistical framework, this cohort was stratified both by care level (ward level, monitoring in critical care, receipt of organ support) during index admission following diagnosis, and the nature of admission (elective versus emergency). This thesis provides strong evidence that patients who survive critical illness receive poorer subsequent CRC care as measured by the Scottish QPI framework. Critical illness is associated with a meaningful reduction in the likelihood of achieving QPI for timely adjuvant SACT receipt, as well as a meaningful increase in delays commencing adjuvant SACT, that persists when including patients excluded by QPI criteria. For patients treated in critical care, critical illness is likely to have a causal impact on both subsequent adjuvant SACT receipt, and long-term overall survival. This impact persists among patients who survived their initial critical illness. In identifying the impact of critical illness on long term cancer outcomes, this thesis provides an opportunity for future work to assess critical illness' impact on other patient centred outcomes, as well as highlighting potentially modifiable factors to improve cancer care quality and long term outcomes.

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Publications

Publications

- Understanding Bayesian analysis of clinical trials: an overview for clinicians.
Critical Care Science. 05-14-2025;37:e20250267 DOI: 10.62675/2965-2774.20250267

Presentations

- SICS 2023 - Critical care utilisation in patients with colorectal cancer in Scotland
- SICS 2024 - Difference in Long Term Survival of Patients With Colorectal Cancer Among Those Who Experience Critical Illness
- St Mungo 2024 - Patients With Colorectal Cancer Who Survive Critical Illness Are Less Likely To Achieve Quality Performance Indicators for Timely Adjuvant Chemotherapy
- St Mungo 2025 - Impact of Critical Illness on Delays Commencing Systemic Anti-Cancer Therapy in Colorectal Cancer

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Declaration

I declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution

Callum George Wilson Taylor

Abbreviations

- 5FU - 5-Fluorouracil
- ACE-27 - Adult Comorbidity Evaluation-27
- ACP - Advance Care Planning
- AJCC - American Joint Committee on Cancer
- AKI - Acute Kidney Injury
- ANOVA - Analysis of Variance
- AP - Abdomino-perineal (resection)
- APACHE II - Acute Physiology and Chronic Health Evaluation II
- ARR - Absolute Risk Reduction
- ASA - American Statistical Association
- ASCO - American Society of Clinical Oncology
- BF - Bayes Factor
- BMI - Body Mass Index
- BRMS - Bayesian Regression Models using Stan (R package)
- CAPIRI - Capecitabine and Irinotecan
- CAPOX - Capecitabine plus Oxaliplatin
- CI - Confidence Interval
- COPD - Chronic Obstructive Pulmonary Disease
- CORECT-R - Colorectal Cancer Repository
- CPR - Cardiopulmonary Resuscitation
- CRC - Colorectal Cancer
- CrI - Credible Interval

- CRM - Circumferential Resection Margin
- CT - Computed Tomography
- DAAH - Days Alive and At Home
- DNA - Deoxyribonucleic Acid
- ECG - Electrocardiogram
- ECMO - Extracorporeal Membrane Oxygenation
- ECOG - Eastern Cooperative Oncology Group (performance status)
- eGFR - Estimated Glomerular Filtration Rate
- eDRIS - Electronic Data Research and Innovation Service (Public Health Scotland)
- EGFR - Epidermal Growth Factor Receptor
- EPAP - Expiratory Positive Airway Pressure
- EPCC - Edinburgh Parallel Computing Centre
- EQ-5D - EuroQol 5-Dimension (quality of life measure)
- ESMO - European Society for Medical Oncology
- ESMO-MCBS - European Society for Medical Oncology Magnitude of Clinical Benefit Scale
- ESS - Effective Sample Size
- FLOX - Fluorouracil, Leucovorin and Oxaliplatin
- FOLFIRI - Folinic acid, Fluorouracil and Irinotecan
- FOLFOX - Folinic acid, Fluorouracil and Oxaliplatin
- FOLFOXIRI - Folinic acid, Fluorouracil, Oxaliplatin and Irinotecan
- FU - Fluorouracil
- GTN - Glyceryl Trinitrate
- HDU - High Dependency Unit
- HFNO - High Flow Nasal Oxygen
- HFRS - Hospital Frailty Risk Score
- HPB - Hepato-Pancreato-Biliary
- HR - Hazard Ratio
- ICD-10 - International Classification of Diseases, 10th Revision
- ICD-O-3 - International Classification of Diseases for Oncology, Third Edition
- ICM - Intensive Care Medicine

- ICU - Intensive Care Unit
- IPAP - Inspiratory Positive Airway Pressure
- IQR - Interquartile Range
- KM - Kaplan-Meier
- LOS - Length of Stay
- MCBS - Magnitude of Clinical Benefit Scale
- MCID - Minimum Clinically Important Difference
- MCMC - Markov Chain Monte Carlo
- MDT - Multi-Disciplinary Team
- MMR - Mismatch Repair
- MRI - Magnetic Resonance Imaging
- MSI - Microsatellite Instability
- NHS - National Health Service
- NHST - Null Hypothesis Significance Testing
- NIBP - Non-Invasive Blood Pressure
- NICE - National Institute for Health and Care Excellence
- NIV - Non-Invasive Ventilation
- OPCS-4 - Office of Population Censuses and Surveys Classification of Interventions and Procedures, 4th Revision
- OR - Odds Ratio
- PAMM - Piecewise Exponential Additive Mixed Model
- PD - Probability of Direction
- PEEP - Positive End Expiratory Pressure
- PICS - Post Intensive Care Syndrome
- PICS-F - Post Intensive Care Syndrome - Family
- PHS - Public Health Scotland
- PS - Pressure Support
- PTSD - Post Traumatic Stress Disorder
- QPI - Quality Performance Indicator
- RDI - Relative Dose Intensity
- ROC - Receiver Operating Characteristic

- ROPE - Region of Practical Equivalence
- RR - Relative Risk
- RRT - Renal Replacement Therapy
- RXT - Radiotherapy
- SACT - Systemic Anti-Cancer Therapy
- SCOT - Short Course Oncology Treatment (clinical trial)
- SD - Standard Deviation
- SICSAG - Scottish Intensive Care Society Audit Group
- SIMD - Scottish Index of Multiple Deprivation
- SMR-01 - Scottish Morbidity Record 01 (inpatient and day case)
- SMR-06 - Scottish Cancer Registry
- TME - Total Mesorectal Excision
- TNM - Tumour, Node, Metastasis (staging system)
- UICC - Union for International Cancer Control
- VEGF - Vascular Endothelial Growth Factor
- WHO - World Health Organization
- XELIRI - Capecitabine and Irinotecan
- XELOX - Capecitabine and Oxaliplatin

Chapter 1

Introduction

1.1 Introduction

This thesis aims to describe and quantify the long term impacts of critical illness on patients with colorectal cancer.

Rather than studying a single pathology, in this thesis I am exploring two distinct disease states, colorectal cancer and critical illness, and how the two interact. For those of us working in critical care, understanding long term outcomes following critical illness is a question of key importance, to allow us to balance the burdens and benefits of critical care when making shared decisions. Through studying outcomes for patients with colorectal cancer, this thesis explores a cancer of high incidence that is commonly treated in critical care.

Colorectal cancer (CRC) is the third most common form of cancer in Scotland, and the second most common cause of cancer death in the United Kingdom. Over 40,000 cases are diagnosed in the United Kingdom each year, 4,000 of these occurring in Scotland (NICE 2020; NHS 2023; HQIP 2021).

Critical illness is common for patients with colorectal cancer; one in six patients with CRC (16%) are treated in critical care within two years of their diagnosis being made. Of these admissions to critical care, approximately half are unplanned (Camus et al. 2014; Puxty et al. 2018; Vincent et al. 2018; Puxty et al. 2015).

In this chapter I aim to provide an introduction to the following questions:

1. What do we currently understand about the outcomes of colorectal cancer?
2. What do we currently understand about the outcomes of critical illness?
3. What do we currently understand about how critical illness and colorectal cancer affect one another?
4. What are the cancer specific and patient relevant outcomes for patients who experience both disease states?

Colorectal cancer and critical illness are both understood to have long term adverse physical, psychological, and social outcomes; whether these illnesses interact to influence patient outcomes is unknown. In particular, whether critical illness affects the likelihood or quality of subsequent CRC care has not previously been explored. Whilst standards do exist to assess the quality of CRC care, these criteria have not been applied to a cohort of patients who have experienced concurrent critical illness.

When making shared decisions about healthcare, both patients and professionals balance the value of achieving or avoiding certain outcomes, against the likelihood of that outcome occurring. Without accurate estimates of these likelihoods, the ability to make fully informed decisions is impaired. In addition, without an accurate understanding of outcomes for certain patient groups, opportunities to improve cancer care will be missed, through a failure to recognise current inconsistencies in cancer care quality.

In this chapter I highlight where there are important limitations to our current understanding of the above questions. For the scope of this thesis, the key area of interest is in understanding how CRC and critical illness outcomes intertwine. Methods are described in more detail in later chapters; in brief this thesis relies on routinely collected national registry data, and mostly describes associations between relevant factors rather than attributing cause. The final results chapter in this thesis does provide some estimates of the causal impact of critical illness on CRC outcomes.

When attempting to understand outcomes for patients with colorectal cancer and critical illness, it remains important to know both what question you are asking, but also who is asking the question. Multiple hospital specialties share the responsibility of care for this patient group. These include but are not limited to: Oncology, General Surgery, and Intensive Care. Each specialty will have their own perspective of what are the “important” questions to ask. The patient experiencing these disease states will have another perspective, and their family will have another differing view. For each person involved, with their own question of interest, the question will change over time as the patient progresses through their cancer course.

This thesis cannot answer all questions for all perspectives for all time points. I cannot separate my own perspective fully, being an intensive care consultant who cares for such patients in the emergency and elective setting. In most chapters I attempt to align my questions with pre-existing metrics of cancer care quality, which tend to investigate outcomes amongst hospital survivors. These measures of cancer care quality have been determined historically by surgeons and oncologists, and relate more clearly to the care provided by such specialties. As such most chapters in the thesis look at outcomes for patients who have survived hospitalisation. The final chapter takes a different approach, closer to the perspective of those that work in critical

care, and looks at all patients admitted to critical care, including the previously excluded group of those that did not survive hospitalisation. This final chapter additionally investigates the causal relationship between critical illness and cancer outcomes, rather than describing associations between relevant variables.

1.2 Colorectal Cancer

1.2.1 Definitions

The Union for International Cancer Control (UICC) maintains the TNM (Tumour, Node, Metastases) cancer staging system and based on this the American Joint Committee on Cancer (AJCC) publish their widely used Cancer Staging Manual. This staging manual defines CRC as cancers from the terminal ileum to the anal canal. Cancers of the appendix and anus tend to be considered differently to ‘colorectal cancers’ by staging systems and treatment guidelines. (Weiser 2018). The majority of colorectal cancers emerge from one of two subtypes: adenomatous polyps (70%) or sessile serrated lesions (15-30%). Another form, well-differentiated neuro-endocrine (carcinoid) tumours, are also excluded from the AJCC definition of CRC (Weiser 2018; Kanth and Inadomi 2021).

Table 1.1, adapted from the AJCC 8th Edition Staging Manual, identifies the ICD-O-3 (International Classification of Diseases for Oncology, Third Edition) codes considered to be colorectal cancer (Weiser 2018).

Table 1.1: ICD-O-3: Classification of Colorectal Cancer

Code	Anatomical Location
C18.0	Caecum
C18.2	Ascending colon
C18.3	Hepatic flexure of colon
C18.4	Transverse colon
C18.5	Splenic flexure of colon
C18.6	Descending colon
C18.7	Sigmoid colon
C18.8	Overlapping lesion of colon
C18.9	Colon, Not Otherwise Specified (NOS)
C19.9	Rectosigmoid junction
C20.9	Rectum, NOS

1.2.2 Epidemiology

Most cases of colorectal cancer are sporadic (~60%). Up to 10% of cases are due to known genetic mutations, and up to 30% are familial (Kanth and Inadomi 2021).

Over the last 25 years there appears to be a currently unexplained rising rate of incidence of colorectal cancer among adults under the age of fifty (Kanth and Inadomi 2021; Möller et al. 2023; Alexandra M. Zaborowski et al. 2021). The reason for this rising incidence of early-onset CRC is not yet fully understood. Some proposed explanatory factors include the increasing prevalence of obesity, type two diabetes mellitus, physical inactivity, and consumption of processed meat (Lowery et al. 2020).

1.2.2.1 Risk Factors

Developing colorectal cancer is influenced by a combination of modifiable and non-modifiable risk factors. Non-modifiable factors include male sex, increasing age, Black or Asian ethnicity, and family history of inflammatory bowel disease or colorectal cancer. Modifiable dietary factors such as increased red and processed meat consumption, and decreased fibre intake are associated with an increased risk of CRC (Bradbury et al. 2019). Other modifiable risk factors include: smoking, increased alcohol intake, decreased activity, and increased BMI (Kanth and Inadomi 2021; Bradbury et al. 2019). As a result of these modifiable risk factors, approximately 20% of colorectal cancers are estimated to be avoidable by obtaining a healthy weight, increasing activity, stopping smoking, and reducing alcohol (Cardoso et al. 2021).

1.2.3 Diagnosing colorectal cancer

The United Kingdom has had a national “NHS Bowel Cancer Screening Programme” since 2006 (Moran et al. 2017; Richards 2019). The screening programme comprises a two-stage process; an initial non-invasive stool screening test followed by a diagnostic procedure when indicated.

Prior to 2015 the initial screening test used was the Faecal Occult Blood test, however since 2019 this has been superseded by the Quantitative Faecal Immunochemical Test (qFIT). qFIT has an estimated sensitivity of ~79% and specificity of ~94% in identifying cases of colorectal cancer (Kanth and Inadomi 2021), and is currently offered in Scotland to people between the ages of 50 and 74 (Richards 2019; NHS inform 2023). qFIT testing is not equally sensitive for all forms of colorectal cancer, with a lower sensitivity for CRC emerging from serrated lesions (Kanth and Inadomi 2021).

For patients whose stool tests are positive, colonoscopy (or an alternative such as CT colonography, or colon capsule endoscopy) would be recommended to allow for examination and biopsy (Kanth and Inadomi 2021).

The overall uptake of CRC screening in Scotland from 2020 to 2022 was 67%. Whilst screening allows for diagnosis at an earlier disease stage, screening uptake is not consistent across Scotland. In the least socioeconomically deprived regions of Scotland, screening uptake was 75%. In the most deprived regions, screening uptake was as low as 54%. (Public Health Scotland 2023). In 2019 in Scotland, 35% of colorectal cancers were identified through screening. In 2020, with COVID-19 resulting in the temporary suspension of the programme, this fell to 20% (Public Health Scotland 2022a).

1.2.4 Staging colorectal cancer

Colorectal cancer can be staged using the TNM scoring system, using the AJCC's Cancer Staging Manual (8th edition) (Compton and Greene 2004; NICE 2020; Amin et al. 2017; Weiser 2018).

1.2.4.1 Tumour

Tumour (T) ranges from TX to T4 and refers to the level of Primary Tumour invasion through the bowel wall. TX and T0 refer respectively to when the primary tumour cannot be assessed, or there is no evidence of a primary tumour. Tis reflects a cancer *in situ*, and is the first stage considered to be dysplastic enough to be recorded on cancer registries (Weiser 2018).

Following Tis the Tumour score progresses from T1 to T4. T1 describes a cancer that has invaded the submucosa of the bowel, T2 a tumour beginning to invade muscularis propria, T3 a tumour that has passed through muscularis propria into surrounding tissues, and T4 when it has directly invaded the visceral peritoneum (T4a), or adhered to an adjacent structure or organ (T4b) (Weiser 2018).

1.2.4.2 Node

Lymph Node spread (N), is categorised from NX to N2. NX and N0 refer to cases where nodes cannot be assessed (NX), or if there is no evidence of node spread seen (N0).

N1 can reflect when one (N1a), or two to three (N1b) regional lymph nodes have tumour present. N1c reflects where cancer is not seen in regional lymph nodes, but is seen separately to the main tumour: in the subserosa, mesentery, or non-peritoneal tissues surrounding bowel. N2 means four or more regional nodes contain tumour, with N2a (four to six nodes), and N2b ($\geq$ seven) (Weiser 2018).

1.2.4.3 Metastasis

Metastasis (M) can be divided into: M0 (no distant metastasis identified), and M1 (distant metastasis found).

M1 is further subcategorised into M1a, M1b, and (as of the AJCC 8th edition) M1c. M1a represents metastasis found at one distant site or organ (excluding the peritoneum). Multiple metastases found within one organ would still be considered M1a. M1b is metastases identified in more than one site or organ. M1c is where metastases affect the peritoneal surface. (Weiser 2018).

1.2.4.4 Anatomic Stage / Prognostic Group

TNM is not the only classification system for CRC, as colorectal cancer can also be staged. Stage ranges from 0 to IVB, and closely corresponds with the previously used Dukes' scoring system (A-D) (Weiser 2018).

Comparison between Stage, Dukes', and TNM is provided in Table 1.2. Stage I disease represents CRC that could have progressed into the muscularis propria. Stage II disease represents CRC that has progressed into surrounding tissues. Stage II can be considered high-risk of recurrence (High-Risk Stage II), either through surgical, pathological, or patient factors. These factors include when: less than 12 lymph nodes are sampled in a surgical specimen, the tumour is T4, the tumour has perforated or caused bowel obstruction, histology is poorly differentiated, local venous or perineural invasion is seen, or circulating tumour DNA is seen (Baxter et al. 2022). Stage III disease reflects disease that has spread into lymph nodes. Stage IV disease is when cancer has metastasised to distant sites or organs. As such, Stage I and II disease must have a TNM score with T(1+)N0M0. Stage III disease must have T(1+)N(1+)M0. Stage IV disease would be T(0+)N(0+)M1. (Weiser 2018).

Table 1.2: Anatomic Stage of Colorectal Cancer and corresponding Dukes' and TNM classifications

Stage	Dukes'	T	N	M
0	-	Tis	0	0
I	A	1	0	0
	A	2	0	0
IIA	B	3	0	0
IIB	B	4a	0	0
IIIA	C	1-2	1/1C	0
	C	1	2a	0
IIIB	C	3-4a	1/1C	0
	C	2-3	2a	0
	C	1-2	2b	0
IIIC	C	4a	2a	0
	C	3-4a	2b	0
	C	4b	1-2	0
IVA	D	Any T	Any N	1a
IVB	D	Any T	Any N	1b
IVB	D	Any T	Any N	1c

1.2.5 Management of Colorectal Cancer

Colorectal cancer can be treated with either 'curative' or 'non-curative' intent. Treatments with the aim of cure may centre on surgical resection, with or without systemic anticancer therapy (SACT). Treatments with the aim of disease control, or the aim of palliative symptom relief, can also involve invasive and non-invasive therapies.

1.2.5.1 Surgical Interventions

The goal for surgical management of CRC with curative intent is the *en bloc* removal of the cancer, with removal of the tumour as a single piece wherever possible. Approaches to achieve this may be endoscopic, (robotic) laparoscopic, or require laparotomy. This thesis primarily investigates the subgroup of patients who undergo surgical resection with curative intent and so the following section also focuses on this form of operative intervention.

For locally infiltrative tumours, surgical resection of the involved bowel segment with at least a 5cm margin and associated lymphatic drainage is recommended (Argilés et al. 2020). Resection of the diseased bowel segment may be followed by anastomosis, where the two free ends of bowel either side of the now removed section are joined together. Alternatively stoma formation may be performed, where one or both free ends of bowel are brought out through the abdominal wall. Stoma formation may be planned to be temporary or permanent. Anterior resection is the surgical removal of diseased bowel segment in the middle or upper rectum.

Table 1.3 provides names for common CRC surgical procedures and the areas of bowel they relate to. Figure 1.1 provides illustration of the anatomical location for each part of the colon.

Table 1.3: Forms of Resection Used in the Surgical Management of Colorectal Cancer

Operation	Caecum	Ascending	Transverse	Descending	Sigmoid	Rectum	Anus
Right Hemicolectomy	X	X					
Extended Right Hemicolectomy	X	X	X				
Transverse Colectomy			X				
Extended Left Hemicolectomy			X	X	+/-		
Left Hemicolectomy				X	+/-		
Sigmoid Colectomy					X		
Hartmann's Procedure					X		
Low anterior resection					X	X	
Abdomino-perineal (AP) resection					X	X	X
Subtotal Colectomy	X	X	X	X	X		
Pan procto-colectomy	X	X	X	X	X	X	X

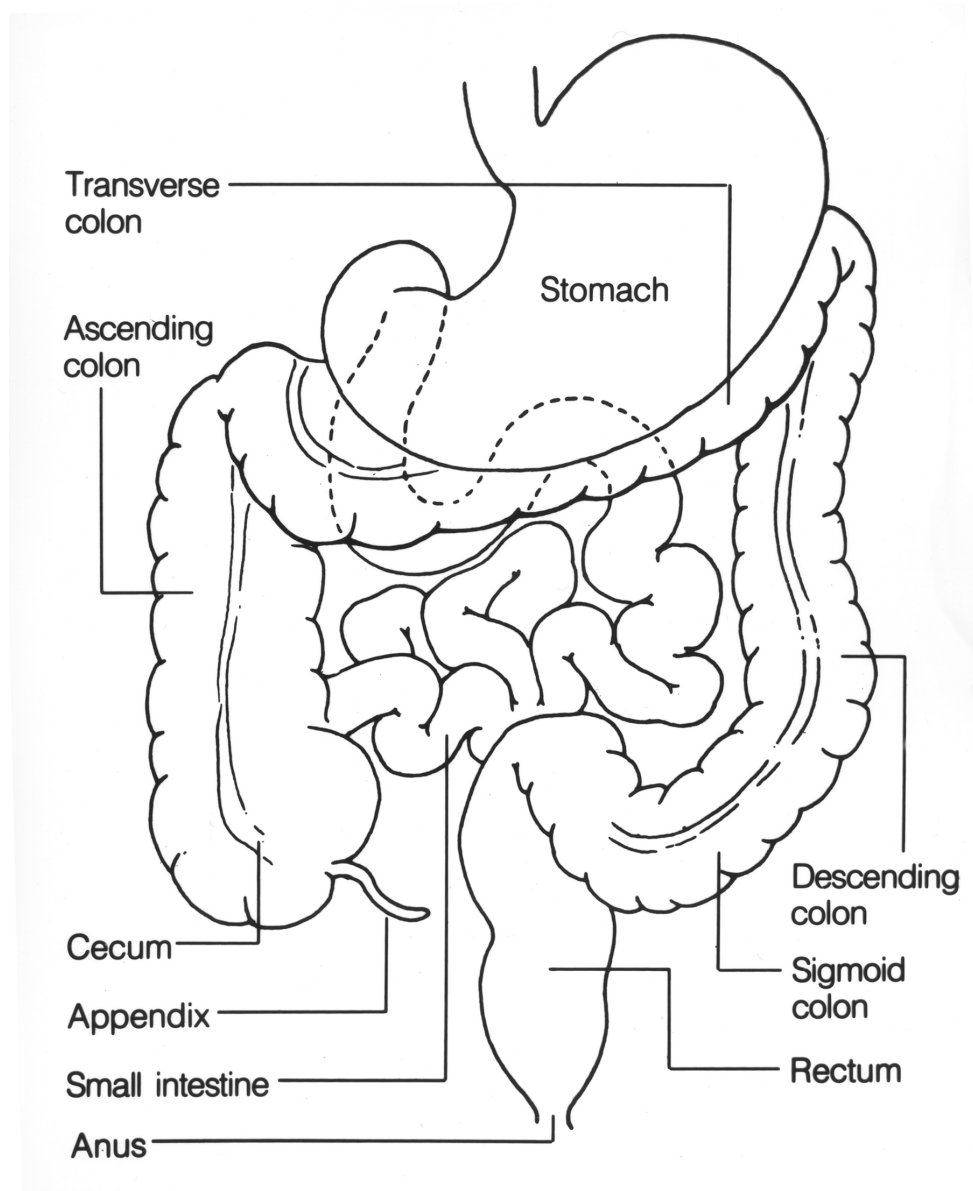


Figure 1.1: Anatomical diagram of the colon, reproduced with permission from National Cancer Institute Visuals Online (National Cancer Institute 2001)

Within the NHS, operations are coded using the OPCS Classification of Interventions and Procedures system (OPCS-4). NHS Scotland provide a reference list of OPCS-4 codes considered to refer to surgical resection of CRC (Dawson 2018). A summarised version of relevant OPCS-4 headers that refer to surgical resection of CRC is provided in Table 1.4. Later chapters in this thesis use a more detailed version of this list to establish whether patients received resection of CRC.

Table 1.4: OPCS-4 Header Codes For Colorectal Cancer Resection

OPCS-4 Heading	Descriptive Title
H04	Total excision of colon and rectum
H05	Total excision of colon
H06	Extended excision of right hemicolon
H07	Other excision of right hemicolon
H08	Excision of transverse colon
H09	Excision of left hemicolon
H10	Excision of sigmoid colon
H11	Other excision of colon
H12	Extirpation of lesion of colon
H29	Subtotal excision of colon
H33	Excision of rectum
H40	Operations on rectum through anal sphincter
H41	Other operations on rectum through anus
X14	Clearance of pelvis

1.2.5.2 Local Disease: Anatomical Stages 0 - III

Current UK and European guidance for management of local colorectal cancer were published in 2020, by the National Institute for Health and Care Excellence (NICE) and the European Society for Medical Oncology (ESMO) (NICE 2020; Argilés et al. 2020). Additionally localised rectal cancer has a more recent ‘living guideline’ produced by ESMO, published in 2025 (Hofheinz et al. 2025)

For patients with Stage 0 and Stage I disease, resection without adjuvant chemotherapy is recommended. ESMO recommend endoscopic resection for cancer *in situ* (Stage 0 disease) (Argilés et al. 2020). NICE states those with Stage I disease should be offered one of; a surgical intervention of Transanal Excision, Endoscopic Submucosal Dissection, or Total Mesorectal Excision (National Institute for Health and Care Excellence 2021).

For locally infiltrating tumours considered resectable, both ESMO and NICE recommend colonic resection (either laparoscopic or open) (Argilés et al. 2020). ESMO recommend this resection should be *en bloc* to ensure adequate staging, and adequate resection of adjacent organs and structures (Argilés et al. 2020).

1.2.5.3 Metastatic Disease: Anatomical Stage IV

For patients with metastatic disease, ESMO guidance was published in October 2022, was updated with the living guideline of 2025, and updated further in April 2026. This also covered recurrent colorectal cancer. This guidance describes resectable metastatic colorectal cancer as a potentially curable condition, with a five-year survival of 20-45% (Cervantes et al. 2023; A Cervantes 2025). As such, both ESMO and NICE recommend considering resection of the primary tumour, in patients considered appropriate at MDT review. Also recommended is referral to a centre that could perform advanced disease resection, or exenteration. Surgical resection can be considered for hepatic and lung metastases in patients considered appropriate at MDT review (Cervantes et al. 2023; National Institute for Health and Care Excellence 2021).

Historically patients were categorised based on how “resectable” their tumour was considered to be. In the most recent guidance there has been a shift of focus, with a recognition that the overall health of the patient will be key to determining appropriate treatment options. As such the current guidelines recommend categorisation by: “Fit” versus “Unfit” patients, when considering suitability for treatment. The 2022 guidance recommends that clinicians consider disease-specific and patient-specific characteristics. Examples given for patient-specific characteristics include: age, performance status, comorbidity and socioeconomic factors. To identify an all-encompassing measure of health, consideration of patient frailty and geriatric assessment are also recommended. (Cervantes et al. 2023).

“Fit” patients with metastatic or recurrent disease are further categorised into Group 1 Fit versus Group 2 Fit. Group 1 comprises patients who need more intensive treatment either due to impending clinical threat, or through having the potential for conversion to curative treatment. This intensive treatment could include neoadjuvant SACT, resection, as well as adjuvant therapy. Group 2 patients contain the remainder of Fit patients, who it is felt that SACT may be able to achieve some form of disease control and increased duration of survival (without cure) (Cervantes et al. 2023).

The inclusion of ‘socioeconomic factors’ as a relevant characteristic is an interesting choice, with potential for significant controversy. The rationale for the choice is not provided in either the published guidance or in the supplementary material, but two potential explanations could be considered. First as a Pan-European document, this guidance covers a range of healthcare systems. Although all countries in Europe have a form of universal health coverage, there is a spectrum encompassing different ratios of private to public healthcare provision (Montagu 2021).

As a first explanation it may be that the authors wish treating clinicians to consider what is financially possible for the patient in front of them. As another potential explanation, socioeconomic deprivation is associated with poor colorectal cancer outcomes. Population based data from Germany (where there is mixed public and private healthcare provision) shows a 5% reduction in 5 year survival when comparing those in the most deprived areas against others in the least deprived (Jansen et al. 2020). Observational data from a state-funded universal healthcare system in Canada revealed lower socioeconomic status was also associated with: more advanced stage of disease on presentation, lower likelihood of receipt of adjuvant and palliative chemotherapy, as well as lower likelihood of survival (Shah and Chan 2021). It may be that the authors of the ESMO guidance are highlighting the association between socioeconomic deprivation and decreased likelihood of treatment success. In highlighting this difference, they could be suggesting that for those more socioeconomically deprived, the balance between benefits and burdens of aggressive treatment may shift slightly away from benefit. As stated above, their rationale is not provided, and so remains unclear.

In a predominantly private North American setting, qualitative work has suggested that health care providers already use socioeconomic status as an influencing factor in decision making. Interviewed professionals felt that they were making decisions based on patients interests (minimising financial strain) and would not make changes that decreased overall the likelihood of a good patient outcome (Bernheim et al. 2008). However, taking such factors into account during decision making risks exacerbating health related inequalities. (Spencer and Grace 2016). The difficulty of allowing socioeconomics to influence health care is a well established problem. Whilst we may optimistically hope that in an UK context, financial strain following critical illness would not impact concurrent cancer care, financial strain among critical illness survivors does exist. Griffiths et al. 2013 identified a fall in income for a third of families of critical illness survivors in the UK at the time of 6 month follow up (Griffiths et al. 2013). In 1969 Johan Galtung provided a mechanism to view the 'social determinants

of health’ as a form of ‘structural violence’, where an inequitable healthcare system and wider society harms the most vulnerable (Galtung 1969; DeBruin et al. 2012). In recognising that many in society fall victim to this structural violence, it becomes clear that the use of socioeconomic factors requires more careful justification than is provided in the ESMO guidance.

1.2.5.4 Systemic Anticancer Therapy (SACT)

1.2.5.5 Forms of Systemic Anticancer Therapy

Referred to as the backbone of SACT for colorectal cancer, fluoropyrimidines have been consistently used in this context for the last thirty years (Cervantes et al. 2023; Vodenkova et al. 2020) 5-Fluorouracil (Fluorouracil, 5-FU) is an intravenous fluoropyrimidine, acting as an “anti-metabolite”, preventing tumour cells from nucleic-acid synthesis. Used in combination with intravenous 5-FU, folinic acid (leucovorin) potentiates the action of 5-FU and acts as a “chemoprotectant” to minimise toxicity symptoms (Vodenkova et al. 2020). An oral prodrug for fluorouracil also exists: capecitabine (Walko and Lindley 2005).

Other chemotherapeutic agents include oxaliplatin, a platinum compound that acts as a cytotoxic through blocking DNA replication (Culy et al. 2000). Irinotecan is often used in combination with 5-FU and oxaliplatin, acting again as a cytotoxic, binding to DNA (Bailly 2019).

The commonly occurring acronyms for SACT regimes and the agents they are comprised of, are provided in Table 1.5.

Table 1.5: Medications Used In Commonly Occurring SACT Regimes

Regime	5-FU	Folinic Acid	Capecitabine	Oxaliplatin	Irinotecan
(modified) de Gramont	X	X			
FOLFOX / Oxaliplatin de Gramont	X	X		X	
CAPOX / XELOX			X	X	
FLOX	X			X	
FOLFIRI	X	X			X
CAPIRI/XELIRI			X		X
FOLFOXIRI	X	X		X	X

Additionally, biological/immunotherapy agents including cetuximab and panitumab (EGFR inhibitors), and bevacizumab (VEGF inhibitors) may be considered. However their role is limited to the treatment of metastatic disease (Cervantes et al. 2023). In particular cetuximab has been described as having revolutionised treatment of metastatic colorectal cancer, providing “renewed hope” for patients (Saoudi González et al. 2024).

1.2.5.6 Local Disease: Anatomical Stages 0 - III

ESMO recommend consideration of adjuvant chemotherapy for patients with intermediate or high-risk stage II disease (Argilés et al. 2020). For patients receiving adjuvant Systemic Anti-Cancer Therapy (SACT), this should be started no later than 8 weeks following surgery (Argilés et al. 2020). Adjuvant SACT is associated with increased 5 year survival, however the impact of survival on low-risk patients is contested.

The two main adjuvant regimens recommended by ESMO in this context are: the de Gramont regimen (5-FU and leucovorin), and capecitabine (Argilés et al. 2020). ESMO also recommend that due to side-effects, or lack of evidence of efficacy: FLOX, irinotecan, cetuximab, and bevacizumab should not be used as adjuvant treatments (Argilés et al. 2020).

For patients with Stage IIB-IIIC disease, NICE also recommend preoperative (neoadjuvant) SACT (National Institute for Health and Care Excellence 2021). Whilst it does not provide specific guidance on treatment regime or timescale, the recommendation was guided by pilot data from the FOxTROT trial, where patients received a 6 week course of neoadjuvant chemotherapy (FOLFOX), followed by surgical resection 4-6 weeks after completion of chemotherapy (Morton et al. 2023).

In their 2020 guidance, ESMO and NICE recommend similar guidance, that the standard of care in Stage III adjuvant chemotherapy should be a combination of fluoropyrimidine and oxaliplatin (such as FOLFOX or CAPOX) (Argilés et al. 2020; National Institute for Health and Care Excellence 2021).

In their clinical practice guidelines, ESMO report adjuvant SACT with a single agent provides an overall survival benefit of 10-15% for patients with Stage III disease, and a benefit of 3-5% for patients with High-Risk Stage II (Argilés et al. 2020; Knapen et al. 2020; Sargent et al. 2009; Gill et al. 2004) Contrasting between Stage III and High Risk Stage II disease, we see a substantial difference in survival benefit following adjuvant SACT. This difference in benefit does not mean that SACT is less effective against cancers of a lower stage; rather it implies SACT is less necessary, that surgical resection alone is closer to sufficient for cure. Among patients at even lower risk of cancer recurrence following surgery (Low Risk Stage II and below), ESMO do not recommend adjuvant SACT, due to lack of evidence for any additional benefit.

The key measure to balance proposed benefits of adjuvant SACT against, would be the proposed burdens. If there were no burdens, all patients with CRC may wish to receive adjuvant SACT on the off-chance it may improve survival. However it is not the case that treatment is risk-free, and the key identified burdens would be treatment toxicity.

Knapen et al. 2020 performed a review of adjuvant colon cancer trials against the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS), a scale I return to in more detail in Chapter 7. In doing so they attempted to ask the question I describe above, how should we balance the benefits and burdens of adjuvant SACT. In their work, investigating the burdens of treatment is an area that was patient-prompted, rather than clinician-led, as the patients included in the ESMO-MCBS working group advocated for the inclusion of measures for Acute (AT) and Late Toxicity (LT) (Knapen et al. 2020). Reporting the incidence of AT and LT, Knapen et al. 2020 note that later trials record these features more often, demonstrating the growing recognition of the importance of such measures.

In trials of adjuvant treatment, there is little consistency in how features of toxicity are measured or reported (Knapen et al. 2020). However, the findings reported by the following trials allow us to make some comment on AT and LT. Peripheral Sensory Neuropathy (PSN) is a recognised common complication of treatment. The ACHIEVE study reported the following high prevalence of PSN following adjuvant SACT (Yoshino et al. 2019). After 3 months of adjuvant treatment, incidence of PSN lasting 3 years was ~10% for patients (9.7%). Among patients who received 6 months adjuvant SACT, incidence of PSN lasting 3 years rose to ~25% (24.3%) (Knapen et al. 2020; Yoshino et al. 2019). The SCOT trial also reported findings of quality of life (QoL) related to PSN (Iveson et al. 2018). Consistent with the findings of ACHIEVE, SCOT reported that patients who received 6 months of treatment had worse neuropathy-related QoL than those who received 3 months treatment. This relative burden of treatment remained identifiable at 5 years follow-up (Iveson et al. 2018).

ESMO recommends that adjuvant SACT should be provided for either three or six months, with NICE reporting the standard duration has traditionally been 6 months (Argilés et al. 2020; NICE 2020). Fortunately, considering that SCOT reported worsening toxicity for patients who received 6 months of treatment, SCOT also reported 3 months treatment was non-inferior in overall survival benefit (Iveson et al. 2018).

The practice changing nature of these findings was reported by Hanna et al. 2022, who noted that following publication of SCOT, the proportion of Scottish patients receiving greater than 3 months of adjuvant treatment fell from 75% to 42% (Hanna et al. 2022).

1.2.5.7 Metastatic Disease: Anatomical Stage IV

As justified in more detail in Chapters 4, 5, and 6, in this thesis I mainly investigate the impact of critical illness on SACT and Survival for patients who have High Risk Stage II or Stage III disease. As such the following section on Metastatic Disease is relatively brief.

ESMO describe Fluorouracil as the “backbone of metastatic colorectal cancer treatment” (Cervantes et al. 2023). Treatment regimens could include: FOLFOX, FOLFIRI, CAPOX, CAPIRI, and FOLFOXIRI, with additional detail of what these entail provided in Table 1.5 (Cervantes et al. 2023).

In patients considered suitable for surgery at MDT, ESMO recommend a 6 month course of FOLFOX, starting 3 months before surgery as the standard of care (Cervantes et al. 2023). Amongst the more frail “Fit” patients, lower toxicity SACT regimens such as a fluoropyrimidine +/- bevacizumab could be considered (Cervantes et al. 2023). Patients who are felt to be “Unfit” for SACT are recommended supportive care with palliative intent (Cervantes et al. 2023).

1.2.6 Auditing Quality of Colorectal Cancer Treatment: The Quality Performance Indicator Programme

In 2008 the Scottish Government published “Better Cancer Care”, documenting a plan to improve the quality and consistency of cancer care. As a result, the National Cancer Quality Steering Group was created, with the role of setting and assessing national cancer treatment targets (Healthier Scotland 2008).

These measures of cancer treatment quality are referred to as “Quality Performance Indicators” (QPIs). There are separate QPIs developed for each major form of cancer. Attainment of these QPIs is intended to be assessed at the level of: an individual MDT, NHS board level, and through national comparisons (National Cancer Quality Steering Group 2025).

Colorectal Cancer QPIs were first developed in 2011 and were applied to patients diagnosed from January 2012 onwards (Figure 1.2). The QPIs are reviewed and updated every three to four years. Currently the treatment of patients with colorectal cancer in Scotland is assessed against Version 5.0 (National Cancer Quality Steering Group 2025).

As appendiceal cancers (accounting for 0.8% of new colorectal cancer cases in Scotland), have a different typical presentation and management, and are not considered ‘colorectal’ in certain staging systems (Weiser 2018) they have been excluded from the Colorectal Cancer QPIs since 2016 (National Cancer Quality Steering Group 2025).

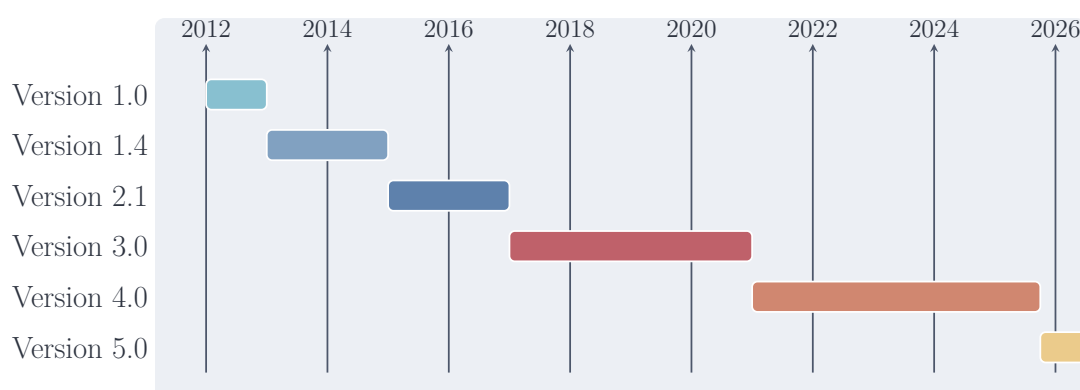


Figure 1.2: Versions of Colorectal QPI Since 2012.
Each coloured bar represents a QPI version and the time period it covered.

1.2.6.1 Current QPIs for Colorectal Cancer

QPI Version 5.0, published in September 2025, applies to cases of colorectal cancer diagnosed from April 2025 onwards. This version has updated certain QPIs, as well as adding and archiving others.

The individual QPIs can be broadly categorised into: pre-operative, peri-operative, and post-operative targets. Described in more detail in Chapter 5, these QPIs assess aspects of care including: pre-operative imaging, surgical margins and lymph node yield, incidence of re-operation and operative complications, access to chemotherapy, as well as other more specific QPIs for certain subgroups.

In Chapter 5 I assess the treatment of patients with CRC against the QPIs published at the time of treatment. These include measures now archived, such as 30 and 90 day mortality following treatment.

The current version of CRC QPI makes some welcome changes. Of particular interest to this thesis, in QPI 11, the window for acceptable delay to commencing adjuvant SACT following surgical resection is narrowed, from 12 weeks in Version 4, to 8 weeks in Version 5 (National Cancer Quality Steering Group 2020, 2025). This change reflects changes in clinical evidence, described in more detail in Chapters 5 and 6.

1.2.6.2 Limitations of QPIs

QPIs are not designed to provide a complete measure of the quality of an individual's cancer care. Rather they are established to allow comparison between regions on a national level, as well as reporting national performance. The authors of the QPI report highlight some areas of “key importance”, that they are currently unable to provide recommendations for; this is either due to insufficient evidence, or a lack of agreed methods to measure quality. As examples of areas of importance not currently measured by QPIs, the following are listed in QPI Version 5.0: side effects and toxicities of SACT, post treatment management, and evaluation of frailty (National Cancer Quality Steering Group 2025).

It remains a key limitation of the current QPIs, that several key factors relating to burdens of treatment remain excluded. In versions V.4 and V.5 the authors note that evaluation of frailty or measurements of side effects and toxicities from SACT are not included in QPI reporting. In QPI V.5 the only measures of treatment complications relate to surgical treatment, with Reoperation Rates, and Anastomotic Dehiscence (National Cancer Quality Steering Group 2025).

In QPI V.5 measures such as 30 and 90 day mortality following treatment have been “dropped”. It may be reasonable to remove measures of short term mortality for a national QPI programme. As noted in Chapter 5, I report low overall incidence of short term mortality. It may also be reasonable to not replace short term mortality with long term measures, considering results of these would not be available in a reasonable timescale. However, the removal of such a measure of risks or burdens of treatment, has not been followed by the inclusion of a different measure of burdens, such as treatment toxicity. Failing to include measures of treatment toxicity, likely due to reasonable concerns on the inconsistency of such data collection throughout Scotland, results in the current programme failing to acknowledge one of the key measures of importance to patients, as noted previously by the ESMO-MCBS working group (Knapen et al. 2020).

The current system of QPI is designed to allow us to measure quality of process of care, rather than quality of outcomes of care. QPIs allow us to identify if we are doing what we think is important, they do not allow us to identify if what we are doing actually improves or worsens patients lives. We could argue that noting this is an unfair criticism of the programme, to assess it against criteria it was not designed to meet. However in the era of routinely collected clinical information on electronic health care records and national registers, I would argue that the QPI programme misses a key opportunity to identify what occurs to our patients following treatment (for better or worse). Despite the above, the QPI programme does provide a wealth of information on the processes of care for patients, and in doing so allows us to contrast the treatment between certain patient groups. I make such a comparison between patient groups’ care quality in Chapter 5.

1.3 Intensive Care And Critical Illness

1.3.1 Introduction To Critical Care

The 2022 Scottish Audit of Adult Critical Care (Scottish Intensive Care Society Audit Group, SICSAG) identified 605 inpatient hospital beds as “critical care”. This included 22 Intensive Care Units (ICU) or combined ICU and High Dependency Units (HDU) (355 beds), as well as 26 Medical, Surgical or Combined HDUs (250 beds), while excluding 7 Obstetric High Dependency Units (SICSAG 2022).

The report included all ICUs in Scotland, and greater than 95% of HDUs. The organisation responsible for publishing standards for Critical Care in Scotland and auditing attainment of these, is the Scottish Intensive Care Society Audit Group (SICSAG) (SICSAG 2022, 2015). In the SICSAG report, published by Public Health Scotland, Critical Care was defined as “specialist hospital wards for the most severely ill or injured patients” treating “patients with a high level of complexity” (SICSAG 2022).

At the level of the United Kingdom, the Intensive Care Society and the Faculty of Intensive Care Medicine published a report on levels of inpatient care in the Summer of 2022. This redefined levels of inpatient care to one of: Ward Care, Level 1 - Enhanced Care, Level 2 - Critical Care, Level 3 - also Critical Care (Intensive Care Society 2021). In this new definition some aspects previously considered High Dependency may fall into either Level One or Level Two. Level One would include patients requiring either more detailed observations or interventions to support a single organ system, that cannot be safely provided on a ward. Level Two would include patients

with needs beyond Level One, including support for two or more organ systems, or advanced support for one organ system. Level Three includes all patients requiring advanced respiratory monitoring and support, or advanced support for two or more organ systems (Intensive Care Society 2021).

1.3.2 Enhanced Monitoring and Interventions

The Levels of Care Report provides an example (Table 1.6) of interventions which would require treatment in at least a Level One environment. If several of these interventions are required, the report recommends treatment in a Critical Care (Level Two or Level Three) environment. In addition to the interventions in Table 1.6, requiring advanced organ support would require treatment in critical care. As stated above, all cases of advanced respiratory support would require Level Three (Intensive) care. The Levels of Care Report and the SICSAG report, do not define what is considered to be advanced support, or where the distinction between basic critical care and advanced may be (Intensive Care Society 2021). This lack of clarity in reporting, likely reflects the lack of agreement between practitioners as to what should be considered “basic” or “advanced”, and the lack of evidence supporting one definition or another.

Similarly post covid pandemic, in my own clinical practice across critical care settings, as a multidisciplinary team (MDT) we have anecdotally acknowledged that treatments previously considered to be ward level interventions are more frequently referred to critical care. Whilst we do not have evidence for why this change in practice is occurring (or even if such a change exists outside the perspective of critical care staff), one potential explanation remains the increased pressure and decreased resources available to hospital wards on a regional and national level (Audit Scotland 2024; Royal College of Nursing 2024; Clarissa et al. 2021).

Table 1.6: Monitoring and Interventions to be provided in Enhanced Care Environments As recommended by the Intensive Care Society Levels of Care Report (Intensive Care Society 2021)

Monitoring	Interventions
Continuous monitoring (ECG, NIBP, SpO ₂)	High flow nasal oxygen
Hourly neuro observations	Goal directed fluid therapy
Continuous invasive arterial blood pressure	Acute Non Invasive Ventilation
Regular Arterial Blood Gas monitoring	Opiate infusion
Continuous central venous pressure	Anticoagulant infusion
	Thrombolytic infusion
	Single vasopressor/inotrope infusion (dose limited)
	Single hypotensive infusion e.g. labetalol, GTN
	Potassium infusion > 60mmol/l over 8 hours
	Ketamine infusion
	Lidocaine infusion
	Naloxone infusion

1.3.3 Advanced Organ Support

1.3.3.1 Respiratory

Acute Respiratory Failure is a common reason for admission to critical care, when patients require more than the supplemental oxygen that can be provided in a ward setting. As seen in Table 1.6, some critical care interventions to support a patient's breathing can be considered basic critical care (enhanced care). These include High Flow Nasal Oxygen (HFNO), and Non Invasive Positive Pressure Ventilation (NIV). Both of these forms of treatment have been developed with the aim of avoiding the burdens of invasive ventilation (Abe et al. 2023).

NIV is used routinely in certain diseases, such as exacerbations of chronic obstructive pulmonary disease (COPD) or decompensated heart failure with pulmonary oedema, where evidence suggests it can reduce need for invasive ventilation and overall mortality (Abe et al. 2023). In other disease states NIV is often used as a tool to avoid invasive ventilation where possible, or when it is felt that invasive ventilation would not be successful in achieving the patient's goals.

HFNO consists of a supply of a large volume of heated humidified air (up to 60L/min) with supplemental oxygen (up to an $\text{FiO}_2 \sim 1$), via wide-bore nasal cannulae. In doing so it matches peak inspiratory flow rates of patients, providing the targeted fraction of inspired oxygen (FiO_2) throughout the respiratory cycle. It also provides a small degree of positive end expiratory pressure (PEEP), which may minimise alveolar collapse and atelectasis.

NIV can be supplied via multiple interfaces including: nasal, face mask, and helmet. NIV supplies air with supplemental oxygen with additional pressure support throughout the respiratory cycle. It supplies an adjustable level of pressure on inspiration to help with lung inflation, this may be referred to as Inspiratory Positive Airway Pressure (IPAP), or Pressure Support (PS). It also supplies an adjustable level of PEEP, also referred to as Expiratory Positive Airway Pressure (EPAP).

In more severe acute respiratory failure, non-invasive support may be inadequate. In cases where intubation and invasive ventilation is indicated, continuing with NIV is associated with worse survival outcomes (Abe et al. 2023). In this patient group, an endotracheal tube is placed and attached to a mechanical ventilator with similar controls to its non-invasive counterpart. Invasive ventilation allows for a greater level of adjustment for individualised patient support. Inspiratory support may be adjusted through targeting a certain volume with each breath (tidal volume) or applying a certain pressure on inspiration. When a patient is sedated to facilitate mechanical ventilation, more granular control of the respiratory cycle can be achieved. Advanced respiratory support with invasive ventilation exists on a spectrum. At the least severe, it may involve levels of support similar to that of NIV. When more severe, a patient may be anaesthetised, with medicines to ensure neuro-muscular blockade, to allow for full control of the respiratory cycle.

In patients with the most severe forms of acute respiratory failure, more advanced forms of extra-corporeal support may be considered. These forms of extra-corporeal membrane oxygenation (ECMO) are performed in few specialist referral centres.

1.3.3.2 Cardiovascular

Patients with cardiovascular failure in critical illness often require support via continuous infusion of vasoactive medicines. These medications are used with the intent of increasing blood (and therefore oxygen) supply to patients' organs, by affecting heart rate (chronotropes), heart contractility (inotropes), or vascular constriction (vasopressors). As noted in Table 1.6, a single vasoactive agent may be considered enhanced care (basic critical care), whereas multiple medications or monitoring may be considered advanced critical care. When enhanced monitoring of a patient's cardiovascular system is required, invasive blood pressure measurements may be recorded using an arterial catheter. To facilitate administration of vasoactive medications, a central venous catheter may be placed. Similarly to advanced extracorporeal support in respiratory failure, certain patient subgroups may require mechanical cardiovascular support at specialist referral centres.

1.3.3.3 Renal

Renal support for Acute Kidney Injury is achieved through the use of renal replacement therapy (RRT). RRT may be provided in either specialist units under the care of Renal Medicine, or in a Critical Care environment. RRT in acute illness involves the circulation of blood through a specialised machine. This may be achieved either through a preexisting route, such as a "tunnelled line" or arteriovenous fistula, or through a temporary specialised central venous catheter.

RRT is provided by a number of modalities, through varying levels of haemodialysis (removal of waste solutes through diffusion) and haemofiltration (removal of solutes via convection), and duration of therapy: intermittent (therapy over a 2-4 hour period) versus continuous (24 hours or more) therapy. A fairly typical approach in Scottish Intensive Care Units would be the use of Continuous Veno-Venous Haemodiafiltration (which uses both dialysis and haemofiltration). However, the use of Intermittent Haemodialysis with Ultrafiltration (to allow management of patient fluid balance), more similar to what is seen in Renal Dialysis Units, is also utilised (Dennen et al. 2010; Jörres 2012).

RRT is less commonly indicated in critical illness than vasoactive and respiratory support. In one 2022 study set in Scotland Acute Kidney Injury (AKI) was common, affecting 41% of patients in a general ICU setting. However among the cohort of patients with AKI, only 21% required RRT. In the same subset of patients with AKI, 69% received cardiovascular support, and 69% received invasive mechanical ventilation. This study found 7% of the total cohort of ICU patients (343/4682) received renal replacement therapy (Andonovic et al. 2022).

1.3.4 Aims of critical care admission

Critical care should be considered for patients who fulfil two criteria; they have a severe illness where critical care is considered to meaningfully increase chance of survival, and that a critical care stay and the possible outcomes from it are in accordance with the patient's values and wishes.

What could be seen initially as a strictly biological question: ‘does the patient have an illness that is likely to improve with critical care?’, can be recognised to be much more subjective when we consider both the idea of a “meaningful increase” in the chance of survival, and the patients’ own priorities. Balancing the benefits and burdens of critical care treatments, is comparable to the decision being made when proposing treatment for colorectal cancer.

As a result, the causes of critical care admission are not simply the forms of critical illness listed above. Like all other medical treatments, choosing to embark on critical care is a decision based on communication between all relevant parties. Inadequate or inaccurate communication may result in a different decision than would have been made with clearer discussions.

In previous studies of patients with solid-organ cancers, when patients had incorrect understanding of their prognosis, they were more likely to choose intensive care and mechanical ventilation, when compared against patients with an accurate understanding (Tang et al. 2016). A separate study found patients who lacked accurate information on their prognosis were less likely to undergo advance care planning (ACP), and more likely to select aggressive forms of treatment or surgery (Winner et al. 2016). Patients with accurate prognostic information are more likely to prefer symptom directed care; patients who discuss their wishes with treating doctors are more likely to receive care consistent with their values (Mack et al. 2010). It may be easier for clinicians to believe that patients do not wish to have potentially upsetting conversations. However, interview based studies have patients with cancer emphasising the importance of being willing to talk about dying in a sensitive, honest, and straightforward manner (Wenrich et al. 2001).

Despite the importance of advance care planning, surveys of intensivists and oncologists find that both specialities report a low rate (less than 10%) of routine ACP among patients with haematological malignancy (Spring et al. 2021). Oncologists are more likely than intensivists to report ACPs being put in place at key stages in cancer treatment, such as commencing chemotherapy, disease recurrence, or the transition point to palliative care (Spring et al. 2021). Intensivists are more likely to report oncologist discomfort as a barrier to ACP conversations occurring (52% intensivists, 32% oncologists) (Spring et al. 2021). This difference in perspective is understandable from both parties. It is likely that the majority of intensivists are unaware of the large proportion of patients in oncology who receive pragmatic ACP, and either undergo treatment without complication, or compassionate end of life care. It is plausible, is that oncologists over-report the number of ACPs they undergo, due to the ‘social desirability’ bias, or the related ‘intention-behaviour’ gap, where we over report what we think we should do, or what we intend to do, rather than what we actually do (Davies et al. 2022). Similarly it is possible that intensivists fall foul of the ‘availability bias’: where more emotionally impactful cases are recalled more easily, and considered to occur more frequently, such as cases where ACPS could have improved care at the end of life. (Saposnik et al. 2016).

For patients with critical illness, the alternative to critical care may be management focusing on symptom relief whilst dying. When the potential benefit from critical care is survival, it could seem strange not to offer it even if the chances of survival are uncertain or small. However, similar to the burdens of adjuvant SACT reported above, treatment in critical care is associated with significant patient burden. Pain is common in intensive care. 70-80% of patients report pain during treatment of critical illness (Carrillo-Torres et al. 2018). Discomfort is also common, with commonly reported triggers including: physical discomfort, sleep deprivation, hunger and thirst, embarrassment, fear, shortness of breath, and difficulty communicating (Latour et al. 2022). Additionally survival from critical illness is also associated with significant longterm impairments.

1.3.5 Outcomes Of Critical Illness; Post-Intensive Care Syndrome, Healthcare Use, and Survival

Critical illness is known to have long lasting consequences for patients. Framed in the domains of physical, cognitive, and mental health impairments, these are collectively known as Post-Intensive Care Syndrome (PICS) (Inoue et al. 2019). This triad of domains can also be expanded and applied to the family members of patients (PICS-F) and also broadened to a global view of patient quality of life, as well as the person's interaction with society (McPeake and Mikkelsen 2018).

Post-Intensive Care Syndrome is common, with a 2018 study noting 56% of survivors of critical illness had new impairments in a single physical, cognitive, or mental health domain 12 months after hospital discharge (Marra et al. 2018; McPeake and Mikkelsen 2018). This study included only patients without pre-existing impairments; a smaller study from 2016 included both new impairments and worsening of existing impairments, finding a similar proportion of all patients (54%) experienced worsening function in at least one domain of Post-Intensive Care Syndrome, 12 months after critical illness (Maley et al. 2016; McPeake and Mikkelsen 2018). The smaller study is likely to be more relevant to intensive care currently, with a growing proportion of patients with pre-existing impairments or comorbidities being admitted.

1.3.5.1 Cognitive

PICS induced impairments in cognition include aspects such as: memory, executive function and attention, and language (Inoue et al. 2019). In addition, critical illness is associated with increased rates of cognitive illnesses such as dementia, with 15% of critical illness survivors being diagnosed in the three years after hospital discharge, in comparison to 12% in the general population (Inoue et al. 2019).

1.3.5.2 Mental Health

In a 2013 cohort of all ICU survivors, 44% of patients reported being significantly anxious or depressed 12 months after hospital discharge (Griffiths et al. 2013). Post Traumatic Stress Disorder (PTSD) in critical illness survivors is thought to occur at an incidence of approximately 20% (Latour et al. 2022). This increased incidence is not limited to the patient. Among family members of patients who were admitted to ICU, up to one third have symptoms associated with PTSD three months after hospital discharge. This includes both family members of those who have survived and those who have died in ICU (Latour et al. 2022).

1.3.5.3 Social

The hospital discharge location for a patient may also be affected by critical illness. In an international cohort of patients with lung cancer treated in intensive care, 200 of the 449 patients (45%) remained alive at 6 months. Of these patients 141 were in their own home at 6 months (32% of total, 70% of survivors), 30 were in hospital (15% of survivors), and 14 were in hospice (7% of survivors) (Soares et al. 2014). Survivors of critical illness are also observed to experience increased rates of hospital readmission (Myles et al. 2017; Evans et al. 2012; Kinoshita et al. 2015; Cosgrove et al. 2019).

Another aspect affected by critical illness is the financial burden experienced by an individual and their family. Among the 2013 cohort of general ICU survivors, 28% had lost work 12 months after discharge (Griffiths et al. 2013). In a single site experience, a third (31%) of patients attending a critical illness follow up service requested consultations with a social welfare service, requiring support with: welfare benefits, return to employment, housing, debt, and legal advice (McPeake et al. 2019). Another 2022 study of caregiver's experiences following critical care, where a caregiver

was the person who provided most of the support for the person with critical illness, found a rate of depression at 27% amongst caregivers prior to any specialist support. The same study found caregiver strain (a measure that includes social, physical, and financial strain) at 30%, and caregiver insomnia at 61% (McPeake et al. 2022).

1.3.5.4 Survival

Survival from critical illness is not guaranteed. The 2023-2024 Intensive Care National Audit and Research Centre (ICNARC) report, included data from 263 adult general critical care units in England, Wales, and Northern Ireland. ICNARC reported an observed critical care mortality of 12.5%, and an eventual hospital mortality of 16.6% among the 190,320 patients admitted to critical care between 2023 and 2024 (ICNARC 2024). Similar to the reduced longevity seen in patients with cancer and critical illness, ICU survivors following any disease type are noted to have both shortened longevity and increased healthcare utilisation. Using national registry data Lone et al. 2016 found a 5 year mortality of 32.3% among ~ 5000 intensive care survivors in Scotland. This cohort of patients contained adults admitted to general intensive care units with medical and surgical admission types. McPeake et al. 2021 in their systematic review and meta-analysis found pooled estimates for hospital re-admission after critical illness at 29.6% at six months, and 53.3% at one year.

1.4 Where Critical Illness and Colorectal Cancer Meet

1.4.1 Admission To Critical Care

To summarise the section beneath, patients with CRC are frequently admitted to critical care, through elective and emergency routes, and often receive organ support during their stay. CRC is the solid cancer most commonly associated with ICU admission, and their ICU outcomes are comparable to patients with other significant comorbidities. As such, there has been a shift in approach to how intensive care approach such patients, with a greater willingness to admit patients with cancer to critical care.

Critical care admission is common for patients with colorectal cancer. Previous work has identified 16% of patients with CRC were admitted to a general ICU within two years of their cancer diagnosis being made (Puxty et al. 2015). Colorectal cancer has been found to be associated with 44% of combined elective and emergency solid cancer ICU admissions, and 17% of specifically emergency solid cancer ICU admissions (Vincent et al. 2018; Puxty et al. 2018, 2015).

Investigating the nature of critical care admission, approximately 46% of patients with colorectal cancer in ICU had been admitted to hospital as an emergency, and 48% of CRC ICU patients (emergency and elective combined) received organ support during their stay (Puxty et al. 2015). In a study of ICU treatment for all patients with solid cancers, using information from 16 adult general intensive care units in Scotland from 2000-2009: CRC itself was the most common reason for ICU solid cancer admission (almost exclusively for peri-operative care), CRC also had the lowest rates of organ support in ICU when compared to other solid cancers (Puxty et al. 2015).

A separate single centre study from Camus et al. 2014 (all patients admitted with CRC admitted to the ICU of a single cancer hospital from 2003 to 2012), identified 70% of patients admitted to intensive care with colorectal cancer had metastatic disease. This is markedly higher than the above Puxty study from 2015, which identified 9.6% of patients with metastatic colorectal disease in the colorectal cancer intensive care cohort (Camus et al. 2014; Puxty et al. 2015). Part of this difference may relate to the fact that the majority of Scottish ICUs in the Puxty study were not “cancer hospitals” and likely have differing approaches to, and treatments for, patients with metastatic cancer than seen in this French cancer hospital.

A patient with colorectal cancer may be admitted to critical care as a result of: their cancer directly progressing, their cancer increasing the risk of other illnesses and inducing them (e.g. venous thromboembolism), an intended admission for monitoring and support after cancer treatment, an unintended admission as a result of complications from cancer treatment, and for reasons unrelated to their cancer admission. Additionally, admission to critical care could be following emergency surgery for a previously unknown colorectal cancer in the case of bowel obstruction or perforation. (Andréjak et al. 2011).

One in ten patients undergoing CRC surgery receive organ support in the post operative period (Dale et al. 2016). Patients that require organ support may have experienced complications from their surgery or anaesthetic, or deterioration in co-existing conditions. Factors associated with post-operative organ support include older age, emergency surgery, social deprivation, comorbidities, and male sex (Dale et al. 2016).

There has been a cultural shift over the last twenty years in how ICU teams view the likely prognosis of patients with cancer and critical illness. This is due to the consistent improvement in survival from critical illness for patients with cancer. A 2011 report found patients appeared to be more likely to benefit from critical care

when admitted early. Traditionally relevant predictors of poor outcome such as invasive ventilation, invasive fungal infection, and even multiorgan failure became less relevant than before (Azoulay et al. 2011). As such the authors of these recommendations aimed to reposition cancer as a chronic condition in the eyes of clinicians, highlighting the similarity in prognosis for patients with cancer to those with heart failure or hepatic cirrhosis (Azoulay et al. 2011). In addition to noting the increased likelihood of good critical care outcomes, the authors of the above piece highlighted the uncertainty in likely admission outcomes, at the point of ICU admission. Similar to recommendations for patients with potentially catastrophic brain injuries, and post cardiac arrest, the authors recommended a “therapeutic trial” of admission in cases with prognostic uncertainty. This admission would involve a short three day trial of ICU treatments without limitation, to gain a clearer impression on the likely prognosis of a patient with cancer and critical illness (Azoulay et al. 2011; Harvey et al. 2018; Nolan et al. 2021).

Greater detail on the outcomes of critical care are provided in the section below.

1.4.2 Outcomes of critical care

1.4.2.1 Survival

For cancer patients in ICU, critical illness is the main determinant of short-term mortality, and short-term outcomes are comparable to critically ill patients without cancer (Taccone et al. 2009; Puxty et al. 2018, 2014).

In a 2014 systematic review of 48 papers, looking at both elective and emergency admissions to ICU for patients with solid cancers, the average ICU mortality was 31%, with hospital mortality at 38% (Puxty et al. 2014). On first glance this is a substantially greater mortality than the 12.5% critical care mortality and 16.6% hospital mortality reported by ICNARC (ICNARC 2024). Some important clarification is that ICNARC reported critical care mortality (ICU and HDU), where Puxty et al. 2014 reported ICU mortality only. The four papers in the systematic review that reported CRC specifically had an average ICU mortality of 19%, and hospital mortality of 35% (Puxty et al. 2014).

In this review, factors that increased likelihood of death in ICU included: any form of organ failure, with invasive ventilation having the greatest increase in risk; an acute medical admission rather than surgical, and patients admitted as an emergency (Puxty et al. 2014). The authors of this review were able to support their findings with a multi-centre retrospective study; showing whilst average ICU mortality was 20% for all patients with solid organ cancers, this rose to 35% for the subset of cancer patients requiring organ support, 40.7% for emergency admissions, and 53% for patients admitted through medical specialities (Puxty et al. 2015). A later study in 2018 looking specifically at patients admitted emergently to ICUs across Europe, found hospital mortality in those with colorectal cancer to be 50.5% (90/178) (Vincent et al. 2018).

When investigating longer term outcomes, the five papers in the systematic review that provided one year mortality information (for all solid cancers) found a wide distribution, from 36-88% (Puxty et al. 2014). A 2021 study looking at non-elective ICU patients (with both solid and haematological cancers), found ICU and hospital mortality rates comparable to the 2014 review. Specifically for those who survived hospital, the authors found an additional 28% six month mortality, a 41% one year mortality, and a 50% two year mortality. After taking into account those who died in hospital this becomes: a 60% six month mortality, a 67% one year mortality, and a 72% two year mortality (Zee et al. 2021). The 2014 review of patients with solid cancers admitted

to surgical ICU either electively or emergently, found a lower six month mortality (31%), and four year mortality (61%) (Puxty et al. 2014). These differences may be accounted for by haematological cancers being associated with poorer outcomes, and elective procedures being associated with better outcomes.

When comparing patients with cancer who experience critical illness and those who do not, one year mortality is higher in those with some measures of critical illness. A single retrospective cohort study of 400 patients from 2000 found one year mortality in patients with cancer and admission to intensive care to be 77%, compared to 45% in those with cancer without ICU admission (Staudinger et al. 2000).

There is a growing body of work to support the treatment of patients with cancer during critical care admission like those with other chronic illnesses, starting to answer the question of “cancer” versus “no cancer” in critical illness outcomes (Taccone et al. 2009; Puxty et al. 2018, 2014). Complementary to this, as noted above there are studies that start to approach the other comparison of “critical illness” versus “no critical illness” amongst patients with cancer, particularly with regards to ICU and one-year survival (Staudinger et al. 2000). However at the time of writing, the impact of critical illness on subsequent cancer outcomes and adjuvant chemotherapy remains poorly studied. There are key gaps in the literature regarding how critical illness impacts:

- Receipt of Subsequent Colorectal Cancer Care - Particularly Adjuvant SACT
- The Relative Quality and Intensity of Subsequent Colorectal Cancer Care
- Long Term Colorectal Cancer Care Outcomes Following Critical Illness

The current evidence base is not non-existent, but it is sparse. One article identified admission to Intensive Care as a factor associated with decreased likelihood of receipt of adjuvant chemotherapy for colorectal cancer. In this work from Kim et al. 2015, for patients with Stage II or III CRC, admission to Intensive Care was associated

with hazard ratio of 2.4 for subsequent omission of adjuvant chemotherapy in multivariate analysis (Kim et al. 2015). In their work they did study but did not find any differences in the numbers of patients admitted to intensive care experiencing delays when receiving adjuvant SACT (Kim et al. 2015). Unfortunately Kim et al. 2015 in their work refer to 'Intensive Care Admission' rather than providing clarity about the level of critical illness, and provide no additional information on the details of such an admission. One other study has identified 'prolonged mechanical ventilation' as a factor associated with increased odds of adjuvant chemotherapy omission (adjusted OR 7.36, CI: 2.77-19.6) (Merkow et al. 2013). Through use of 'prolonged mechanical ventilation', more detail is provided on the severity of critical illness beyond intensive care admission. Unfortunately Merkow et al. 2013 do not provide details on the number of patients experiencing prolonged ventilation, considering this group to be one form of post operative complication amongst many. As they report 15% of the total 1,714 patients experienced any complication, that the most frequently occurring complication had a rate of 10% (170), and the least common occurring had a rate of 1% (17), it seems that the cohort who experienced prolonged ventilation had a size between 17 and 170 patients. Considering the wide confidence intervals in their reported findings, and that they do not report association with delay on adjuvant chemotherapy (presumably being unable to due to small group sizes), it appears likely that Merkow et al. 2013 group of patients with prolonged ventilation are small (Merkow et al. 2013).

Outside of CRC specifically, Benguerfi et al. 2024 studied patients with all forms and stages of solid organ cancer who were admitted to ICU, and the factors associated with cancer treatment resumption. Of their 219 patients, 23 had colorectal cancer. Within their total cohort, 81 (59.6%) received any form of cancer treatment after ICU discharge.

With regards to long term cancer outcomes after intensive care admission, one single centre study provides information on 18 month survival, for patients with a range of 20 cancer types (Praça et al. 2024). In their study of 3,348 patients including 312 admitted to ICU (with 401 CRC, 54 admitted to ICU), Praça et al. 2024 note that admission to ICU was associated with reduced 18 month survival (HR, 1.84; 95% CI, 1.29-2.64). With a similar criticism to papers mentioned above, whilst Praça et al. 2024 provide novel information, the relevance is difficult to interpret due to the combination of multiple cancer types and cancer stages in their analysis. Like other papers, they are also limited by the description of Intensive Care Admission, rather than any greater specificity on the level of critical illness.

1.4.2.2 Physical and Health Related Quality of Life

Among patients with haematological and solid malignancies admitted to ICU, among survivors one year after admission, measures of health related quality of life are lower than before admission (Oeyen et al. 2012; Normilio-Silva et al. 2016). This deterioration is greatest among patients with haematological malignancies when compared to those with solid cancers. Of note, survivors with gastrointestinal cancers had the highest measures of quality of life (Oeyen et al. 2012).

EQ-5D is a measure of health related quality of life and uses a scoring system that includes mobility, self care, activities, pain, and anxiety/depression, scored from 0 (worst possible), to 100 (best possible) (Balestroni and Bertolotti 2015). A 2022 study of mixed ICU survivors predominantly without cancer; survivors experiencing usual care (i.e. no access to specialist follow up clinic), had median scores of 55. When comparing these results to a population based norm across similar age ranges, the

population average score for EQ-5D would be approximately 80-90 (Henderson et al. 2022; Janssen et al. 2021). Targeted interventions can improve EQ-5D scores, this study found the median score in those receiving specialist follow up increased to 70 (Henderson et al. 2022; Janssen et al. 2021).

When looking at a cohort of medical and surgical intensive care patients, including those without malignancies, a 2013 study found that 6 months after hospital discharge, approximately one in four survivors required assistance with activities of daily living (Griffiths et al. 2013). Among the same cohort 73% reported moderate to extreme pain 12 months after ICU discharge (Griffiths et al. 2013).

A 2018 systematic review reported moderate to high quality evidence that patients who experience critical illness have impairments in all measurements of the WHO International Classification of Functioning, Disability and Health Framework (Ohtake et al. 2018).

1.4.2.3 Performance Status and Frailty

Emerging from the interplay between physical, psychological, and social states of an individual; frailty reflects an individual's ability to interact with the world around them (their functional status), and their ability to recover from illness and injury. As a syndrome it is greater than a patient's list of co-morbidities, physical impairments, or muscle mass and respiratory capacity. Rather it is considered more of a global (ill)health state (Ginesi et al. 2022; Winter et al. 2021; Brummel et al. 2020).

Traditional administrative datasets fail to routinely collect information on the patient and the ways they experience and interact with the world around them. As a result many electronic frailty indices are closer to comorbidity indices. In response, some work attempts to distinguish between "medical frailty" and "functional frailty" (Street et al. 2021; Ginesi et al. 2022). Frailty indices that use comorbidity information such as the Hospital Frailty Risk Score (HFRS) can still aid in prediction of hospital survival and other relevant measures. The HFRS uses cluster analysis to determine a set of diagnoses (ICD-10 codes) that correspond with frailty syndrome in older patients. As a medical model of frailty, the HFRS shows some agreement with more functional measures of frailty such as the Rockwood Frailty Index (Clinical Frailty Score) when predicting patient outcomes (Gilbert et al. 2018; Street et al. 2021). Unfortunately, as described in more detail later, my work in this thesis suffers from the same limitation, where frailty had not been captured in routinely collecting data. As of 2020, data collected for critical care patients in Scotland now routinely includes a measure of frailty, the Clinical Frailty Score (CFS).

Another measure of global health and performance status, the Eastern Cooperative Oncology Group score (ECOG) is a commonly used measure among patients with cancer, and can be used to identify potential contraindications to SACT and other treatments (Argilés et al. 2020).

Table 1.7 demonstrates the different grades of ECOG and how they relate to a person's physical ability (Oken et al. 1982).

One 2021 study looking at elective patients admitted to critical care, found both an association with critical illness and worsening performance status, and a relationship between poor initial ECOG and likelihood of not surviving critical illness. With the work of Kim et al. 2015 above, a potential explanation for decreased receipt of adjuvant SACT would be through the worsening performance status of patients who

Table 1.7: ECOG Performance Status Scale

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

experience critical illness. Another potentially overlapping explanation for any decreased SACT receipt would be through the impact of PICS as detailed above. Despite this average worsening in ECOG, of those that survived to two years post ICU admission, the majority (77%) had a good ECOG status of 0 or 1 (Zee et al. 2021). This may be related to increased mortality among patients with worse ECOG status.

1.4.2.4 The Cancer Journey Following Critical Care - All Forms of Cancer

It is important to note that despite the increased limitations noted above, previous work investigating patients with haematological and solid malignancies, found the vast majority (92%) of interviewed ICU survivors expressed a preference to be readmitted to ICU in a future critical illness (Oeyen et al. 2012).

When investigating cancer treatment and illness progression after critical illness, the 2014 study of patients with lung cancer treated in ICU, found 26% of hospital survivors had experienced cancer progression or recurrence at 6 months. Further anticancer treatment was recommended to 39% of hospital survivors, and in 34% the anticancer plan required reduction or modification. This reduction or modification of treatment was associated with an increased mortality in patients (Soares et al. 2014).

In a separate study of 76 patients with Lung Cancer and Critical Illness, among the patients admitted to critical care there was a 65% hospital mortality. Among hospital survivors, only four patients (4/27) subsequently underwent lung cancer treatment (Andréjak et al. 2011).

There is a paucity of information on subsequent anticancer therapy, or outcomes broader than survival, among patients with colorectal cancer who experience critical illness. A 2014 single-centre study of 65 CRC patients who survived an ICU admission, found 31% were unable to continue with their planned SACT following ICU discharge. Adherence to the planned SACT regimen after discharge was a strong predictor of longer term survival. However this study was unable to explore which factors were associated with changes to treatment plans (Camus et al. 2014). The majority of these trials are greater than a decade old. As such they may no longer reflect either the changing practices of admissions of cancer patients to intensive care, nor the current practices and outcomes in CRC management. As such we require more recent, more precise estimates on CRC outcomes following critical illness (Puxty et al. 2018).

In addition to mortality, other measures of how a patient and their family experience their death can be considered relevant. Place of death and the interventions during dying are associated with the quality of dying and death (Gutiérrez-Sánchez et al. 2021). Cancer care interventions can be associated with differing experiences of dying. A 2014 UK study found patients receiving chemotherapy when terminally ill were more likely to undergo CPR, treatment in intensive care, and death in intensive care (Wright et al. 2014). As noted earlier, death in critical care is a common occurrence for those admitted. On a national level, a retrospective study of over 700,000 deaths in Scotland found similar numbers of patients dying in critical care (5.1% of all deaths) when compared to hospices (6.1%) (Mayes et al. 2021).

1.4.3 Unanswered Questions and Aims of Thesis

Critical illness is common among patients with colorectal cancer. How critical illness affects the likelihood and quality of subsequent anticancer treatment in colorectal cancer is poorly understood. Both critical illness and cancer are seen to impair longer term survival, function, and patient and family centred outcomes. It is less clear how cancer and critical illness interact, whether there is an additive or even synergistic association with the above factors.

As such, this work aims to investigate the outcomes following critical illness for patients with colorectal cancer. After initially describing the demographics of those with colorectal cancer in Scotland, it will assess the differences in demographics between three main cohorts:

- “*Ward Care*”: Those who are admitted to hospital but not critical care:
- “*Monitoring*”: Those who are admitted to critical care but do not receive organ support.
- “*Organ Support*”: Those who are admitted to critical care and receive organ support.

In making this stratification into three groups, we will add novel information to the literature, where previous work tended to stratify only by ICU admission or not.

Considering that patients who present to hospital electively or emergently have likely already commenced on different cancer journeys, this thesis will also stratify by nature of admission, resulting in a total of six subcohorts. This will be expanded upon in the following chapters.

Within each chapter I will describe each subcohort, differences between each subcohort, and use bayesian modelling to identify factors associated with any identified difference.

To further establish the scope of work for this thesis, and its methods, the following three chapters act to describe practicalities and rationale behind methods, as well as an overview of the total cohort demographics. Chapter 2 explains and justifies the use of a Bayesian statistical framework for this thesis. Chapter 3 describes the methods to compile and clean the provided datasets into datasets suitable for analysis. Chapter 4 provides an overview of the demographics of the cohort of patients within this dataset, as well as describing key differences between each of the six subcohorts.

After establishing the foundations in the above chapters, the questions this thesis attempts to answer in the following chapters are:

- Chapter 5: Does surviving critical illness affect the quality of CRC care as measured by the Scottish QPI system?
- Chapter 6: Does surviving critical illness affect the quality of CRC care in relation to SACT receipt, form, quality, and intensity?
- Chapter 7: Does surviving critical illness affect the long term survival likelihood for patients with CRC?

As mentioned at the start of this chapter, the majority of my work takes a perspective more suited to assessing post critical illness cancer outcomes, that may be most relevant to those working in Oncology. Additionally, the chapters listed above will take a non-causal approach to the question of critical illnesses association with cancer outcomes.

In the three years since beginning this work, there has been a growing understanding and appreciation for causal models in the medical literature. The final chapter, Chapter 8, will take a more causal approach to the question of interest. In the final chapter, rather than investigating solely the cohort of patients who survive critical care, I will investigate critical care outcomes for all critical care admissions, and cancer outcomes for those who survive their hospitalisation. In doing so I will be able to comment more strongly on any identified causal impact, and take the perspective of a critical care clinician, at the point of critical care admission.

Taking on my perspective of a critical care clinician, this final chapter will stratify patients in critical care more clearly by severity of illness, separating those who received no organ support, short courses (≤ 24 hours) or long courses (> 24 hours) of organ support in critical care.

Chapter 2

Bayesian Statistics

2.1 Introduction

The aim of this methodology chapter is to explain and justify the Bayesian statistical techniques found in this thesis. Understanding that the likely audience are clinicians trained with and used to more classical frequentist approaches, this chapter will provide a rationale for the use of a different paradigm. It explains Bayesian statistics in two stages; first a conversational summary of Bayesian principles, second a more detailed description of how Bayesian clinical papers could be presented. In this second section, I provide the perceived advantages of a Bayesian approach, and my own rationale for using this statistical method. In the final third of this chapter, I describe the workflow I used for each question of interest.

The first third of this chapter introduces the key terms and concepts in Bayesian inference; taking the reader from a point of no previous exposure to Bayes to a place where they could follow a conversation. This section will introduce the concept of *probability distributions*, *prior* and *posterior* probabilities, different forms of these distributions, as well as *likelihood*. Finally the first section will introduce *Bayes Theorem*, as well as the *marginal likelihood*.

The second section of this chapter builds on these introductory components, and aims to provide the reader with the knowledge required to read and critique a Bayesian clinical trial. Focusing on the Results, Methods, and Discussion sections of such a trial, this section explains the commonly reported statistics seen in the results section, describes what a reader should expect from the methodology section, and compares the perceived advantages and disadvantages of Bayesian techniques to frequentist approaches. It is these advantages that prompt my own use of Bayesian techniques in this thesis.

The final third of this chapter provides the template I developed for my own analyses.

As noted in Chapter 1, Chapter 8 has been developed as a relatively stand-alone chapter, with some differences in methodology. These differences are detailed more clearly in the methods section of Chapter 8.

2.2 Step One - The Ground Work: Enough Theory For a Conversation

2.2.1 Bayes in a Single Sentence

In a broad-brushed sense, Bayesian statistics allows us to: numerically describe our estimated beliefs before testing a hypothesis, describe how strongly we hold these beliefs, and update these beliefs after we receive new information.

2.2.2 Parameters

To describe our belief in a hypothesis, and to describe the hypothesis itself, we use a variety of values. These values are referred to as the *parameters* or *parameter estimates* of a statistical model. Example parameter estimates could include; the probability of a single event occurring (a patient's illness resolving), how many events we expect to occur if we were to run a trial on multiple patients, and our certainty in the above two estimates being true (Kurt 2019).

When describing these parameter estimates, which can either be inserted into or retrieved from a statistical model, the first difference between Bayesian and frequentist techniques appears. Unlike a frequentist approach, a Bayesian statistical model does not take or produce *point estimates* (a single value to represent the parameter). Instead, a Bayesian model takes and produces the parameter estimates as *probability distributions*, which represent the range of possible values as well as how likely each value is. As an example: rather than saying the percentage chance of a single event occurring is 60%, a Bayesian model might describe a range of values from 30% to 90%, with values closer to 60% being more likely than the values at the limits of the range, as shown below in Figure 2.1.

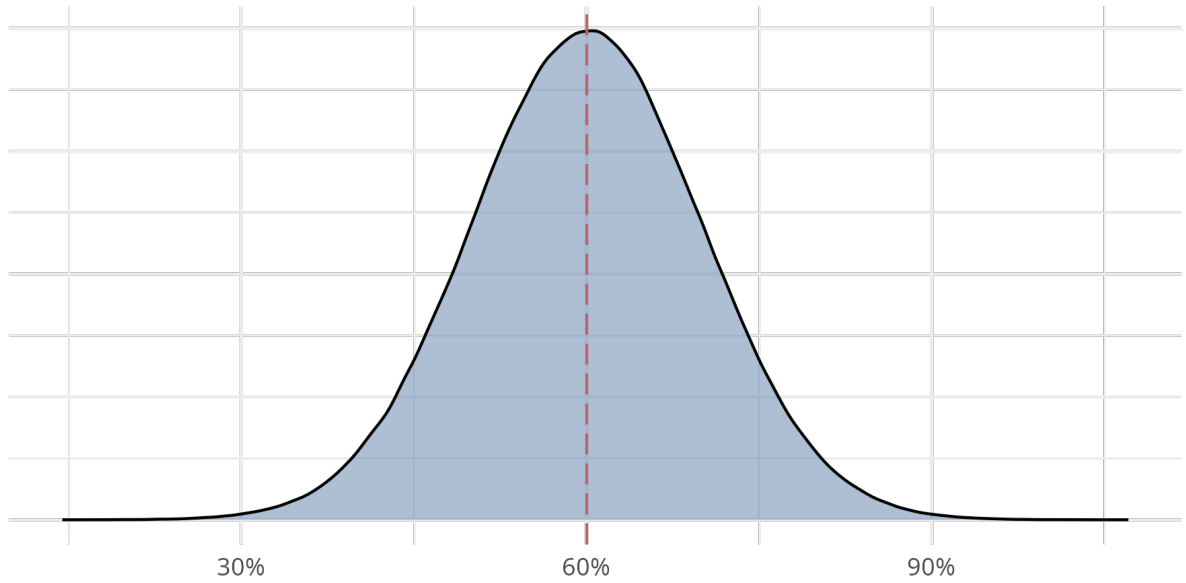


Figure 2.1: Probability distribution (solid outline) compared to the point estimate (dashed).
Reproduced with permission from Taylor et al. 2025.

How these distributions are denoted depends on the family of the distribution being used. One family well known to clinicians would be the normal or Gaussian distribution. In this we can define the central point of the probability distribution (the mean, μ), and the size of the tails spreading out either side of the central point (through the standard deviation, σ). We can note the probability of our event of interest occurring as $P(\theta)$, where P stands for Probability, and θ (theta) means the parameter we are interested in describing (Kruschke 2014) :

$$P(\theta) = \text{Normal}(\mu, \sigma)$$

In Figure 2.1 the plotted probability distribution can be described by:

$$P(\theta) = \text{Normal}(\mu = 0.6, \sigma = 0.1)$$

2.2.3 Distributions

These probability distributions of parameter estimates allow us to describe what we believe to be true about a certain hypothesis. We can use probability distributions to describe our beliefs both before we gain additional information from a clinical trial, and after that new information has been taken into account. The probability distribution describing our belief before we get new information is known as the *prior distribution*, the distribution after additional information is taken on board is known as the *posterior distribution*.

2.2.4 Prior Probability Distributions and Shape of Distributions

Our prior distribution allows us to describe our belief in a hypothesis (e.g. the size of a treatment effect) before our trial collects any new information on the subject. However this does not mean that a prior distribution itself has to be based on no information. Our prior distribution can be shaped by any relevant information, such as previous clinical or laboratory work. Here one of the major criticisms of Bayesian analysis starts to raise its head: how we interpret previous studies can be subjective. If done without caution this subjective nature could push our prior distribution too far towards assuming benefit or harm, which in turn could shape our results in a way the trial data do not suggest.

The shape a prior distribution takes can be described in terms of the certainty it has, and the place it sits from benefit to harm.

First, if we were to take a prior distribution that was centred on the most likely outcome being “no treatment effect”, we could refer to this as a *neutral* distribution. If we increased our certainty of there being no treatment effect, reducing the range of possible values and decreasing the probability of benefit or harm, we would have created a more *informative* prior, known in this case as a *sceptical* distribution. In Figure 2.2, the example informative prior is a sceptical prior.

If we were to decrease the strength of our belief in no treatment effect, stretching the range of possible values much further into benefit and harm, we would have created an *uninformative* or *diffuse* prior. One form of an uninformative prior, which states that all outcomes are equally probable, is called a *flat* prior. As shown in Figure 2.2, the shape of a flat probability distribution is a flat line.

If we interpreted previous information as suggesting there was a treatment effect, and push the majority of our probability distribution towards that, our prior probability distribution can be referred to as an *optimistic* or *enthusiastic* prior. Like our neutral prior, depending on the strength of belief, this distribution could be strongly or weakly informative, changing from a plot of sharp peak to a rolling hill. Last, if we were to interpret previous information as saying there was harm from treatment, we would create a *pessimistic* prior distribution.

At this point a reader may feel that Bayesian research could not be objective, considering the different forms each prior could take. This context dependent nature becomes potentially more concerning, when we note that these terms above are purely descriptive and not strictly defined. If previous evidence were to imply a treatment benefit, and we shaped our prior to model this as accurately as we could, not particularly pushing it in an even more optimistic or pessimistic direction, then you can end up with the seemingly conflicting situation where a probability distribution states the most probable outcome is benefit, and yet gets called a “neutral prior”.

How the choice of prior distribution is accounted for is described further in section 2.3.2.1, but in brief, clinical trials using a Bayesian approach are expected to: provide justification of their use of prior distributions, use a variety of prior distributions, and show how their choice of prior distribution could affect the results of an analysis. An initial defense of Bayesian assumptions (revisited in section 2.3.3.4), may also state that some of the subjectivity of a Bayesian analysis also exists in frequentist trials, and that the Bayesian approach is merely more “up-front” about its assumptions (Kruschke 2014; Schoot et al. 2021; Zampieri et al. 2021) .

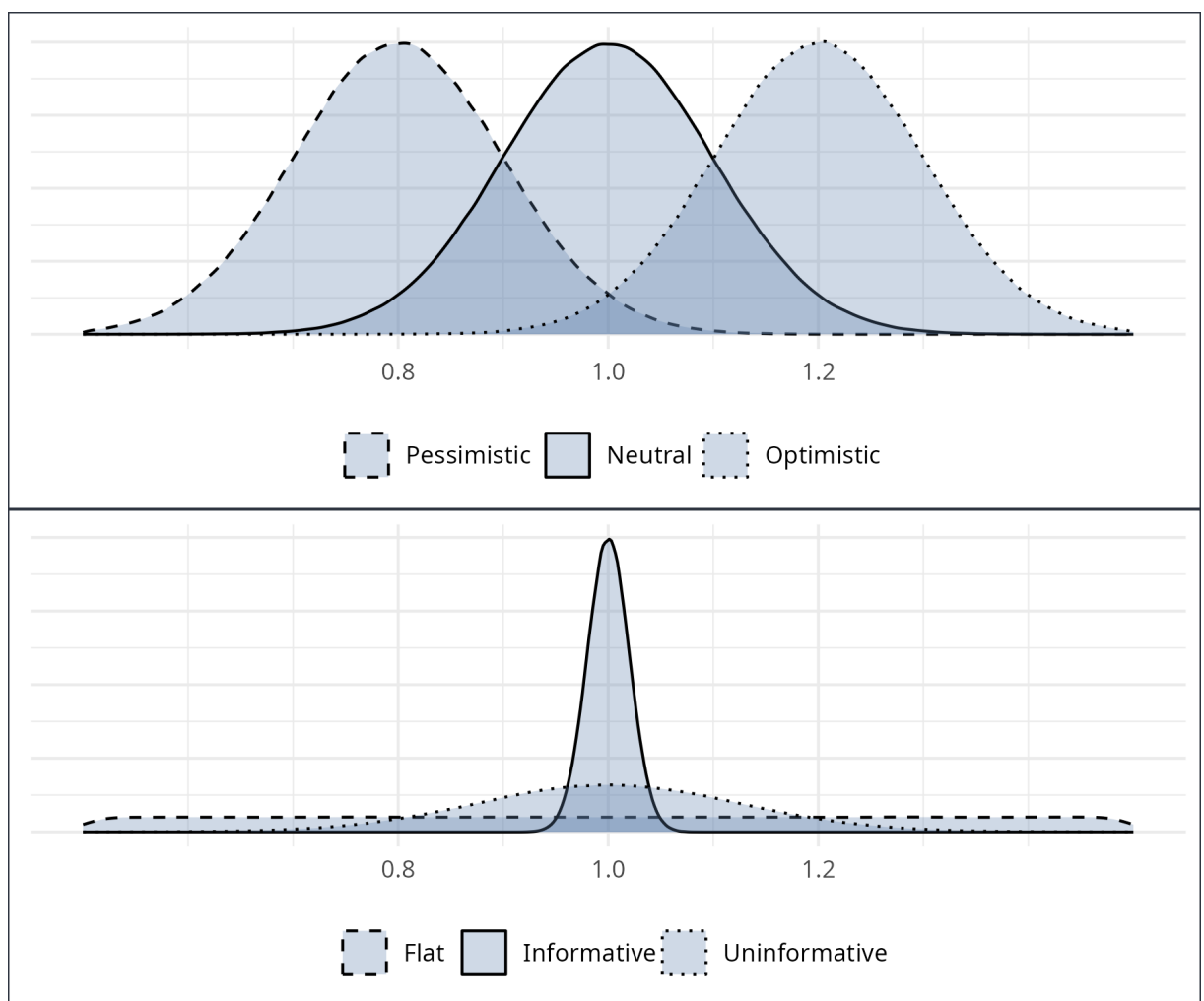


Figure 2.2: Illustrative prior distributions showing: (A) distributions with differing central points (pessimistic, neutral, optimistic), and (B) distributions with differing levels of information (informative, uninformative, flat). Reproduced with permission from Taylor et al. 2025.

2.2.5 Likelihood

As noted so far, a piece of clinical research that takes a Bayesian approach will generate a *prior distribution* and assess how new information shapes it into a *posterior distribution*.

For us, this new information will be the evidence collected by clinical research. To assess how probable it is that our hypothesis is true, we take into account the “*likelihood*” of our evidence.

Likelihood in this context means: “If we were to assume that our hypothesis described by the prior distribution is true, how likely would it be for us to get the trial outcomes that we did?” The implication of unlikely data being observed, is that either our trial is just a rare occurrence and the hypothesis is still true, or that there are problems with our hypothesis and our beliefs need to change.

In this description of likelihood, we are talking about the probability of one thing occurring (our observed data) if another condition was met (our hypothesis being true). This type of probability is referred to as a *conditional probability*, and is noted as $P(B | A)$ which stands for the probability (P) of our trial evidence (B) occurring if the hypothesis (A) were true.

Our description of a likelihood has some similarities to the principles underlying Null Hypothesis Significance Testing, and these are explored further in section 2.3.1.7.

2.2.6 Posterior

Our observed evidence (in the likelihood) and our prior probability distribution are combined to form our new estimate, the *posterior probability distribution*. In combining the prior and likelihood, their relative sizes and strengths are taken into account. A trial of 1000 patients will have more influence on how a probability distribution changes than a trial of 10 patients would. A prior distribution we are more certain in will be harder to be shifted by new evidence (Kurt 2019).

As the basis of the results of our trial, this posterior distribution may be described graphically, or with summary figures (described in section 2.3.1) Additionally if we were to run a future clinical trial, we could use this posterior distribution as the new prior distribution.

2.2.7 Bayes' Theorem and Marginal Likelihood

At this point it feels reasonable to introduce Bayes' theorem. Named after the work of Reverend Thomas Bayes who wrote in the 1700s, and expanded on by the work of Pierre-Simon Laplace (Schoot et al. 2021) .

Bayes' theorem describes the relationship between our prior estimates of the probability of our hypothesis ($P(A)$), the likelihood of our observed evidence ($P(B | A)$), and the posterior estimates ($P(A | B)$). Here we have also described the posterior distribution as a conditional probability. It is the probability of our original hypothesis (A) being true, given we observed certain outcomes (B) in our trial.

The theorem itself can be written as:

$$P(A | B) = \frac{P(A) \cdot P(B | A)}{P(B)}$$

In the theorem above there is one last component yet to be described: $P(B)$. This is the *marginal likelihood* or *marginalised likelihood*, and can be thought of as the likelihood of the observed evidence, regardless of which underlying hypothesis is true (Kurt 2019; Kruschke 2014). As an example: in a trial where we saw 7 out of 10 patients survive, and we want to estimate the probability of survival for any individual patient, the likelihood ($P(B | A)$) is based on the likelihood of data occurring under one hypothesis (say that the percentage chance for an individual patient was 50%). The marginalised likelihood considers all hypotheses, from the percentage chance being just greater than 0%, to just below 100% (Kruschke 2014) .

It is this marginal likelihood that makes calculation of the posterior probability distribution often computationally intense, and sometimes impossible. To sidestep this, modern statistical techniques use MCMC (Markov Chain Monte Carlo) to take *samples* of the posterior distribution, allowing an estimated posterior distribution to be shaped.

2.2.8 Summary

The first section of this chapter introduced terms and concepts required for an initial overview of Bayesian analysis. Describing probability distributions, how Bayesian approaches take *prior* beliefs and the *likelihood* of any observed information, to form *posterior* estimates about the probability of our hypothesis. Additionally this sec-

tion introduced different ways a *prior probability distribution* could be shaped, and the potential this has to skew subsequent results, before describing Bayes' theorem, the *marginal likelihood*, and briefly touching on the concept of *sampling* from the posterior distribution.

The second section will introduce concepts required to understand and critique a Bayesian clinical trial. It will describe methods used to summarise the posterior distribution, as well as methods to compare hypotheses. The second section will also introduce methods that can be used to account for the choices of prior distribution through *sensitivity analysis*, as well as describing other advantages and disadvantages of Bayesian techniques compared to frequentist in a clinical research setting.

2.3 Step Two - Bayesian Journal Club

This section takes the assumption that readers have been involved in interpreting frequentist clinical research papers at a journal club level. As such, it highlights the key differences in results, methodology, and discussion for a Bayesian research paper. This section uses pre-existing guidance on how Bayesian research should be presented, that have been published in non-clinical, clinical, and critical-care contexts.

2.3.1 Results: Posterior Distribution

2.3.1.1 Summarising Posterior Distribution: Point Estimates and Credible Intervals

In a Bayesian analysis of a clinical trial, results are presented and interpreted through use of the posterior distribution. Consensus guidance on how to present Bayesian analysis recommends that a posterior probability distribution should be shown as a plot (Ferreira et al. 2020a; Zampieri et al. 2021). However, this recommendation isn't universal as Kruschke, a statistician writing on the subject, argues that in most contexts simple distributions can be adequately described numerically (Kruschke 2021). All authors tend to agree that the majority of distributions can and should be described with a mixture of point estimates and ranges (Kruschke 2021; Ferreira et al. 2020a; Zampieri et al. 2021) .

2.3.1.2 Central Tendency

As a first example of a point estimate, stating the *central tendency* of a posterior distribution is recommended by consensus guidance (Ferreira et al. 2020a; Zampieri et al. 2021; Kruschke 2021). The central tendency describes the centre of the “peak” of a posterior distribution, where the most probable estimate for the value of interest lies, as shown in Figure 2.3. In a fully symmetrical distribution this point may be the *mean*, however it is uncommon for a posterior distribution to be fully symmetrical (Kruschke 2014). Instead, either the median or mode tend to be recommended as point estimates for central tendency. Which measure is most appropriate depends on the nature of the posterior distribution and the form of outcome variable (Kruschke 2021).

If we consider the central tendency to be a way of describing our “best guess” of the true value of a model’s outcome, we can consider the spread of the distribution around the central tendency, in the form of the *credible intervals*, as a way of describing our (un)certainty.

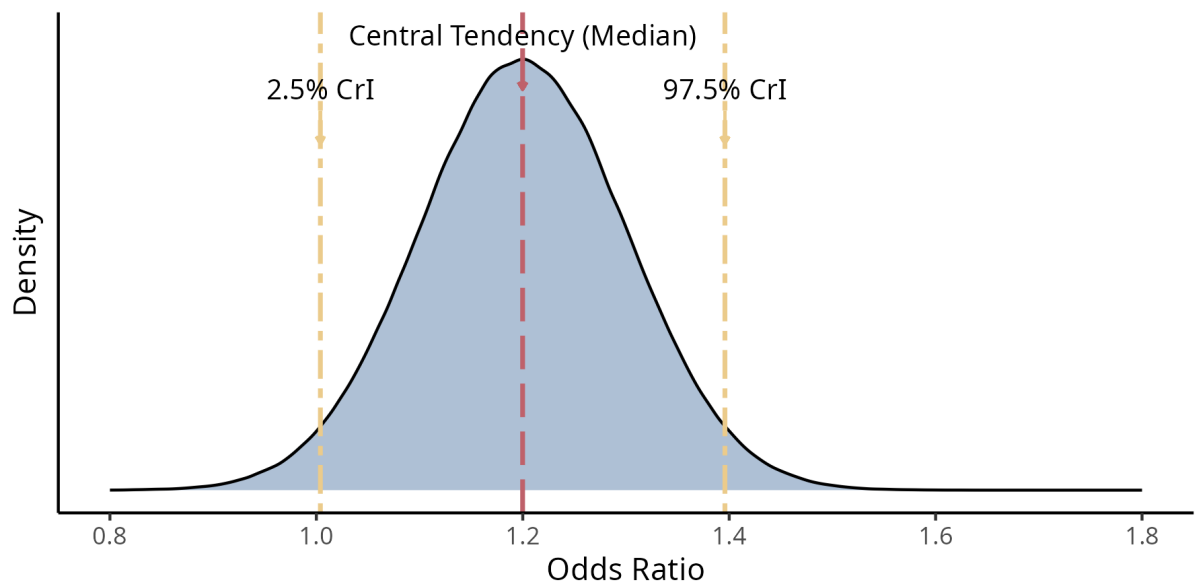


Figure 2.3: Posterior distribution showing central tendency with 95% credible intervals.
Reproduced with permission from Taylor et al. 2025.

2.3.1.3 Credible Intervals

Kruschke, Ferreira, and Zampieri all recommend that as well as a central tendency, results of a Bayesian analysis should also include measures of a credible interval (Ferreira et al. 2020a; Zampieri et al. 2021; Kruschke 2021). Similar to the central tendency, the specific method used to describe credible intervals will depend on the form of the posterior distribution. Readers of a paper may see reference to techniques such as the “*highest density interval*” or “*equal tailed intervals*” (Kruschke 2021).

Clinicians may be familiar with reviewing confidence intervals in a frequentist analysis and consider a 95% confidence interval to represent the range of values where we can be 95% confident that the “true” value sits. Unfortunately this is a misinterpretation of a 95% confidence interval, and is closer to describing a 95% credible interval. A 95% credible interval describes the spread of the posterior distribution between two values, a lower and upper limit. We can say the true value of our outcome variable sits within this upper and lower limit, with a 95% probability of being correct. In contrast a confidence interval means something arguably less intuitive. A 95% confidence interval also describes a range of values with a lower and upper limit. However, here “95” means that if we were to repeat our experiment infinitely, 95% of the produced confidence intervals would contain the true value of our outcome variable (Ferreira et al. 2020b). At this point, a potential advantage of Bayesian analysis becomes apparent; if credible intervals are closer to what we intuitively think of when using confidence intervals, we might as well use an analysis that provides a credible interval.

2.3.1.4 Probability of Effect

In critiquing a Bayesian piece of clinical research, our outcome variable will depend on the clinical trial, similar to frequentist clinical trials. Some example forms of the outcome variable include: estimates of the odds ratio or log odds ratio for an intervention, the absolute risk reduction, or relative risk reduction (Zampieri et al. 2021; Yarnell et al. 2021). Using measures of odds ratio or risk reduction, our results would report whether an intervention or risk factor is associated with an effect on the outcome of interest.

In classical frequentist trial interpretation, we start to come up against problems of “statistical” versus “clinical significance”. In this dichotomy we see the potential scenario where an intervention has a measurable effect (is “statistically significant”), whilst the effect is not of enough magnitude to be relevant in a clinical context (“clinically significant”). Whilst the term “statistically significant” is not directly applicable to Bayesian research, there is a comparable set of concepts that may be reported in a Bayesian paper. In a Bayesian clinical paper we can expect to see results sections that report the presence of an effect regardless of magnitude, and also report the probability of an effect size large enough to be relevant to clinical practice.

2.3.1.5 Probability of Any Effect: Probability of Direction

One measure for effect regardless of size is the *Probability of Direction* (PD).

In an example clinical trial, where the outcome measure is the probability of cure from illness, we might plot a probability distribution of our estimated Odds Ratio (OR), where an OR of less than one indicates a decreased odds of cure, and an OR of greater than one indicates an increased odds of cure. In this context, the PD would summarise how much of the bulk of the probability distribution sits either side of one, and so can be inferred as summarising the probability of a treatment effect existing in a certain direction (helpful or harmful). Ranging in values between 0 and 100%, in the context of our example trial a PD of 95% can be interpreted as a 95% probability of the odds being greater than one, and there being positive treatment effect, where a PD of 5% would mean a 95% probability of the odds being less than one, and treatment having a harmful effect. A PD of 50% would mean there is no certainty in the treatment having a positive or negative treatment effect. Similar to a frequentist p-value, the PD does not provide any estimate on treatment effect

size (Makowski et al. 2019b,a). The PD can though provide useful information about the probability of the presence or absence of a treatment effect. Routinely however, clinical researchers and those reviewing their papers would wish to know about the probability of an effect size large enough to be clinically meaningful.

2.3.1.6 Probability of “Clinically Significant” Effect

One of the measures used to estimate the probability of a clinically significant effect size, in fact looks for the opposite of this. *ROPE (Region of Practical Equivalence)*, describes the probability that an intervention’s effect size is below a predetermined threshold of clinical significance. As clinical significance is context dependent, most guidance expects the authors to provide not just the measure of ROPE, but also the thresholds used for clinical significance, and justification for these (Ferreira et al. 2020a; Zampieri et al. 2021; Kruschke 2021). It is not common for the PD to be recommended as output in a Bayesian clinical paper, but most guidance do recommend including the measures of ROPE (Kruschke 2021; Zampieri et al. 2021).

ROPE is not the only measure for clinically (in)significant results. Another example used by Yarnell and colleagues, reported the probability that an outcome’s effect size was greater than a predetermined “*minimum clinically important difference*” (*MCID*). In doing so they are in effect reporting an “one-directional inverse ROPE”, although they do not describe it as such. In their article, Yarnell et al. 2021 took the convention of reporting an intervention with >50% probability of having an effect size greater than the MCID, as being of “potential benefit” (Yarnell et al. 2021).

A threshold of MCID set at “more probable than not”, is certainly a necessary bar to cross, however in certain contexts it may not be sufficient to recommend treatment with this level of certainty. Yarnell recognises this and suggests that for certain treatments a higher threshold of certainty may be required (Yarnell et al. 2021). Other authors expand on this, highlighting in certain circumstances you may wish not only to report a variety of thresholds of confidence in reaching MCID, but also the probability of a treatment being associated with a larger effect size. In their recommendations for Bayesian analysis of clinical trials, Zampieri et al. 2021 recommend reporting the probability that a treatment is associated with “outstanding benefit”, and “severe harm”, as well as the above measures of MCID or any effect (Zampieri et al. 2021).

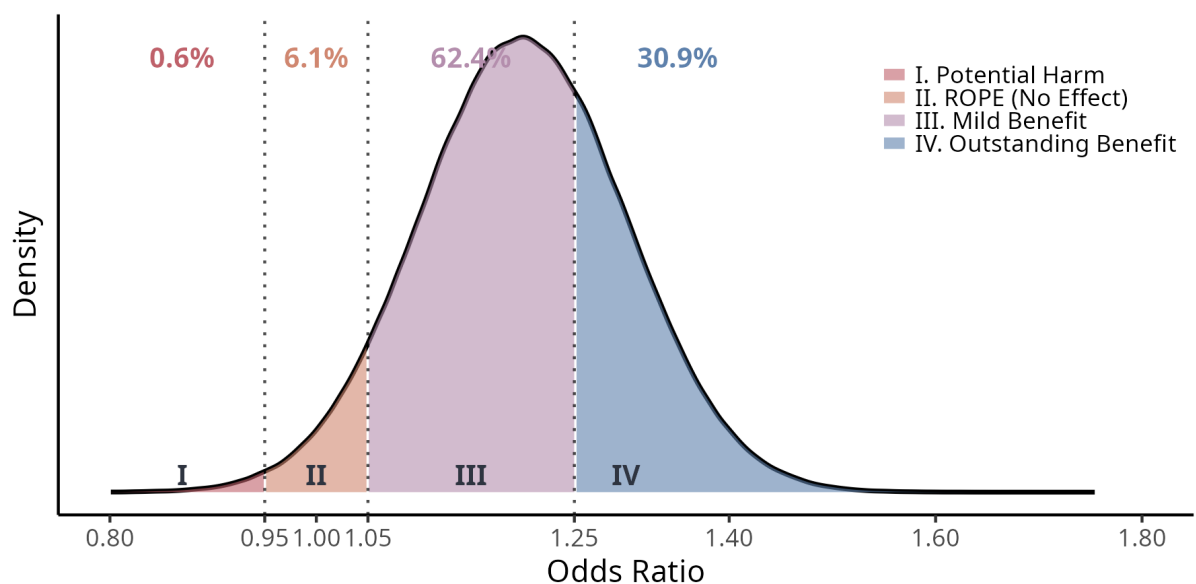


Figure 2.4: Posterior distribution split at regions for harm (I), ROPE (II), mild benefit (III), and outstanding benefit (IV)

Figure 2.4 uses some illustrative thresholds for ROPE and clinically significant benefit when reporting the posterior estimate of Odds Ratio for treatment. In this example the percentage change of clinically significant benefit would be the sum of “Mild” and “Outstanding Benefit” (Zampieri et al. 2021).

The methods described above have an element of subjectivity, different groups of people will have their own opinion of what is a meaningful effect size, and what is a good enough chance of that effect size existing. Kruschke emphasises the importance of both recording and justifying any such “decision thresholds”. He also raises the argument that our desire to declare an intervention to be significant or not could simply be a form of “compliance with ritual”, and that an alternative approach would be for authors to simply summarise the posterior distribution and leave the results at that (Kruschke 2021). However whilst there may be an ideological purity to this suggestion, it is self evident this would not make the task of interpreting research practical for day-to-day clinical work. Zampieri et al. 2021 take a different approach, recommending that predetermined setting of MCID and other metrics allows for less potential bias, increased transparency, and increased repeatability (Zampieri et al. 2021). Additionally, that a Bayesian analysis can report multiple probabilities of different effect sizes, without falling foul of the risks of repeated analysis, is an advantage in comparison to frequentist analysis, as noted in section 2.3.3.2.

2.3.1.7 Comparing Likelihoods: Null Hypothesis Significance Testing

The methods of summarising the posterior distribution described so far, attempt to report the probability of any effect size as well as the magnitude of an effect size. In frequentist reporting of clinical trials, the question of any effect size is usually approached with *Null Hypothesis Significance Testing (NHST)*.

In this paradigm of frequentist NHST, trial data is assessed at how likely it would be to occur, if the null hypothesis (of no treatment effect) was correct. If the data would be considered extremely unlikely to occur when the null hypothesis was true, occurring less than 5% of the time in such a scenario, the null hypothesis is rejected.

This technique is not testing the probability that the alternative hypothesis is true, nor is it testing the probability that the null hypothesis is correct or incorrect, instead it is looking at how likely it would be to see the observed data if the null hypothesis was true (Sidebotham and Barlow 2022).

Phrased in that way we see our classical approach to clinical trials focuses on a conditional probability, that of seeing the observed data if a particular hypothesis is true. We have seen a version of this conditional probability in Bayes' theorem. There we referred to it as the *likelihood* ($P(B | A)$). NHST is investigating the likelihood of data under the null hypothesis: $P(B | A_{null})$

In Bayesian analysis a different approach can be used, where the likelihood of data occurring given the null hypothesis being true, can be compared to the likelihood of data occurring given the alternative hypothesis being true. This comparison does not need to be between the null and alternative hypotheses, it could also be between two different forms of the alternative hypothesis. This ratio of the likelihoods of two hypotheses is known as the *Bayes Factor (BF)*:

$$\text{Bayes Factor} = \frac{P(B | A_{alt})}{P(B | A_{null})}$$

Similar to NHST, the BF does not describe the probability that the alternative hypothesis is correct, it simply describes how much more likely you are to see the observed data under one hypothesis when compared to another. There is some general consensus as to what is considered a “good” Bayes Factor, arising from the suggested values from Jeffreys, as noted in the table below adapted from Jamil et al. 2016:

Table 2.1: Bayes Factor Interpretation Guidelines adapted from Jamil et al. 2016

Number	Strength
< 0.001	Extreme evidence to support A_{null} over A_{alt}
0.03 - 0.001	Very strong evidence
0.1 - 0.03	Strong Evidence
0.3 - 0.1	Moderate Evidence
1 - 0.3	Anecdotal Evidence
1	No evidence
1-3	Anecdotal Evidence To Support A_{alt} over A_{null}
3-10	Moderate Evidence
10-30	Strong Evidence
30-100	Very strong evidence
> 100	Extreme evidence

As a ratio of one likelihood over another, if Bayes Factor becomes smaller than 1, the data is more likely to be seen in the numerator hypothesis rather than the denominator. A BF of 0.01 is as strong as a BF of 100, just for the other hypothesis (the null hypothesis in our example above) (Kruschke 2014) .

As a Bayesian analysis allows you to directly report the probability that your hypothesis of interest is correct, it is less common to see a Bayes Factor reported in the results of a Bayesian clinical trial. As such the consensus pieces of guidance do not include it in their recommended output for Bayesian research trials. However the BF may still appear in a journal club setting, and has been used in a critical care context, one example being in estimating the prevalence of “false positive” and “false negative” critical care clinical trials (Sidebotham and Barlow 2022). Another key use for Bayes Factors is in the role of null hypothesis significance testing when analysing contingency tables, as a replacement for chi-squared tests (Srimaneekarn et al. 2023; Jamil et al. 2016)

2.3.2 Methods: Priors and Model

In Section 2.2.4 we noted that the choice of prior probability distributions can impact on the results of a piece of research. It is therefore unsurprising that every piece of guidance on interpreting Bayesian clinical trials recommends that the priors used should be reported (Kruschke 2021; Ferreira et al. 2020a; Zampieri et al. 2021). Not only should these priors be reported, they should also be “explained and justified”. Similarly the inclusion of any previous work to set such a prior should be justified (Ferreira et al. 2020a). Ferreira expands on potential sources for the prior distribution in another article, listing: “meta-analysis, previous studies, expert opinion, or biophysical theory”. They do note that expert opinion could be controversial, as it clearly introduces a more subjective element (Ferreira et al. 2020b). As well as justifying the prior, Schoot et al. 2021 recommend we should describe our prior in terms of certainty: “informative” versus “weakly informative” (Schoot et al. 2021).

2.3.2.1 Sensitivity Analysis (Justification of Results)

As priors can influence results, consensus guidance is that Bayesian clinical research should report a *sensitivity analysis* of priors, a process that demonstrates how different choices in prior selection could generate differences in estimated results (Kruschke 2021; Ferreira et al. 2020a; Zampieri et al. 2021). Due to the large number of choices being made when selecting priors, the process of sensitivity analysis using different priors is considered both “crucial” and “controversial” (Kruschke 2021).

To summarise the guidance available, recommendations tend to state that a sensitivity analysis should include some or all of the following distributions: informative, uninformative, optimistic, pessimistic, and sceptical. If an informative prior is used for primary analysis, this should also be compared to other plausible informative prior distributions (Kruschke 2021; Ferreira et al. 2020a; Zampieri et al. 2021).

A sensitivity analysis can be reported graphically, showing how the scale and location of an estimated posterior distribution changes with each choice of prior distribution. Kruschke recommends superimposing these posterior distributions in the same plot to allow for visual comparison (Kruschke 2021).

The sensitivity analysis can also be reported numerically, with summary statistics for these multiple forms of the posterior distribution, as well as summarising the prior distribution they are generated from (Kruschke 2021). Zampieri also recommend including the average differences in these measures of central tendency between distributions (Zampieri et al. 2021).

There is no universal consensus on what the sensitivity analysis should show or how it is performed. Most authors tend to recommend simply that the analysis is performed and results reported, leaving the interpretation of the analysis up to the reader (Kruschke 2021; Ferreira et al. 2020a; Zampieri et al. 2021). However some recommendations are made to help with this interpretation. Kruschke notes that an analysis that uses uninformative priors, should show that another choice of uninformative priors would result in close to the same posterior distribution, to demonstrate that enough information for the results is being provided by the trial data (Kruschke 2021). He also highlights that if an approach uses “default priors”, something recommended

by Zampieri (Kruschke 2021; Zampieri et al. 2021), the methods need to demonstrate that such a default doesn't include impossible values (e.g. allowing a person to have a negative height or one greater than biologically possible) (Kruschke 2021; Zampieri et al. 2021).

The use of “default priors” that follow a set structure has been recommended by Zampieri along with guidance for situations where levels of prior information are Weak, Moderate, or Strong (Zampieri et al. 2021). In the case of moderate information, they describe setting an optimistic prior centred on an optimistic result, but allowing for at least a 15% probability of harm, a pessimistic prior allowing for a 15% probability of benefit, and a neutral prior centred on no effect, where 95% of probability sits within an OR of 0.5 to 2 (Zampieri et al. 2021).

Ferreira also notes that the larger the amount of data collected by a trial, the less the prior influences the results, and so the less we have to be concerned about the choice in prior. Taking this idea further, they suggest that we could interpret a trial where changing prior distribution changes our estimated results, as an inconclusive trial (Ferreira et al. 2020a).

2.3.2.2 Model Validity

When reviewing a Bayesian research trial, the reader should find the paper has explained: the choices made for the prior distributions, the estimates of the posterior distribution, and how different choices of the prior distribution affect the results of the analysis. The next component a research paper could provide, is a demonstration that their predictive model itself “works”. By this we mean the paper documents both that the mechanics of the model itself worked, as well as demonstrating that the results of any predictive model are accurate.

To demonstrate that the model's mechanics worked, first guidance states that the model used needs to be specified. This includes stating the software used, as well as the family of statistical model, and the settings of the algorithm itself (Ferreira et al. 2020a; Kruschke 2021). As a reader of a trial, Kruschke puts we should expect the authors to report their model ran in a way that suggests it is "representative, accurate, and efficient" (Kruschke 2014). In generating a posterior distribution, researchers run their statistical model multiple times, each time being referred to as a "*chain*". Analysis should report that all chains are in agreement as to what they believe the true posterior distribution to be. This agreement between chains is termed "*convergence*". One measure of convergence that should be reported is the $\hat{R}$ (*R-hat*) (also called the *Gelman-Rubin statistic* or *shrink factor*). A reader should expect to find authors report adequate convergence by stating that $\hat{R}$ has reduced to close to 1.

Not only should these chains agree with one another (converge), they should also be accurate, in that new information wouldn't change their estimate of the true posterior distribution. As such, a measure to show that the model contains enough information should also be reported. This measure of information is known as the *effective sample size (ESS)* or *autocorrelation factor*. In general an ESS of 10,000+ would demonstrate a model has taken enough samples of the posterior distribution to be accurate (Kruschke 2014).

To improve reproducibility of results, there are other measures authors should include, in regard to settings used in analysis (Kruschke 2014). These include reporting the amount of chains used in model creation, and the amount of "steps discarded" or "burn in phase" (Ferreira et al. 2020a; Kruschke 2021).

2.3.2.3 Model Predictive Accuracy

Lastly when assessing the relevance of a model created, Kruschke and Ferreira recommend showing some measure of model “goodness of fit”. Similarly to predictive models generated using non Bayesian techniques, such a measure means to show that any predictions generated by a model, are found to be correct when tested (Kruschke 2021; Ferreira et al. 2020b). These measures can be performed visually with plots of model predictions using “Posterior Predictive Checks”, or through measures seen in other classification problems, such as the receiver-operator curve (ROC).

2.3.3 Discussion: Comparison To Frequentist Papers

The last key aspect recommended in both Kruschke’s and Ferreira’s checklists is that authors should explain why they have chosen to use Bayesian techniques for their analysis (Kruschke 2021; Ferreira et al. 2020a) .

Accepting there are costs when shifting from one technique (frequentist clinical research) to another, authors should be able to justify why this switch is worth undertaking, either through demonstrating advantages of a less common approach, or disadvantages of current techniques. In this next section I aim to provide additional justification of my Bayesian research thesis, highlighting the positive aspects of such a switch.

In brief, I have chosen to take a Bayesian approach for this thesis as doing so:

- Allows us to use models to directly answer our questions of interest, in a manner that is intuitive to a reader

- Provides additional results that frequentist methods lack, allowing us to estimate a variety of effect sizes and the probability of each effect size occurring
- Allows us to reanalyse each question of interest from a variety of starting assumptions
- Forces us to consider carefully each assumption made during in model generation

2.3.3.1 Advantage 1. The probability of the hypothesis being tested versus NHST

As noted already in this chapter (Section 2.3.1) one of the key advantages of a Bayesian approach is that it allows you to directly answer your research question.

In a clinical trial an intuitive form of our question of interest could be: “how likely is it that treatment X affects condition Y?”, or “what is the most likely size of the effect of treatment X on condition Y?”

As highlighted above in Section 2.3.1.7, summarising the probability distribution allows us to directly answer our research questions, in a way that frequentist use of NHST does not. Admittedly, this Bayesian approach does lack some components that clinicians often find useful when interpreting clinical results. Namely the convention of using a p-value of ≤ 0.05 to indicate a significant result. However as explained in Section 2.3.1.7, the p-value comments on the conditional probability of seeing data under a null hypothesis, it is not a comment on the probability of a hypothesis being true or false, and so does not directly answer the question of interest. (Zampieri et al. 2021; Ferreira et al. 2020b).

The critique of current use of p-values in NHST comes from a greater range of opinions than simply those promoting Bayesian alternatives. The American Statistical Association (ASA) noted in a position statement in 2016:

“Scientific conclusions and business or policy decisions should not be based only on whether a p-value passes a specific threshold... The widespread use of ‘statistical significance’ (generally interpreted as ‘ $p \leq 0.05$ ’) as a license for making a claim of a scientific finding (or implied truth) leads to considerable distortion of the scientific process” (Wasserstein and Lazar 2016).

Given the comments of the ASA, our comparison here of Bayesian approaches to NHST could be seen as a straw man argument, where the Bayesian approaches were given the benefit of doubt, with assumptions that they were being performed well, and frequentist approaches were misleadingly framed as being performed more poorly. However as noted by the ASA, the above description of the use of p-values and statistical significance is a “widespread” practice rather than a misinterpretation of how research is performed and reported.

As a smaller point on answering the question of interest, again as noted in 2.3.1.3 , use of credible intervals allows us to state the probability of the true value sitting within a range, where confidence intervals do not. However whilst some may see this as a clear advantage, for others this may be closer to quibbling over semantics.

2.3.3.2 Advantage 2. Estimating Effect sizes

A clearer advantage of a Bayesian piece of research, is seen in its ability to estimate the probability of a variety of effect sizes.

Where a classical frequentist trial could comment on whether it observed a difference between treatment and control, powered to a certain effect size, Bayesian analysis allows us to estimate this size itself. As explained above in Section 2.3.1.6, a Bayesian analysis allows us to estimate the probability of a meaningful clinical effect, as well as the probability of dramatic benefit, or the probability of associated harm (Yarnell et al. 2021). This approach would not be possible with a classical frequentist analysis. A frequentist analysis could determine some form of MCID, ensuring a 95% confidence interval does not cross the threshold of MCID. However directly attributing a probability to a certain effect size, and varying this multiple times in the same analysis, is something possible in Bayesian analysis but not routine frequentist (Yarnell et al. 2021).

2.3.3.3 Advantage 3. Looking From Different Perspectives: What would the pessimist need to be convinced?

A range of priors should be interrogated in the sensitivity analysis of Bayesian research: taking the spectrum from our “best guess” to uninformative, and from optimistic assumptions about possible treatment effects to pessimistic.

Whilst one prior distribution should be selected as the most appropriate, use of a range of priors allows different thresholds of evidence to be evaluated in different contexts. In cases where teams have reason to believe a proposed treatment is less likely to be effective for their patient population, applying a pessimistic prior could be useful, as if it still demonstrates a benefit to treatment, the treating team may be willing to commence a treatment they would otherwise be cynical of.

While it may be appropriate to consider different thresholds of evidence/certainty for different patient groups, ultimately these differences should be interrogated through further research. Without this there is a risk that applying different thresholds could result in problems of equitable access to therapies, or discrimination against protected characteristics.

On an individual patient level, there may be a role for using different prior distributions, and different decision thresholds, when undertaking shared decision making and in gaining adequately informed consent. Individualising these may allow decisions to be framed in keeping with a patient's own values and belief systems.

2.3.3.4 Advantage 4. Quantifying Our Assumptions

In a Bayesian analysis authors are expected to clearly document and justify their use of prior distributions. In doing so they are acknowledging the assumptions made in an analysis. Assumptions are not unique to Bayesian research, Zampieri highlight that a standard frequentist trial involves assumptions of: incidence of the condition of interest, size of treatment effect that a trial should detect, the acceptable probability of falsely rejecting a true null hypothesis, and the acceptable probability of failing to reject a false null hypothesis (Yarnell et al. 2021; Kruschke 2021; Zampieri et al. 2021). However, with the relative novelty of Bayesian research comes a greater degree of skepticism and requirement to justify assumptions. This enhanced oversight can be seen as an advantage. It forces the authors of a piece of research to confront and interrogate their assumptions. In doing so we can hope they will make reasoned and justifiable decisions.

2.3.3.5 Disadvantage 1. The Computational Burden

Of the disadvantages listed below, this first one is perhaps the least relevant to the reader of a paper, although it is one of the larger burdens when generating Bayesian analyses (Winter et al. 2023).

Bayesian techniques can be costly in both time and computational burden when compared to more classical approaches (Martina Perez et al. 2022; Kruschke 2021). This computational burden comes from the sampling from the posterior distribution, through MCMC (Markov Chain Monte Carlo) (McElreath 2020). As the sample size of data increases, sampling from the posterior distribution becomes more burdensome (Winter et al. 2023). Traditionally, this time burden precluded the use of MCMC, however advances from 2000 onwards, most recently with Stan (a probabilistic programming language), implemented new algorithms to allow the use of MCMC in a practical way (Bürkner 2017a).

2.3.3.6 Disadvantage 2. When You Lack Prior Information

When attempting a Bayesian analysis, a key aspect is the use of priors in combination with trial data. The use of prior information can be criticised if done improperly. Similarly, if a major aspect of Bayes is to use previously gained information, then a Bayesian approach may seem less relevant when no prior information is available.

However a Bayesian trial does not require information gained from previous clinical trials, and as noted by Zampieri, as long as we can be reasonably confident that we can exclude extreme effect sizes, a sensible starting point may be a moderate neutral prior (Zampieri et al. 2021). We will see in Section 2.3.3.8, that historically it appears that trial investigators have over estimated effect sizes rather than under, and excluding extreme effect sizes in most cases is likely to be a safe technique.

2.3.3.7 Disadvantage 3. The Lack of Local Expertise

On a practical note, as well as the computational cost of a Bayesian approach, there can also be an institutional cost or burden of difficulty. When one approach (frequentist clinical research) is default, use of a different method with comparable results can be seen as wasted energy. One piece comparing Bayesian and frequentist work refers to this as the “inherent conservatism among clinicians concerning statistics” (Skrepnek 2007). This comment could be expanded into “*understandable* inherent conservatism”. If those undertaking clinical research have many competing aspects to their work, the effort involved in switching away from a technique you know works may make little sense when considering your other priorities. Additionally for those who want to take on a different approach, a lack of colleagues comfortable with these techniques can increase the risk of errors in either interpreting or performing Bayesian research. Having a group of practitioners able to interrogate methods sections increases the chance of errors being found, and correspondingly, having fewer interpreters comfortable doing so increases the chance of errors getting through.

2.3.3.8 Disadvantage 4. The Subjective Nature

In most descriptions of Bayesian analysis, the ability to take prior knowledge into account would be framed as a clear advantage. However for many clinicians, this aspect may be seen as an additional level of complexity, and an opportunity for subjectivity to be introduced, skewing results away from the truth. Zampieri's recommendations aim to provide reassurance with their proposed approach, where they standardise the choice of priors for all analyses, with only the limits of the ROPE left to the individual study (Zampieri et al. 2021). They argue that this approach could "promote transparency and increase the rigor and reproducibility of results" (Zampieri et al. 2021).

2.3.3.9 Head To Head Comparison

A common critique of Bayesian approaches in medicine, is seen when an initially frequentist trial is reanalysed with Bayesian techniques. The perception among readers can be that the authors did not get the results they wanted, so they tried again with a Bayesian method to get a second shot at a "positive trial".

Yarnell et al. 2021 investigated this; their team reviewed all multicentre trials published between 2008 and 2018 in five relevant journals, where the primary outcome was mortality in a group of critically ill patients. Identifying 82 papers, they re-performed the analysis of each with predetermined Bayesian techniques (Yarnell et al. 2021). They aimed to identify the level of disagreement between frequentist and Bayesian techniques, and any factors that increased risk of disagreement.

The key scenarios where the two approaches could disagree in their results were when:

- Frequentist reported “positive” but Bayesian analysis found probability of MCID (Minimum Clinically Important Difference) $< 50\%$
- Frequentist reported “negative” but Bayesian analysis found probability of MCID $> 50\%$

In the first scenario, this could be seen where a Bayesian trial found the PD tended to the positive, but that the most likely values of effect size sat within the ROPE. In the second scenario, if a frequentist trial had been powered to detect a large absolute risk reduction (ARR) and failed to detect it, it may report a negative result. However the same frequentist trial would be “underpowered” to correctly identify a smaller ARR, one still larger than the MCID. The Bayesian reanalysis would be able to identify if there was a greater than 50% chance of this smaller but meaningful treatment effect size (Yarnell et al. 2021).

When looking at this second scenario of “negative frequentist positive Bayesian”, another explanation that critics of a Bayesian approach could raise, is that the prior distribution selected could be so biased in favour of an effect existing, it outweighs truly “negative” data. To prevent bias from optimistic priors, Yarnell’s key comparison to frequentist analyses used a sceptical prior, where the most likely effect on Absolute Risk Reduction was set at 0 (Yarnell et al. 2021). They also performed their analysis with predetermined sceptical, uninformative, and enthusiastic priors (Yarnell et al. 2021). Although they did not take the approach later recommended by Zampieri to also include a pessimistic prior (Zampieri et al. 2021). The MCID was generated for each paper through surveying a group of critical care clinicians and taking the median of their responses. This approach produced values similar to published consensus values (Yarnell et al. 2021).

As seen in Table 2.2; Yarnell found that Bayesian reinterpretation using sceptical priors, agreed with the original frequentist interpretation in 73 out of 82 papers (89%) (Yarnell et al. 2021). To focus on where these approaches diverged: 7 (9%) of the 78 trials found to be negative under frequentist analysis had a greater than 50% probability of meeting the threshold of MCID, 2 of the 4 trials found to be positive under frequentist analysis had a less than 50% probability of meeting the threshold of MCID.

Table 2.2: Results of Yarnell's Comparison of Bayesian And Frequentist RCTs

	Bayes Positive	Bayes Negative	Total
Frequentist Positive	2	2	4
Frequentist Negative	7	71	78
Total	9	73	82

Notably however when an “enthusiastic” (optimistic) prior was used, the rate of disagreement rose substantially, with 20/78 (26%) papers being subsequently reinterpreted as “positive” by a Bayesian analysis (Yarnell et al. 2021).

To explain the difference seen between the Bayesian reinterpretation and the original papers, Yarnell and colleagues found their estimates of MCID tended to be lower than what the original authors had powered their papers for (Yarnell et al. 2021). This implies either that original trial authors are more optimistic about the potential benefit of proposed treatments (a plausible bias, considering authors are a group of people motivated enough to perform a trial on the subject), or that original authors may be setting their estimates of effect size “pragmatically” large, to allow for a smaller sample size when recruiting.

As an example paper where Bayesian reinterpretation suggested the possibility of benefit after negative frequentist analysis; Yarnell estimated a 10% ARR in the 2018 paper “Extracorporeal Membrane Oxygenation [ECMO] for Severe Acute Respiratory Distress Syndrome” by Combes et al. 2018. With a predetermined MCID set at 5.5%, Yarnell estimated a 77% probability that the true effect size of ECMO was greater

than this MCID (Yarnell et al. 2021). In the original analysis Combes and colleagues had powered their trial to detect a 20% Absolute Risk Reduction (predicting 40% mortality in treatment group, 60% in control (Combes et al. 2018). However Yarnell's 95% credible intervals ranged from -2% to 22%, not only allowing for the possibility of no clinically important effect, but also allowing for the possibility of harm from treatment. They used the posterior distribution to estimate this possibility of harm ($ARR < 0$) at 5% (Yarnell et al. 2021).

In their reanalysis Yarnell strongly emphasises that their work should only be used as hypothesis generating and not to recommend treatments. Their paper shows both the advantages and potential problems from Bayesian reanalysis. Where the original paper could only report a failure to demonstrate their predetermined estimated effect size, the Bayesian reanalysis could provide results that show: best estimate of effect size, probability of clinically meaningful benefit, as well as probability of harm. It shows where a frequentist trial of treatment may fail due to overly large estimates of effect size. It also demonstrates that some of the concerns about Bayesian reanalysis have merit; optimistic priors resulted in much more discordance (26%) between frequentist and Bayesian interpretations of the same information.

This study by Yarnell confirms that advocates of sensitivity analyses and decent sample sizes are correct to do so. As sample sizes increased in their review, differences between posterior distributions from optimistic and sceptical priors decreased, showing more resilient results. The authors here referred to trials which "failed" this form of sensitivity analysis as not managing to "accrue sufficient information to resolve uncertainty about treatment effect". Additionally, where some may criticise the use of a 50% threshold to mean possible benefit, this paper demonstrates another advantage of Bayesian analysis, as the same analysis can be re-performed with different thresholds for certainty or magnitude of MCID (Yarnell et al. 2021).

2.4 Step Three - Thesis Workflow

In this section, I describe the workflow I use for most chapters in this thesis, building from the recommendations from authors cited in the sections above. Each question of interest followed the same analysis framework.

2.4.1 Descriptive Statistics, Identification of Differences - Null Hypothesis Significance Testing

Beginning with describing the dataset, each variable of interest is described in Chapter 4, the relevant results chapter, or in both. Continuous variables are reported with median, and interquartile range. Categorical or logical variables are reported with counts and percentages.

When describing groups, and assessing unadjusted differences between them, I use Bayesian Contingency Table Analysis (analogous to Chi-Squared test) and ANOVA to provide Bayes Factors (BF) (See Section 2.3.1.7 for further detail on BF, and Table 2.1 for interpretation guidelines).

I chose to use BF rather than more routinely reported frequentist methods for a few key reasons. As noted above in this chapter, Bayes Factors allow us to ask: ‘How more likely is it than not, that there is a difference between these groups, considering we observed this data?’, rather than the classical frequentist NHST: ‘Assuming the null hypothesis is true, how likely would it be that we observe this data?’. Considering that our question of interest is ‘How likely is it that there is a difference between

these groups?', use of a BF provides a simple answer close to our question of interest. Additionally use of a BF allows for a granular level of interpretation, where tools such as Table 2.1 allow us to assess how more likely our hypothesis of a difference between groups is, when compared to the null hypothesis.

2.4.2 Modelling - Variable Selection

To understand the association between survival of critical illness and each question of interest in this thesis, a series of multivariable models will be generated to adjust for other differences between each subcohort of patients. An important choice here, is to decide which variables are included in each multivariable model. In this thesis initially I have taken one approach based on the following rationale:

- The approach should be recognised as one valid approach amongst many in the medical literature
- The approach should be widely used in clinical research papers
- The approach should use a relatively 'objective' threshold for variable inclusion in final model

This method used for variable inclusion is 'univariable screening'. A series of single variable analyses are performed against the question of interest. Inclusion into later models was based on the Probability of Direction (See Section 2.3.1.5). A threshold of a Probability of Direction of $\geq 95\%$ was selected as the threshold for inclusion in the final model. A PD of $\geq 95\%$ can be considered equivalent to a p-value of <0.1 , a commonly used threshold in workflows that use univariable screening.

Meeting the PD threshold means that a variable is considered to have an impact on the question of interest, but does not make any comment on the magnitude of such an impact. These univariable models are demonstrated both in graphical and tabular form, to fully demonstrate the estimated posterior distribution.

The criteria and decisions above for variable inclusion were choices that I made in 2022, at the beginning of this thesis process. At the time it appeared that my other choices with Bayesian modelling would ask a lot of a clinical reader who was more accustomed to an alternative approach. As such I aimed to keep other aspects of statistical decision making similar to other published work. As noted towards the end of this thesis, in Chapter 9, at the time of writing (2026) there is a growing acceptance of Bayesian statistical frameworks in medical literature, and work undertaken now would not need to provide such choices to allow for familiarity of the reader. Chapter 8 has been undertaken more recently, and different choices to determine variable inclusion have been made, making use of Directed Acyclic Graphs (DAGs) and causal inference, detailed more in chapter 8 itself.

Several valid criticisms of the use of univariable screening can be made, it can fail to identify the association of variables that are conditional with one another, it can be susceptible to confounding. However, it is a commonly used method frequently seen in the medical literature as ‘valid enough’. As examples, the key paper published to date to describe relationship between severity of illness and likelihood of chemotherapy receipt (Kim et al. 2015) takes this approach. Other work using univariable screening when studying the relationship between intensive care and outcomes for patients with cancer include published work on: identifying factors associated with ICU admission in patients with lung cancer (Puxty et al. 2020), survival of cancer patients requiring mechanical ventilatory support (Azoulay et al. 2001), and work assessing hospital survival of critically ill solid cancer patients (Vincent et al. 2018).

As an example of single variable models, in variables with binomial outcomes, a series of Bayesian Bernoulli models (with uninformative priors) were completed.

Values of each models coefficients would be exponentiated to provide Odds Ratios, then summarised with tables and figures to provide median, 95% credible intervals, and Probability of Direction. Variables meeting the PD threshold of $\geq 95\%$ (analogous to $p < 0.1$) would be selected for further investigation through inclusion in multivariable models.

2.4.3 Multivariable Model - Formula and Default Prior Specification

After relevant variables were determined in single variable models, Multivariable models are developed for the question of interest. Overlapping variables are excluded (e.g. Named Comorbidity versus Comorbidity Counts) and such decisions are made on model brevity. As nature of admission and level of support in hospital were key questions of interest, these variables were included in each multivariable model regardless of single variable analysis results. Nature of Admission To Hospital and Support Received In Hospital were considered to be interacting variables, by this we mean that the association between support in hospital and the question of interest can differ, dependent on the nature of admission to hospital.

Priors for each model are chosen based on the recommendations from Zampieri et al. 2021. As noted in Section 2.3.2.1 this means that for each question of interest I choose to use default priors, rather than more data-driven priors based on estimates from previously published work. I make this choice due to the lack of reliable estimates for most variables of interest.

Multivariable models are developed repeatedly using differing priors (uninformative, sceptical, optimistic, and pessimistic). Zampieri and colleagues recommend that an uninformative / weakly informative prior should have 95% of the probability distribution sit between odds ratio (OR) values of $\frac{1}{2}$ and 2 (i.e. $N(\mu = 0, \sigma = 0.355)$). For a sceptical prior, they recommend that 95% of the probability distribution should sit between OR values of $\frac{1}{1.5}$ and 1.5. For Optimistic, and Pessimistic priors they recommend a distribution centred on the expected OR, that still allows for the opposite to the expected outcome occurring (e.g benefit was expected but harm is observed).

This results in the default values as detailed below:

- **Uninformative** $\sim$ Normal(Mean (μ) = 0, Standard Deviation (σ) = 0.355)
- **Sceptical** $\sim$ Normal($\mu = 0, \sigma = 0.205$)
- **Optimistic** $\sim$ Normal($\mu = 0.15, \sigma = 0.205$)
- **Pessimistic** $\sim$ Normal($\mu = -0.15, \sigma = 0.205$)

2.4.4 Model Specification and Execution

Models are run with 10 Chains, each with 1000 burn-in/warmup steps, and followed by 4000 training/post-warmup steps. The use of multiple chains allowed for assessment of convergence, and the choices of warmup and post-warmup were to allow for adequate sample size.

Each model is repeated four times, once for each of the Uninformative, Sceptical, Pessimistic, and Optimistic priors.

Due to the paucity of previously published work on most of my questions of interest, I choose in this thesis to use Uninformative priors as the default prior. This choice provides some similarity to commonly published frequentist work, in that our testing starts with the assumption of no difference between groups (Mean OR of 0). Additionally, it allows our starting belief of no difference to be held weakly, rather than the other choices of default prior, which more strongly encode belief of ‘No Association’, ‘Positive Association’, or ‘Negative Association’. Results reported from multivariable analysis always used the models trained with Uninformative priors.

2.4.5 Model Results

Estimates from the default model choice are reported both graphically and using tabular information, as recommended by Kruschke 2021; Ferreira et al. 2020a; Zampieri et al. 2021.

Results following multivariable regression included tables showing: Central Tendency (median estimate of impact of variable), 95% Credible Interval, Probability of Direction, probability of effect falling within Region of Practical Equivalence, probability of effect falling within Clinically Meaningful Increase in Odds, probability of effect falling within Clinically Meaningful Decrease in Odds.

Results were reported additionally in figure form, showing the probability distribution for posterior estimates. With the Region of Practical Equivalence shaded, this demonstrates where the bulk of the posterior probability distribution lies.

In all models nature of hospital admission and level of support in hospital are treated as interacting variables. This means that results of these variables of interest are initially output in a manner not immediately interpretable: ‘main effects’ and ‘interaction term’. To aid interpretation I recombine coefficients, in effect presenting each combination of nature of admission and support level as if they were a single composite variable. The advantage of doing this rather than actually combining into a single composite variable, is that it allows us to review the association of each level of support conditional on nature of admission, as well as also assessing the association of an emergency admission to hospital in isolation.

Another assumption is made at this point, in the definition of the Region of Practical Equivalence (ROPE) /Minimum Clinically Important Difference (MCID) This definition will understandably differ for each question of interest. In this thesis I use definitions of MCID where published guidance provides an accepted value. For example in Chapter 7, when investigating the association between critical illness survival and long term survival from CRC, I am able to use the published ESMO Magnitude of Clinical Benefit Scale (Cherny et al. 2025). However in other chapters, such as Chapter 5, no published work identifies an MCID for receipt of Quality Performance Indicators in cancer care. When no estimate for MCID is published, an alternative approach is necessary. In this thesis I choose to take a statistical approach to define Minimum Clinically Important Difference (MCID) where ROPE is set at the range of -0.1 to 0.1 of a standardised parameter, as recommended by Makowski et al. 2019a; Kruschke 2018. So for the QPI example I defined region of practical equivalence (ROPE) as 10% of the standard deviation from the baseline target (Makowski et al. 2019a). This choice suffers from lack of clinician assessment of accuracy, where 10% of standard deviation from target may or may not be ‘clinically meaningful’. However it is an accepted approach when an agreement on what is MCID has not been made, and does not suffer from the problem of differing opinions between different clinicians involved.

2.4.6 Sensitivity Analysis, Validity Checks, Model Accuracy

Following the multivariable model with uninformative priors, sensitivity analyses are performed, allowing interpretation of how differing choice of model priors (Sceptical, Optimistic, Pessimistic) would impact model estimates for each variable.

Figures demonstrate how the distribution for each variable's estimates differs depending on choice of model priors. Tables provide estimates of central tendency on our key variable of interest, and how that estimate differs dependent on choice of model priors.

Each model provides estimates of model convergence ($\hat{R}$) and effective sample size, to ensure model validity. Finally, for each model Posterior Predictive Checks are performed, comparing the actual outcomes of interest (y), against those predicted by our model (y_{rep}), ensuring that the model reflects the dataset accurately.

2.4.7 Model Template

A template followed for each question of interest was:

1. Clean Data
2. Reorder Data observed for differences in proportions between subcohorts
3. Single Model (Univariable, UV) Analysis
4. Specify Multivariable Model Formula
5. Specify Multivariable Model Priors
6. Run Each Multivariable Model
7. Provide Multivariable Model Results
8. Provide Sensitivity Analysis

9. Assess Model Validity

10. Assess Model Accuracy

2.4.8 Statistical Software

All analysis was performed on the EPCC National Safe Haven service, using R version

4.2.0. Key additional packages included:

- targets (1.11.3) (Landau 2021)
- brms (2.22.0) (Bürkner 2017b)
- rstan (2.32.7) (Stan Development Team 2025)
- tidyverse (2.0.0) (Wickham et al. 2019)
- gtsummary (2.3.0) (Sjoberg et al. 2021)
- kableExtra (1.4.0) (Zhu 2024)
- here (1.0.1) (Müller 2020)
- pammttools (0.7.3) (Bender and Scheipl 2018)

2.5 Conclusion

In this chapter I have aimed to provide an introduction to the fundamental aspects of Bayesian inference, as well as the concepts and terminology seen when interpreting a Bayesian research trial. In doing so I aimed to provide the reader with a high level understanding of what a Bayesian analysis is, how a trial should be reported, and what these reported methods and results actually mean.

Ultimately I aimed to show that a Bayesian approach for this thesis, allows for a more direct answer to our common questions of interest, allows us to interrogate our results in ways that frequentist approaches do not, and is a valid alternative to classical frequentist techniques.

Based on recommendations from guidance published on the use of Bayesian statistics in medical literature, I have provided my own approach for data interpretation and analysis used throughout this thesis. In the next chapter I describe the datasets used in this thesis, and the steps I take to prepare them for analysis.

Chapter 3

Methods

3.1 Research Environment

All data used for analysis in this thesis were stored on the Public Health Scotland National Safehaven, managed by PHS Electronic Data Research and Innovation Service (eDRIS), and maintained by the University of Edinburgh Parallel Computing Centre (EPCC).

The creation of a raw dataset was undertaken by Hanna et al. 2021. Their work created a population level dataset of Scottish patients with colorectal cancer, gathering thirty-two healthcare administrative datasets into one Trusted Research Environment (TRE), allowing for others to subsequently undertake their own research. Dr Hanna's work was part of the national Cancer Research UK funded colorectal cancer repository (CORECT-R), aiming to characterise variations in colorectal cancer care across the UK. (Hanna et al. 2021).

3.2 Data Sources - Work Undertaken By Dr Hanna and colleagues

In the initial curation of this dataset, approval was gained by Hanna and colleagues from the national Public Benefit and Privacy Panel for Health and Social Care in Scotland. Data was pseudonymised by the national Community Health Index Indexing and Linkage Service, meaning that no directly identifiable patient information was sent from its original location to eDRIS. Directly identifiable information (patient community health identifiers and other such information) were removed, and datasets were deterministically linked with a new unique subject identifier.

The dataset created by Hanna et al. 2021, was a part of a wider UK colorectal cancer repository. The Scottish Cancer Registry (SMR06) was used for an initial patient index. Dr Hanna requested health care records on all individuals in SMR06 with an ICD-10 diagnosis of C18,19,20 (colorectal cancer), from 1st January 2006 to April 2018. Where individuals identified in this initial search had linked records identified in the other datasets (see Table 3.1 for datasets relevant to this thesis), these records were also requested.

The process of relevant dataset identification, communication with relevant teams, submission to PBPP, approval from PBPP, and eventual dataset release into the research environment took several years. Time from initial contact to first dataset release was two and a half years (Hanna et al. 2021).

A filtered list of the datasets included in the CORECT-R Scotland specification, including only those that I use in this thesis, is provided in Table 3.1. The larger list of datasets included in the CORECT-R research environment also includes; data on outpatient, mental health, and emergency department attendances, as well as data on financial costs of attendances, community prescriptions, and ambulance service calls.

Table 3.1: Datasets from in the CORECT-R Scotland specification, used by this thesis
Adapted from Hanna et al. 2021

NRS Deaths
NRS (2006-2018)
This dataset is collected by National Records Scotland (NRS), which is a Scottish government institution. It contains information on date, cause and place of death for all deaths registered in Scotland since 1974. PHS is granted access to extracts from this dataset for research/linkage purposes.
Inpatients and day cases (SMR01)
PHS (1997-2018)
SMR01 comprises patient level episode data on hospital inpatient and day case discharges from acute specialities in Scotland. Data is available in computerised format from 1968.
Cancer Registry (SMR06)
PHS (2006-2018)
SMR06 is also known as the Scottish Cancer Registry and was established 1954. This dataset collects information relevant to the diagnosis and management of malignant neoplasms, as well as carcinoma in situ and some benign tumours. Data is collected annually. CORECT-R Scotland has requested information on patients with a diagnosis of CRC only. This dataset contains CRC staging information based on both TNM and Duke's staging classifications.
SACT (ChemoCare WoSCAN)
WoS Cancer Network (2006-2018 but reliable data from 2012 onwards)
Regional chemotherapy prescription dataset. ChemoCare is the electronic data system that captures prescription of systemic anticancer agents and supportive medications in hospitals in Scotland. This does not include all hospital prescriptions, and would not, for example, include medications written on a drug prescription chart for patients during an inpatient stay. It would provide information on chemotherapy and supportive medications received by a patient whether they received that treatment as an inpatient or an outpatient.
SACT (ChemoCare SCAN)
SCAN Cancer Network (2012-2018)
Regional chemotherapy prescription dataset (as for WoSCAN).
SACT (ChemoCare Grampian)
Grampian Cancer Network (2006-2018 but reliable data from 2012 onwards)
Regional chemotherapy prescription dataset (as for WoSCAN).
SACT (ChemoCare Tayside)
Tayside Cancer Network (2006-2018 but reliable data from 2012 onwards)
Regional chemotherapy prescription dataset (as for WoSCAN).
Continued on next page

Table 3.1 - continued from previous page

SACT (ChemoCare Highlands)
Highlands Cancer Network (2006-2018 but reliable data from 2012 onwards)
Regional chemotherapy prescription dataset (as for WoSCAN).
Cancer Audit (QPI WoS)
NHS Greater Glasgow and Clyde (2013-2018)
National prospective audit dataset collected and stored regionally on an annual basis (April each year). NHS boards are required to report their activity against QPIs as part of a mandatory national cancer quality programme. Healthcare Improvement Scotland is responsible for the external quality assurance of cancer services against tumour specific QPIs. This dataset contains CRC staging information based on both TNM and Duke's staging classifications. It also includes surgical operation codes and anaesthetic data such as the ASA score.
Cancer Audit (QPI SCAN)
NHS Lothian (2013-2018)
National prospective audit dataset (as for WoS).
Cancer Audit (QPI NoSCAN)
NHS Tayside, NHS Grampian and NHS Highland (2013-2018)
National prospective audit dataset (as for WoS).
SICSAG
Scottish Intensive Care Society Audit Group (2006-2018)
SICSAG is the Scottish Intensive Care Society Audit Group dataset and contains both episode level and daily information provided for each patient.

3.3 Data Linkage and Variable Definitions - Work Undertaken By Myself

3.3.1 Cohort

Hanna et al. 2021 undertook substantial work over several years navigating the process of extracting routinely collected administrative and healthcare datasets, and centralising them within a single research environment. Their initial dataset collated all patients with recorded CRC diagnoses within a set time period in the Scottish Cancer Registry.

As my own question of interest related to a subcohort of patients (requiring hospital admissions), and I used a different statistical software than Dr Hanna and colleagues (R as opposed to Stata), all code used for my own data ‘import, tidying, transformation, visualisation, modelling, and communication’ was written by myself (Wickham 2023). Each dataset had its key patient identifier, the Community Health Index, removed by PHS prior to release into the TRE. PHS have their own processes of CHI seeding (where CHI is returned to health care records using probabilistic linkage methodology) used when they link datasets. (Public Health Scotland 2026). Probabilistic linkage methods are required when linking error prone datasets, however are not immune to errors in linkage (Harron et al. 2017).

My own work did not require any further probabilistic linkage, as it was reliant on the patient identifier values provided by PHS. As such whilst it would not introduce any further such error, it would also not automatically remove such an error. In response to this, at each point of data cleaning and transformation, I undertook data checks and validation. These included the following checks (with examples given):

- Data Completeness - Review for incorrectly included/excluded patients
- Duplicated Data - Checks for same patient occurring multiple times
- Invalid data - Data recorded as logical (true/false) when should be categorical
- Inconsistent data - Surgery recorded months before diagnosis being made
- Extreme Outliers - Hospital duration recorded as several years
- Data Consistency - SMR coding for missing data being misinterpreted as 'true' values

Where possible, errors were corrected. When correction was not possible, data was excluded. Duplicated patients would be filtered to the first occurrence of such a patient. Patients where diagnosis made significantly after surgery were excluded (with exceptions made for when diagnosis made during surgery). Date ranges were reviewed to filter dates which SMR use as code for missing data (1900-01-01, etc). Extreme outliers were excluded for certain variables (extremes between CRC diagnosis and hospital admission, extremes between surgical resection and adjuvant chemotherapy receipt). Where extreme outliers have been excluded is recorded at the relevant points throughout the thesis.

Additional limitations of the use of routinely collected data became apparent during data cleaning and validation, such as the presence of missing data. Whilst data imputation is a recognised approach to missing data (Sterne et al. 2009), the majority of datasets were complete and did not require any imputation. The degree of missing data is described in more detail in Chapter 4. The sole variable with significant missing data (Anatomic Stage - 68% missing), would most likely be Missing Not At Random, considering the work of Di Girolamo et al. 2018 who identified that for patients with CRC, socio-economic factors and age correspond with the levels of missing data on stage (Di Girolamo et al. 2018). Rather than relying on complete case analysis for Anatomic Stage, I chose to exclude Anatomic Stage (as recorded for SMR06) as a variable during modelling within this thesis.

As noted in Table 3.1 the time period for which datasets were available varied. Figure 3.1 demonstrates the availability of each dataset, highlighting periods of overlap and gaps in data collection. As seen in Figure 3.1, whilst the planned cohorts could be identified for all patients from 2006 onwards, data on QPIs was present only for patients following 2013 (when the QPI scheme was established), and chemotherapy prescription data from 2012 onwards. I imported provided files in the format of “csv”, “xls”, and “xlsx” into a single sqlite database, with initial data type validation.

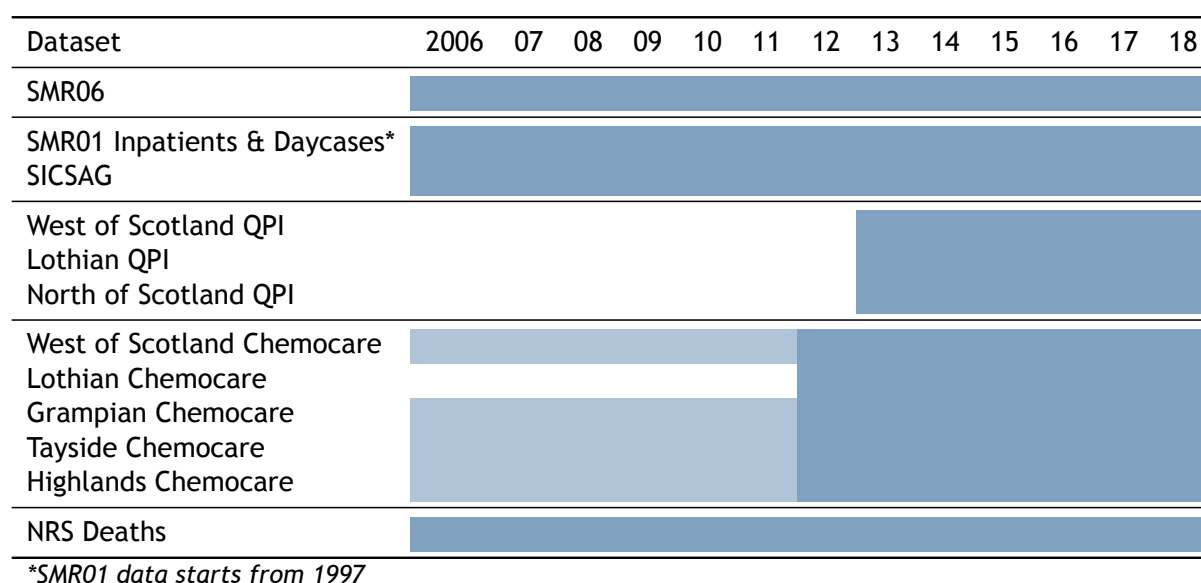


Figure 3.1: Key Dataset Coverage by Year
Dark Blue: Dataset Fully Available Light Blue: Dataset Partially Available

For the purpose of this thesis, data was collated from SMR06, SMR01, National QPIs, SICSAG, NRS deaths, and Chemocare datasets. Patients with an ICD 10 Cancer Site code beginning with C18, C19, or C20 were included, as the initial creation of the dataset by PHS had included all records from the cancer registry. Where patients had multiple records in SMR06, the first recorded incidence date and information for each patient was used. An alternative approach would be to use first diagnosis at a certain stage of illness, allowing the identification of the point of illness more likely to be associated with critical illness and healthcare utilisation. Unfortunately as noted later in Chapter 4, the high levels of missing data for anatomic stage (68% missing) prevents any reliance on SMR06 staging information for total cohort definition. Stratification

by first admission provides additional advantages for several of the later chapters in this thesis, where I investigate post curative surgical resection outcomes for patients with High Risk II and Stage III disease. Selecting index admission following diagnosis includes for the greatest proportion of admissions where curative surgical resection was undertaken, whilst remaining consistent with the rest of the thesis as a whole.

To identify the index hospital admission for each patient with CRC, I used SMR01, filtered to exclude day cases and only include hospital admissions. As SMR01 records each transfer to another location, ward, or specialty as an individual record; each collection of these records required grouping into discrete hospital stays. An index hospital admission was the hospital stay where either: cancer incidence date occurred during admission, or was the first hospital admission that occurred following cancer incidence date, with an upper limit of two years following diagnosis.

To identify patients admitted to critical care, I used data from the Scottish Intensive Care Society Audit Group (SICSAG). SICSAG and SMR01 records were linked using patient index and hospital admission date. Where patients had multiple admissions to critical care during their hospital stay, these were condensed into a single record, where length of stay would be the sum of critical care admissions. If SICSAG hospital admission date did not correspond with SMR01 recorded hospital admission date, but did fall within a window between SMR01 admission to discharge, it was considered as part of that SMR01 admission.

To identify patients with critical illness in critical care, I used the daily recorded information for patients in critical care, detailing the forms of organ support received. Critical illness was considered to be the receipt of Cardiovascular, Respiratory, or Renal Organ Support. Cardiovascular support was the receipt of single or multiple vasoactive medications. Respiratory support was the receipt of noninvasive or invasive ventilation. Renal support was the receipt of renal replacement therapy. As noted

elsewhere in this thesis, most substantially in Chapters 8 and 9, this definition of critical illness expands on previous work, where admission to critical care was considered sufficient. However, experiencing less than 24 hours of organ support may not meet most intensivists' definition of critical illness. In Chapter 8 I provide a greater degree of stratification, separating those who receive less than, and greater than 24 hours of organ support.

To identify hospital survivors, information from NRS Deaths was used. A hospital survivor was considered to be an individual who did not die during their hospital admission, or the 30 days following hospital discharge. The requirement of 30 days post discharge survival was to avoid classifying patients being discharged from hospital when they were not expected to survive as 'survivors' (Flaatten and Reinikainen 2015).

The combination of these sources to create my cohorts of patients, both patients linked to admission and hospital survivors, is demonstrated in Figure 3.2.

3.3.2 Subcohorts

The nature of admission linked to the index admission on SMR01 was used, to identify both the nature of the index hospital admission and the admitting specialty. Index admissions were categorised as "Elective" versus "Emergency" (at points referred to as "Non-Emergency Admission": TRUE vs FALSE) admitting hospital specialty was condensed into "Medical" versus "Surgical" (at points referred to as "Surgical Admission": TRUE vs FALSE).

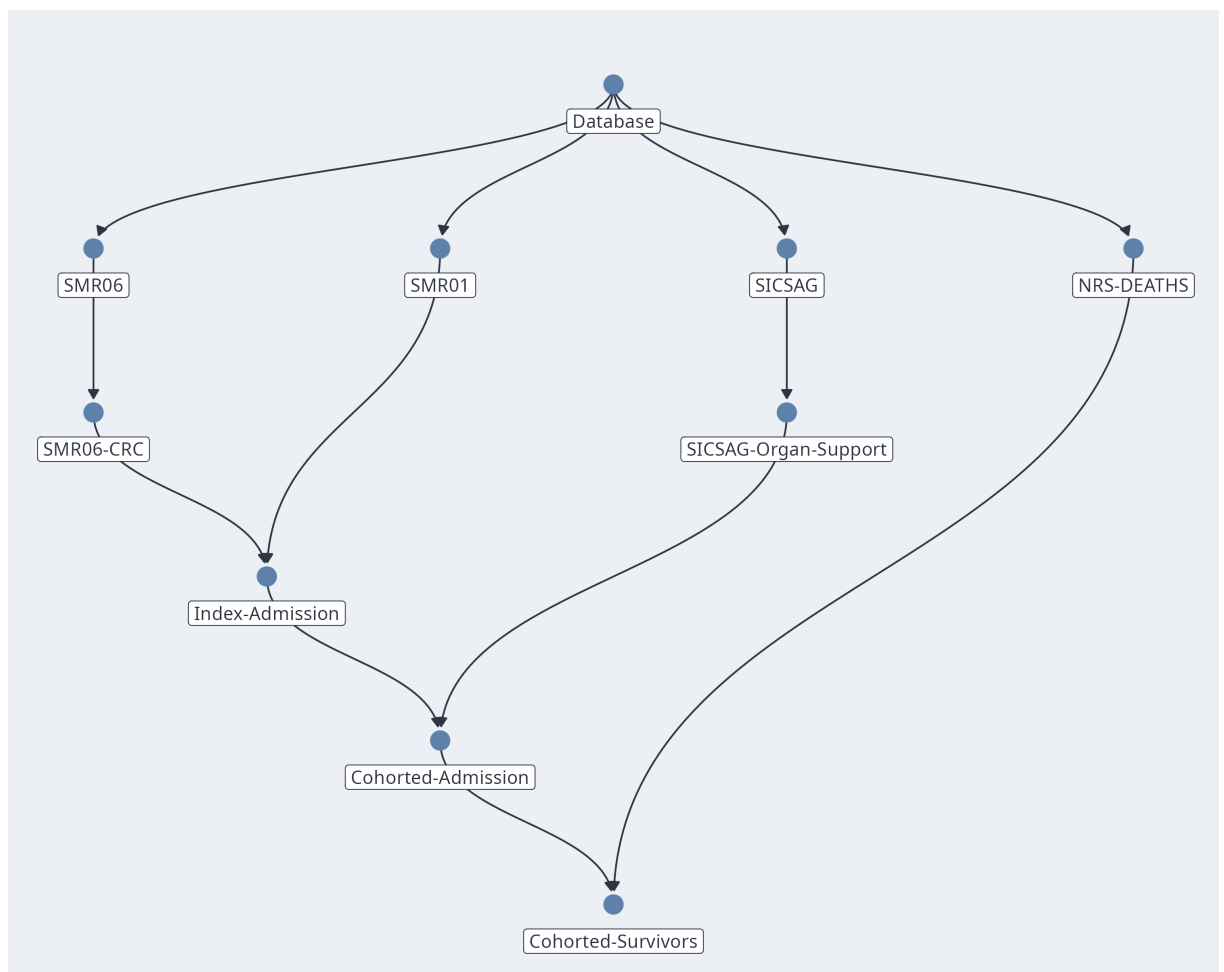


Figure 3.2: Creation of Cohorted Survivors, linkage of each national registry dataset to create a cohort of hospital survivors

Using the method noted above in cohort creation, patient set was stratified further into “Ward Level” (with no critical care admission), “Monitoring” (critical care admission without organ support), and “Organ Support” (critical care admission where organ support was provided) subcohorts.

3.3.3 Patient Characteristics

Age for each patient used records from SMR06, to determine Age in years at the time of diagnosis with CRC.

Socioeconomic circumstances were measured using the Scottish Index of Multiple Deprivation (SIMD). It provides an area-based measure of socioeconomic circumstance, based on the postcode of residence. Area-based measures of deprivation such as this one can incorporate data about individual living standards, along with broader issues such as crime, the physical environment, access to services or social capital. However, the system only allows a measure of relative deprivation within Scotland and not absolute deprivation (Fraser 2020). SIMD quintile was determined using recorded postcode on SMR01 records. As differing versions of SIMD were published throughout the time period of this dataset, each patients’ index admission was linked to the version of SIMD published closest in time prior to admission. Whilst SIMD decile was provided with SMR01, this was condensed to quintile for brevity, patient group size, and consistency with other relevant published work.

Comorbidity records are provided to some extent throughout the datasets. SICSAG data provides information on a limited number of significant comorbidities as required for APACHE II scoring. However this range of illnesses is restricted to a short list of disease processes and only patients with the most severe forms are identified. Furthermore, these data are not present for those patients treated at a ward level.

SMR01 admissions provide comorbidity information in their discharge coding (in the form of ICD coding) For each patient, SMR01 comorbidity codes were extracted for the five years prior to diagnosis with colorectal cancer. Whilst SMR01 records were available going to 1997, records were limited to 5 years to partially compensate for some comorbidities potentially improving with time. Several comorbidity scoring and categorisation systems are available. This work uses the categorisation system provided by the Charlson Comorbidity Index (CCI) as a starting point (Charlson et al. 1987; Johnston et al. 2015). As solid organ cancer (something everyone in my cohort definition has) provides a disproportionate weight for comorbidity scoring in CCI, the weighted CCI score was not used. Instead information is provided on presence or absence of each of the main categories within CCI: Cardiac, Respiratory, Renal, Diabetes, and Dementia. A count of comorbidity categories additional to cancer are provided: None, One, or Multiple. Using SMR01 to extract diagnostic codes for Charlson Comorbidity Index is a recognised approach, assessed and found to be suitable by Robertson et al. 2019 (Robertson et al. 2019). However Robertson and colleagues also acknowledge there is ‘no recognised gold standard’ approach, and other work has identified that the original Charlson weights do not adequately represent the risks for patient outcomes in certain patient populations (Johnston et al. 2015; Robertson et al. 2019). As such I consider it justifiable to use count of Charlson comorbidities rather than the weighted score, for this population. Use of a comorbidity count with an upper limit of 2+, categorising patients into three groups of: No (Additional) Comorbidity, One Comorbidity, Multiple Comorbidities has been successfully used by other Intensive Care research (Simpson et al. 2020).

3.3.4 Cancer and Hospitalisation Characteristics

Using SMR01 records and their provided OPCS coding, information on procedures during Index Hospitalisation was identified. These include: Number of operations recorded (None, One, Multiple), Receipt of upper or lower gastrointestinal endoscopy during admission (TRUE/FALSE), and receipt of surgical resection of CRC (TRUE/FALSE). Like other measures in this thesis, reliance on OPCS coding does depend on the validity of data as initially coded. However considering that use of OPCS in this manner is the same method undertaken by PHS in the national cancer QPI programme, this appears to be an acceptable data source (ISD Scotland 2022).

Linking SMR06, SMR01, and SICSAG, both by patient identifier and hospital admission identifier, provided information on: duration in days between diagnosis of CRC and admission to hospital, length of hospital admission in days, and length of critical care admission in days.

SICSAG information was used to categorise: nature of critical care admission (Planned: TRUE/FALSE), APACHE II Score, and forms of organ support received.

SMR06 data was used to note: nature of cancer diagnosis (Screening, Incidental Finding, Clinical Presentation, Other), anatomic stage (clinical and pathological stage calculated using recorded TNM scores in SMR06), and objectives of treatment (Curative, Non-Curative, Unknown).

As discussed in more detail in Chapter 4, incomplete staging information was noted. To compensate for this an additional proxy measure of “Metastatic Disease Known” was created. This combined both Anatomic Stage IV disease if known, and SMR01 ICD records. Whilst informative to some degree for description of patient groups, this proxy measure is not included in modelling, due to the large proportion of missing data.

3.3.5 Variables of Interest

3.3.5.1 QPI

For each Quality Performance Indicator, Healthcare Improvement Scotland provide definitions (referred to as measurability criteria) for the question of interest. These measurability criteria provide inclusion and exclusion criteria for the relevant population being investigated, and detailed definition of what it means to meet the measure of care quality (Dawson 2018). As a result, I transcribed the same 21 criteria into the research environment without alteration.

3.3.5.2 SACT

As described further in Chapter 6, my questions of interest relating to chemotherapy focused on a subset of patients: those with High-Risk Stage II and Stage III Colorectal Cancer, who had received surgical resection of their cancer. This cohort is not the only patients with colorectal cancer who would be expected to receive adjuvant SACT. Patients with Stage IV disease may receive adjuvant SACT following potentially curative resection of their primary tumour. However these patients with curative stage IV disease are known to have a different prognosis to those with non-metastatic

disease (Cervantes et al. 2023). It is also a reasonable assumption that such patients would have differences in length of hospital stay, and utilisation of critical care resources, considering the physiological burden of substantial operations such as pelvic exenteration.

As such I decided to focus on the more homogenous group of patients as defined by QPI 11 (described in more detail in Chapter 5, in brief the patients with High-Risk Stage II and Stage III disease, who receive curative surgical resection, and are eligible for adjuvant SACT). I used the QPI dataset and linked this to Scottish Chemocare prescription data to extract relevant information.

The first two questions ask information on receipt of adjuvant SACT, and time from surgical resection to start of adjuvant SACT. Such information is provided by the QPI dataset without reliance on chemocare prescription data, even for patients who would usually be excluded from QPI reporting for reasons such as age.

The remainder of the questions of interest ask for more detail on SACT administration, to address Regime Choice, Dose Delays Within Regime, and Course Length, Chemocare prescription data was used. These variables were calculated using the recorded prescription information for each patient.

3.3.5.3 Survival

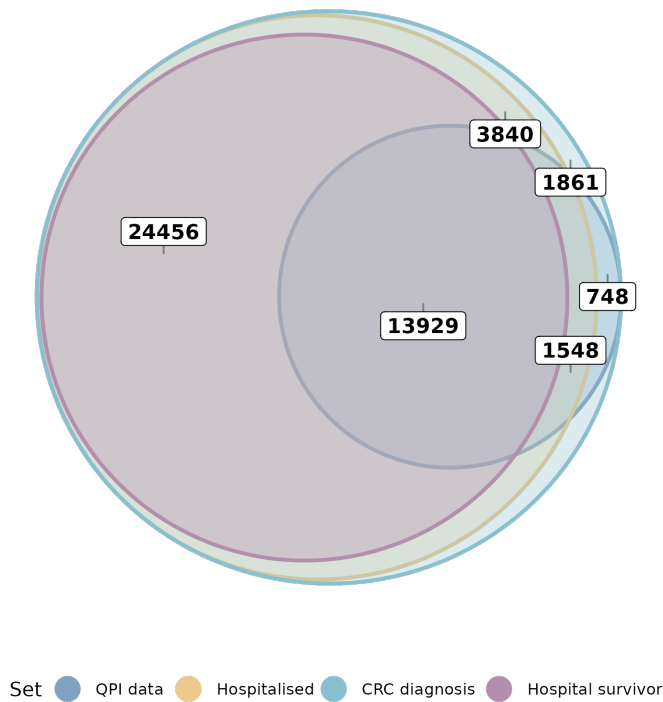
The dataset has survival information provided by NRS Deaths. Overall survival time was calculated from 30 days post hospital discharge to date of death or censoring. Censoring was performed at five years following hospital survival, or at the last recorded death in NRS Deaths (December 2018), whichever occurred first.

3.4 Dataset Construction for Analysis

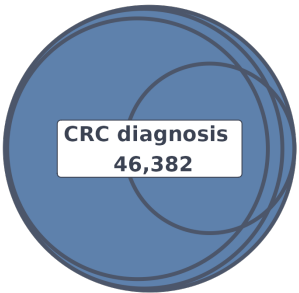
Each chapter of analysis has differing requirements for dataset construction and variable inclusion. An example of dataset connection is provided in Figure 3.4. The illustrative diagram in Figure 3.4 is not provided with the goal to fully describe each variable's creation and dataset linkage. Rather, it is to demonstrate that each question of interest required linkage of multiple original and intermediate datasets, with variables being defined and created at varying stages through the process, before a final dataset for analysis was generated. Similar illustrative examples demonstrating the multi-stage pipelines for QPI, SACT, and Survival chapters are provided in the Appendix.

The work of this thesis predominantly focuses on patients who survived their index hospital admission. Figure 3.3 demonstrate the overlap between the total population of patients with CRC, the set of patients which could be linked to hospital admissions, the set of those surviving their index hospital admission, and those with QPI data available.

A



B



C



D



E*

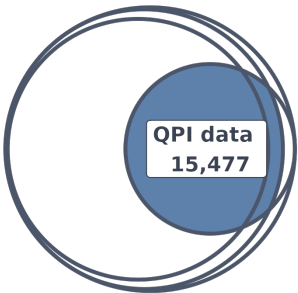


Figure 3.3: Euler Diagram of Patients Within Total Cohort (A) All Patients Noted in SMR06: Individual Groups and Intersections (B) Count of All Patients Noted in SMR06 (C) Count of Patients With SMR01 Index Admission (D) Count of Patients Surviving Index Admission and Following 30 Days (E) Count of Patients With SMR01 Index Admission and QPI Data (*Not Total of QPI Data, Some Patients Lacked Index Admission Data)

3.5 Conclusion

Despite being a relatively brief chapter, the reality is that the work undertaken in dataset construction, validation, and cleaning took up the bulk of the research time for this thesis.

Undertaking this work in a trusted research environment (TRE) remained essential to protect potentially identifiable patient information. However use of the research environment did result in additional friction points. As all code written in the environment is considered potentially sensitive information, it would need to undergo the same output checking as data from analyses. Within eDRIS no automated data output checks are undertaken, meaning each output request is reviewed manually by a member of PHS staff. Reflecting the pressure that code output requests would place on staff, guidance from eDRIS recommends only extracting the most essential scripts. As a result this thesis does not include much of the code written for analysis, falling short of the recommendations of many best practice guides for reproducible research (Streiber et al. 2025). All code however will remain available on PHS servers, with potential for release on a case-by-case basis.

As a learning point for myself for future work, eDRIS and many other TREs do allow for the import of code snippets. It would be reasonable to design analysis outside of the research environment, then importing the code into the TRE. Taking this approach would also allow me to more efficiently undertake a workflow as recommended by Gelman, where all models are first undertaken using simulated data to test assumptions (Gelman et al. 2020). This approach would also allow me to provide a form of analysis code to reviewers, whilst continuing to protect potentially identifiable information (as information only goes into TRE, not out), and avoiding any additional burdens on colleagues managing the TRE.

Whilst the TRE does allow for unsupervised import of simple text snippets, inclusion of packages of software require a greater degree of inspection by eDRIS staff. In the initial stages of my thesis, the research environment was using a Windows operating system incompatible with many of the standard R packages for Bayesian analysis. Getting approval for the installation of working versions of these packages took several months, and delayed some initial forms of analysis. When the TRE switched to a Linux operating system partway through my thesis, this again introduced several breaking changes that I had to fix before continuing with my work. Although fortunately, the switch to this operating system did also fix the initial problems I faced with certain R packages.

As a strength, all data cleaning within this thesis undertook well established ‘tidy’ principles for data analysis (Wickham 2023). My use of a Make-like pipeline, the {targets} R package ensured that any breaking changes made during TRE upgrade, or my own changes to variable definitions, could efficiently be accounted for, and any necessary code be easily re-run (Landau 2021).

As a researcher, this thesis represents the first interactions I have undertaken with several national administrative datasets, such as SMR01, SMR06, and the deaths register. Looking back at the end of this thesis, I can see several of my approaches resulted in dead ends, or with inefficient solutions, or even were attempted solutions to problems that didn’t truly exist. Whilst these inefficiencies are a limitation for my thesis, I’m fortunate enough that the experience gained over 3 years of interaction with these datasets will provide a strength for future work.

Equally however, several of the ‘dead ends’ I encountered with data cleaning in this thesis represent my crashing into the realities of time constraints, both from my own planned MD, and from wider data access to a TRE funded externally. This reflects a limitation of my own approach to this work, in considering the thesis as a single piece

of work, where I aimed to validate data cleaning for all chapters prior to undertaking analysis for all chapters. A more effective method would have been to undertake each ‘research question’ as a project to undertake from start to finish, before moving onto the next. Several opportunities for future work exist in these aspects currently considered ‘dead ends’, discussed in more detail in the final chapter of this thesis, Chapter 9.

In the next chapter, Chapter 4, I start to discuss the results of the data analysis of the cleaned and validated datasets. I provide details on patient numbers, baseline characteristics, cancer related measures, and eventual hospital outcomes. The statistical framework for the descriptive analysis of these cohorts is described in more detail in the previous chapter, Chapter 2.

Chapter 4

Demographics

This study had access to records from the Scottish Cancer Registry (SMR06), of new diagnoses of CRC recorded between 2006-01-01 and 2018-12-21.

Within SMR06, 46,382 unique patients were recorded as being diagnosed with colorectal cancer (ICD10: C18, C19, or C20) within this time period. Of this cohort, 43,773 could be linked with an inpatient stay recorded in SMR01 within two years following their cancer diagnosis. Of those admitted to hospital, 38,385 were considered a hospital survivor, having survived both the hospital admission and the 30 days following discharge. In this thesis I primarily investigated differences in patient, admission, and cancer characteristics of these 38,385 patients, with the CONSORT diagram in Figure 4.1 describing their inclusion. Chapter 5 uses additional inclusion and exclusion criteria as defined by the QPI Measurability Criteria (Dawson 2018). Differences in population selection are explained in that chapter's methods.

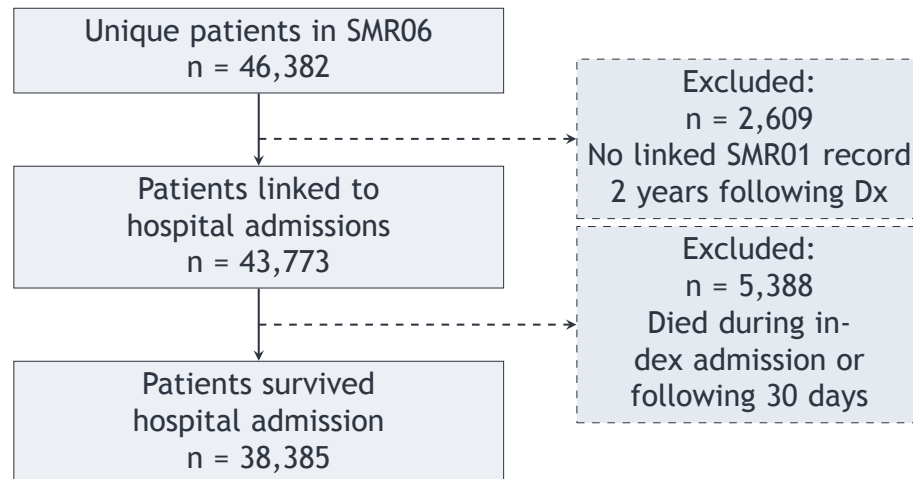


Figure 4.1: CONSORT diagram, patients included for description in demographics chapter (hospital admissions, patients included as hospital survivors for most subsequent analyses)

Hospital survivors themselves were stratified further, both by nature of hospital admission, and level of support during admission. Details are provided in the list below and also in Figure 4.2:

1. Ward Level: Survived Admission Without Admission To Critical Care
2. Monitoring: Survived Admission and Critical Care, Without Requiring Organ Support
3. Organ Support: Survived Admission and Critical Care, Requiring Organ Support

Hypothesising that patients admitted electively to hospital were likely to be on a different treatment and outcome course than those who presented emergently, I separated cohorts further by the nature of their hospital admission. This stratification and subcohort size is demonstrated in Figure 4.2:

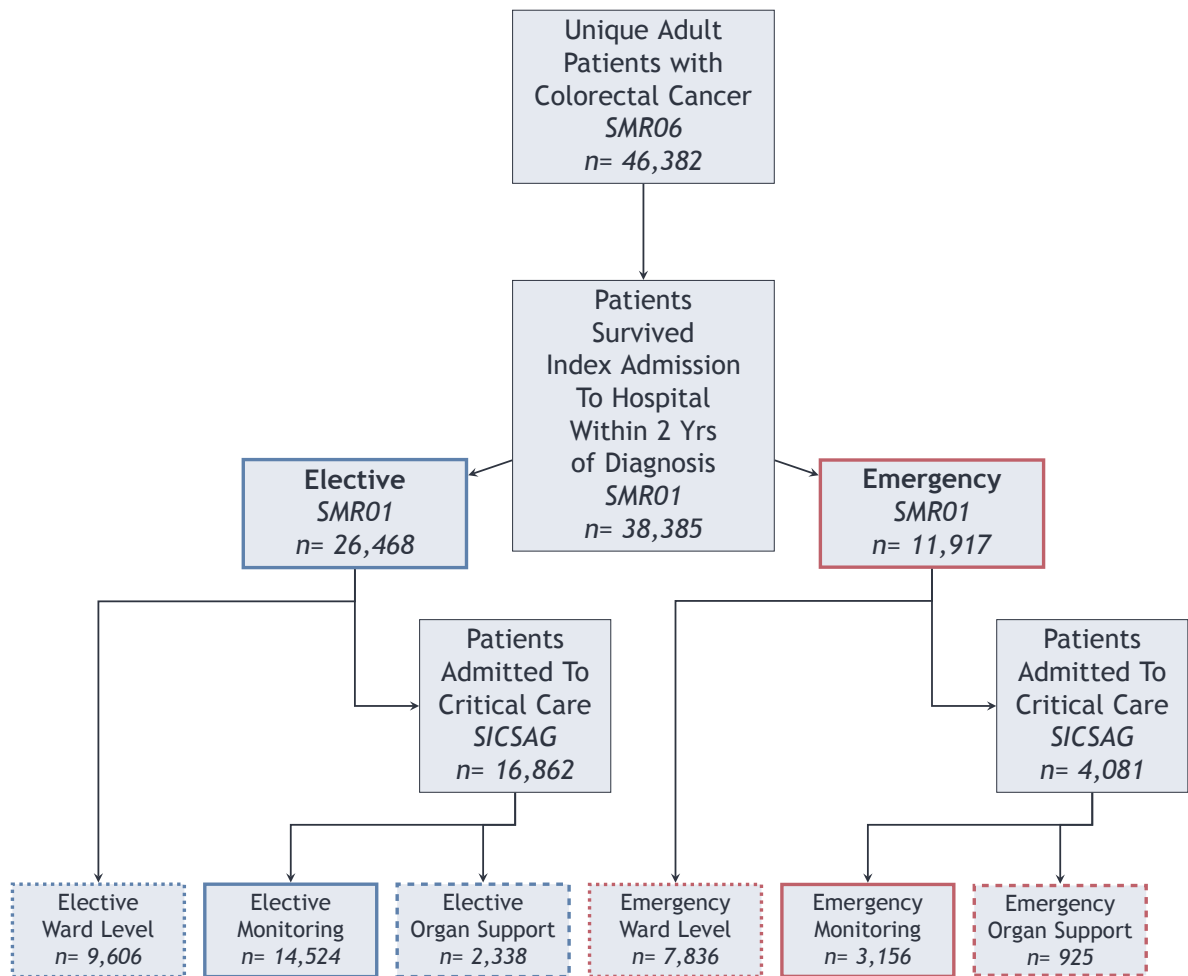


Figure 4.2: Stratification of cohort of adult patients with CRC into subcohorts, with identification of data sources used for categorisation, and patient numbers within each subcohort

4.1 Aims

I aimed to describe the six subcohorts, and any differences in the following:

- Age
- Sex
- SIMD Quintile
- Number of (Charlson) Comorbidities Additional To Cancer
- Presence of Disease: Cardiac, Respiratory, Renal, Diabetes, Dementia
- Nature of Admission to Hospital: Surgical, Non-Surgical
- Non-Operative Procedures During Admission: Endoscopy
- Number of Operations During Admission
- Interval From Diagnosis To Admission To Hospital (days)
- Duration of Hospital Stay (days)
- Duration of Critical Care Stay (days)
- Nature of Critical Care Admission: Planned, Unplanned
- Severity of Illness in Critical Care: APACHE II
- Form of Organ Support in Critical Care: Cardiovascular, Respiratory, Renal
- Method of Cancer Detection: Screening, Incidental Finding, Clinical Presentation
- Anatomic Stage of Cancer (As First Recorded in SMR06)
- Presence of Metastatic Disease (Anatomic Stage in SMR06, Comorbidities in SMR01)
- Objectives of Treatment: Curative, Non-curative
- Hospital Outcomes (Survival)

4.2 Results

4.2.1 Patient Groups

Provided in SMR06 were 46,382 unique adult patients diagnosed with CRC. Of these I was able to link 43,773 patients to an index hospital admission, and such stratify into subcohorts.

Of the total population of patients with CRC (SMR06), median age at diagnosis was 71 years (IQR 63 - 80), with 45% female patients.

Of the total population of unique adults with CRC who could be linked to an index hospital admission, an overview of demographics is provided in Table 4.1.

Values for hospital survivorship stratified by hospital subcohort are provided in Table 4.2. In-hospital survival is commented in greater detail in Chapter 8, but in brief: hospital survival (including thirty days post discharge) was 88% of all admissions (n=38,385). Survival differs substantially between elective and emergency admissions, and between different levels of support during hospital admission. Amongst Elective - Monitoring survival was greatest at 98% (n=14,524). Elective - Organ Support had survival at 87% (n=2,338), and Emergency - Organ Support was the subcohort with greatest mortality, where survival was 68% (n=925).

As the aims of my thesis were to primarily investigate hospital survivors, the following results and discussion will focus on the 38,385 patients who survived their index hospital admission. Similar to the overall cohort diagnosed with CRC, the median age was 71 years (IQR 62, 79) and 45% were female.

Table 4.1: Characteristics of Patients Linked To Index Admission
Description of the total cohort of patients with CRC admitted to hospital, not limited to hospital survivors

Characteristic	Overall N = 43,773
Cohort	
Elective: No Critical Care	10,189 (23%)
Elective: Crit Care - No Organ Support	14,756 (34%)
Elective: Crit Care - Organ Support	2,687 (6.1%)
Emergency: No Critical Care	11,185 (26%)
Emergency: Crit Care - No Organ Support	3,589 (8.2%)
Emergency: Crit Care - Organ Support	1,367 (3.1%)
Hospital Outcome	
Survived	38,385 (88%)
Died	5,388 (12%)
Age At Diagnosis	72 (63, 80)
Female Sex	19,975 (46%)
SIMD (quintile)	
1	8,264 (19%)
2	9,051 (21%)
3	9,109 (21%)
4	8,912 (20%)
5	8,397 (19%)
Missing	40 (0.09%)
Additional Charlson Comorbidities Known	
None	32,214 (74%)
One	8,541 (20%)
Multiple	3,018 (6.9%)
Comorbidities (Named)	
Cardiac	3,613 (8.3%)
Respiratory	4,241 (9.7%)
Renal	2,280 (5.2%)
Diabetes	4,353 (10.0%)
Dementia	826 (1.9%)
Surgical Admission	37,197 (85%)
Operations During Admission	
None	15,347 (35%)
One	24,102 (55%)
Multiple	4,324 (9.9%)
Diagnosis To Admission (days)	33 (0, 71)
Duration Hospital Stay (days)	9 (5, 17)
Method of First Detection	
Screening examination	5,740 (13%)
Incidental finding	1,177 (2.7%)
Clinical presentation	36,343 (83%)
Other / Not Known	513 (1.2%)
Anatomic Stage	
0	359 (2.6%)
I	1,864 (13%)
IIA	2,848 (20%)
IIB	731 (5.2%)
III	4,732 (34%)
IV	3,392 (24%)
Unknown	29,847
Metastatic Disease Found	11,869 (27%)
Objectives of Treatment	
Curative Intent	26,087 (60%)
Non-curative Intent (palliative)	14,836 (34%)
Not Known	2,850 (6.5%)

Continuous Variables: Median (Q1, Q3). Categorical Variables:
n (%)

Table 4.2: Hospital survivorship for adult patients with CRC during their index admission to hospital following diagnosis

Stratified by nature of admission and level of support received during admission

Characteristic	Overall N = 43,773	Elective			Emergency		
		Ward Level N = 10,189	Monitoring N = 14,756	Organ Support N = 2,687	Ward Level N = 11,185	Monitoring N = 3,589	Organ Support N = 1,367
Hospital Survivorship							
Survived	38,385 (88%)	9,606 (94%)	14,524 (98%)	2,338 (87%)	7,836 (70%)	3,156 (88%)	925 (68%)
Died	5,388 (12%)	583 (5.7%)	232 (1.6%)	349 (13%)	3,349 (30%)	433 (12%)	442 (32%)

n (%)

4.2.2 Hospital Survivors

I identified 38,385 unique adult patients diagnosed with CRC, where hospital admission records were available, and the patient survived their index hospital admission. These patients were diagnosed between January 2006 and December 2018. Full description of demographics are provided in Table 4.3, variable levels considered to differ meaningfully are noted by their Bayes Factor (BF). As detailed in Section 2.3.1.7, $BF > 10$ are considered strong evidence for a difference between groups, values less than 0.1 are considered strong evidence for similarity between groups.

Table 4.3: Characteristics of Subcohorts of Hospital Survivors

Characteristic	Overall	Elective	Elective	Elective	Emergency	Emergency	Emergency	Bayes Factor
	N = 38,385	Ward Level	Monitoring	Organ Support	Ward Level	Monitoring	Organ Support	
	N = 9,606	N = 14,524	N = 2,338	N = 7,836	N = 3,156	N = 925		
Age At Diagnosis	71 (62,79)	71 (63,79)	69 (61,76)	71 (64,77)	75 (65,83)	71 (62,79)	73 (64,80)	>100
Female Sex	17,438 (45%)	4,426 (46%)	6,399 (44%)	911 (39%)	3,729 (48%)	1,574 (50%)	399 (43%)	>100
SIMD (quintile)								
1	7,237 (19%)	1,732 (18%)	2,588 (18%)	403 (17%)	1,690 (22%)	600 (19%)	224 (24%)	>100
2	7,846 (20%)	1,996 (21%)	2,888 (20%)	495 (21%)	1,644 (21%)	631 (20%)	192 (21%)	<0.01
3	7,979 (21%)	2,043 (21%)	2,957 (20%)	519 (22%)	1,600 (20%)	666 (21%)	194 (21%)	<0.01
4	7,906 (21%)	2,021 (21%)	3,025 (21%)	540 (23%)	1,533 (20%)	615 (20%)	172 (19%)	<0.01
5	7,382 (19%)	1,807 (19%)	3,052 (21%)	380 (16%)	1,360 (17%)	640 (20%)	143 (15%)	>100
Additional Charlson Comorbidities								
Known								
None	28,936 (75%)	7,624 (79%)	11,383 (78%)	1,552 (66%)	5,337 (68%)	2,421 (77%)	619 (67%)	>100
One	7,093 (18%)	1,517 (16%)	2,501 (17%)	573 (25%)	1,738 (22%)	547 (17%)	217 (23%)	>100
Multiple	2,356 (6.1%)	465 (4.8%)	640 (4.4%)	213 (9.1%)	761 (9.7%)	188 (6%)	89 (9.6%)	>100
Comorbidities (Named)								
Cardiac	2,843 (7.4%)	583 (6.1%)	842 (5.8%)	248 (11%)	869 (11%)	199 (6.3%)	102 (11%)	>100
Respiratory	3,552 (9.3%)	685 (7.1%)	1,195 (8.2%)	320 (14%)	916 (12%)	310 (9.8%)	126 (14%)	>100
Renal	1,721 (4.5%)	383 (4%)	449 (3.1%)	142 (6.1%)	536 (6.8%)	144 (4.6%)	67 (7.2%)	>100
Diabetes	3,716 (9.7%)	794 (8.3%)	1,336 (9.2%)	322 (14%)	877 (11%)	272 (8.6%)	115 (12%)	>100
Dementia	518 (1.4%)	105 (1.1%)	69 (0.5%)	13 (0.6%)	288 (3.7%)	32 (1%)	11 (1.2%)	>100
Surgical Admission	33,982 (89%)	8,417 (88%)	14,490 (100%)	2,332 (100%)	4,802 (61%)	3,051 (97%)	890 (96%)	>100
Endoscopy During Admission	3,989 (10%)	1,569 (16%)	381 (2.6%)	74 (3.2%)	1,547 (20%)	337 (11%)	81 (8.8%)	>100
Operations During Admission								
None	11,458 (30%)	3,949 (41%)	801 (5.5%)	171 (7.3%)	6,017 (77%)	392 (12%)	128 (14%)	>100
One	22,953 (60%)	5,123 (53%)	11,641 (80%)	1,567 (67%)	1,629 (21%)	2,394 (76%)	599 (65%)	>100
Multiple	3,974 (10%)	534 (5.6%)	2,082 (14%)	600 (26%)	190 (2.4%)	370 (12%)	198 (21%)	>100
Diagnosis To Admn (days)	36 (0,75)	36 (10,64)	51 (31,98)	59 (35,115)	0 (0,34)	0 (0,23)	0 (0,18)	>100
Hospital Duration (days)	9 (5,15)	6 (2,10)	9 (7,14)	15 (9,28)	8 (3,17)	15 (10,24)	25 (15,42)	>100
Critical Care Duration (days)	1 (0,3)	-	3 (1,4)	5 (3,8)	-	3 (2,4)	5 (3,8)	>100
Critical Care Planned	14,220 (37%)	-	12,084 (83%)	1,313 (56%)	-	734 (23%)	89 (9.6%)	>100
APACHE II	15 (11,20)	- (-,-)	15 (11,20)	15 (12,19)	- (-,-)	16 (11,20)	17 (14,20)	>100
Organ Support								
Cardiovascular	2,497 (6.5%)	-	-	1,837 (79%)	-	-	660 (71%)	>100
Respiratory	1,473 (3.8%)	-	-	949 (41%)	-	-	524 (57%)	>100
Renal	170 (0.4%)	-	-	106 (4.5%)	-	-	64 (6.9%)	0.87
Method of First Detection								
Screening	5,643 (15%)	1,731 (18%)	3,043 (21%)	434 (19%)	306 (3.9%)	100 (3.2%)	29 (3.1%)	>100
Incidental	1,002 (2.6%)	246 (2.6%)	285 (2%)	69 (3%)	324 (4.1%)	53 (1.7%)	25 (2.7%)	>100
Clinical	31,340 (82%)	7,517 (78%)	11,051 (76%)	1,822 (78%)	7,109 (91%)	2,976 (94%)	865 (94%)	>100
Other	400 (1%)	112 (1.2%)	145 (1%)	13 (0.6%)	97 (1.2%)	27 (0.9%)	6 (0.6%)	<0.01
Anatomic Stage								
0	269 (2.2%)	86 (2.9%)	20 (0.4%)	4 (0.4%)	149 (6.1%)	6 (0.6%)	4 (1.1%)	>100
I	1,818 (15%)	557 (19%)	849 (18%)	165 (17%)	182 (7.5%)	43 (4.4%)	22 (5.9%)	>100
IIA	2,759 (22%)	682 (23%)	1,348 (28%)	240 (25%)	269 (11%)	169 (17%)	51 (14%)	>100
IIB	668 (5.4%)	117 (4%)	252 (5.3%)	49 (5.2%)	93 (3.8%)	109 (11%)	48 (13%)	>100
III	4,480 (36%)	960 (33%)	1,946 (41%)	384 (41%)	569 (23%)	430 (44%)	191 (52%)	>100
IV	2,453 (20%)	549 (19%)	360 (7.5%)	103 (11%)	1,165 (48%)	222 (23%)	54 (15%)	>100
Unknown	25,938	6,655	9,749	1,393	5,409	2,177	555	
Metastatic Disease Found	9,516 (25%)	1,898 (20%)	3,354 (23%)	517 (22%)	2,407 (31%)	1,089 (35%)	251 (27%)	>100
Objectives of Treatment								
Curative Intent	25,309 (66%)	6,147 (64%)	12,043 (83%)	1,963 (84%)	2,521 (32%)	2,009 (64%)	626 (68%)	>100
Non-curative Intent (palliative)	10,460 (27%)	2,778 (29%)	1,459 (10%)	240 (10%)	4,864 (62%)	884 (28%)	235 (25%)	>100
Not Known	2,616 (6.8%)	681 (7.1%)	1,022 (7%)	135 (5.8%)	451 (5.8%)	263 (8.3%)	64 (6.9%)	<0.01

Continuous Variables: Mean (IQR). Categorical Variables: N (%). Bayes Factor (BF): Evidence for group differences. Continuous variables analysed using ANOVA Bayes Factor from median and IQR. Categorical variables analysed using contingency table Bayes Factor. $BF \geq 10$ considered strong evidence of difference between groups. $BF \leq 0.1$ considered strong evidence of no difference between groups

4.2.3 Hospital Admission

Differences in the size of the six subcohorts was apparent; elective admissions (26,468) accounted for 69% of the total population. Distribution of patients between each of the six subcohorts is shown in Figure 4.2 and Table 4.4. When stratified by the nature of admission, level of support during admission differed between elective and emergency cohorts. 63% of elective admissions were treated in critical care, almost double the 34% of emergency admissions treated in critical care.

Among elective admissions, those receiving monitoring in critical care were the largest subcohort (14,524), accounting for 55% of elective patients. Among emergency admissions, the largest subcohort was those treated at ward level (7,836), accounting for 66% of emergency patients. Those receiving organ support in critical care were the smallest group amongst elective and emergency admissions. The percentage of patients receiving organ support was similar among elective (8.8% of elective admissions) and emergency (7.8%) patients.

Table 4.4: Size of each subcohort of hospital survivors with CRC
Stratified by nature of hospital admission and receipt of support during hospital admission

	Ward Level	Monitoring	Organ Support	Total
Elective	9,606	14,524	2,338	26,468
Emergency	7,836	3,156	925	11,917
Total	17,442	17,680	3,263	38,385

4.2.4 Patient Characteristics

Median age differed between the six subcohorts ($BF > 100$). The total population median age at time of CRC diagnosis was 71 (IQR 62-79). Emergency patients tended to be slightly older, particularly Emergency - Ward Level patients, where the median age was 75 (65-83), and Emergency - Organ Support patients where the median age was 73 (64-80).

The proportion of female patients differed between subcohorts ($BF > 100$). In both elective and emergency admissions, Organ Support had the smallest proportion of female patients, with 39% in Elective - Organ Support (contrasted against 44% in Monitoring), and 43% in Emergency - Organ Support (50% in Monitoring).

SIMD is developed by Public Health Scotland so that each quintile is of equal size, making up 20% of the Scottish population (Fraser 2020). At the extremes of affluence (SIMD Quintile 5) and deprivation (SIMD Quintile 1), subcohorts differ in proportion ($BF > 100$). Patients from the most deprived SIMD quintile appear to be disproportionately represented in the Emergency admissions, when compared against Elective. This is demonstrated in Figure 4.3. In the Emergency - Organ Support subcohort, where 24% patients came from SIMD 1. Patients from SIMD 5 were disproportionately lacking from Organ Support subcohorts: accounting for 15% of Emergency - Organ Support.

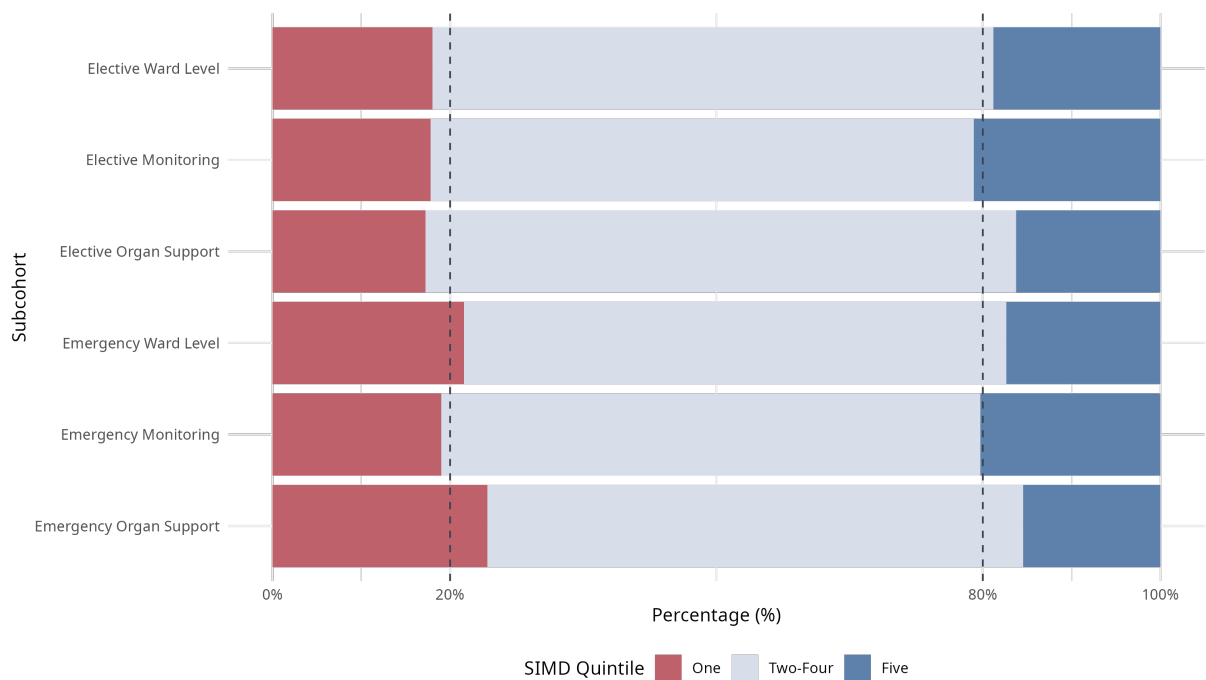


Figure 4.3: Proportion of patients in each subcohort within each SIMD quintile
 Extremes of affluence (Quintile 5) and deprivation (Quintile 1) are highlighted
 Expected proportion of 20% in each quintile shown as dotted line

4.2.5 Comorbidities

Among the total population, the majority of patients ($n = 28,396$, 75%) had no additional comorbidity to the CRC identified. 18% of the cohort had one additional comorbidity, and 6% had multiple comorbidities. Within the subcohorts, multiple comorbidities were more frequently observed amongst those receiving Organ Support ($BF > 100$). 9.1% of Elective - Organ Support patients had multiple comorbidities, in contrast to 4.4% in Elective - Monitoring patients. 9.6% of Emergency - Organ Support patients had multiple comorbidities, in contrast to 6% in Emergency - Monitoring patients. Emergency - Ward Level patients had greater comorbidity than Elective - Ward Level patients, where 9.7% of Emergency - Ward Level patients had multiple comorbidities, contrasted against 4.8% of Elective - Ward Level patients. Among the total population, the most commonly recorded additional comorbidities were Diabetes (9.7%) and Respiratory disease (9.3%). Cardiac (7.4%) and Renal (4.5%) followed, with Dementia the least commonly recorded (1.4%). The difference in proportions of pa-

tients with each named comorbidity is shown in Figure 4.4. Each named comorbidity was more frequently observed in the Organ Support subcohorts, with the exception of Dementia, where a disproportionate majority of patients were treated at a ward level.

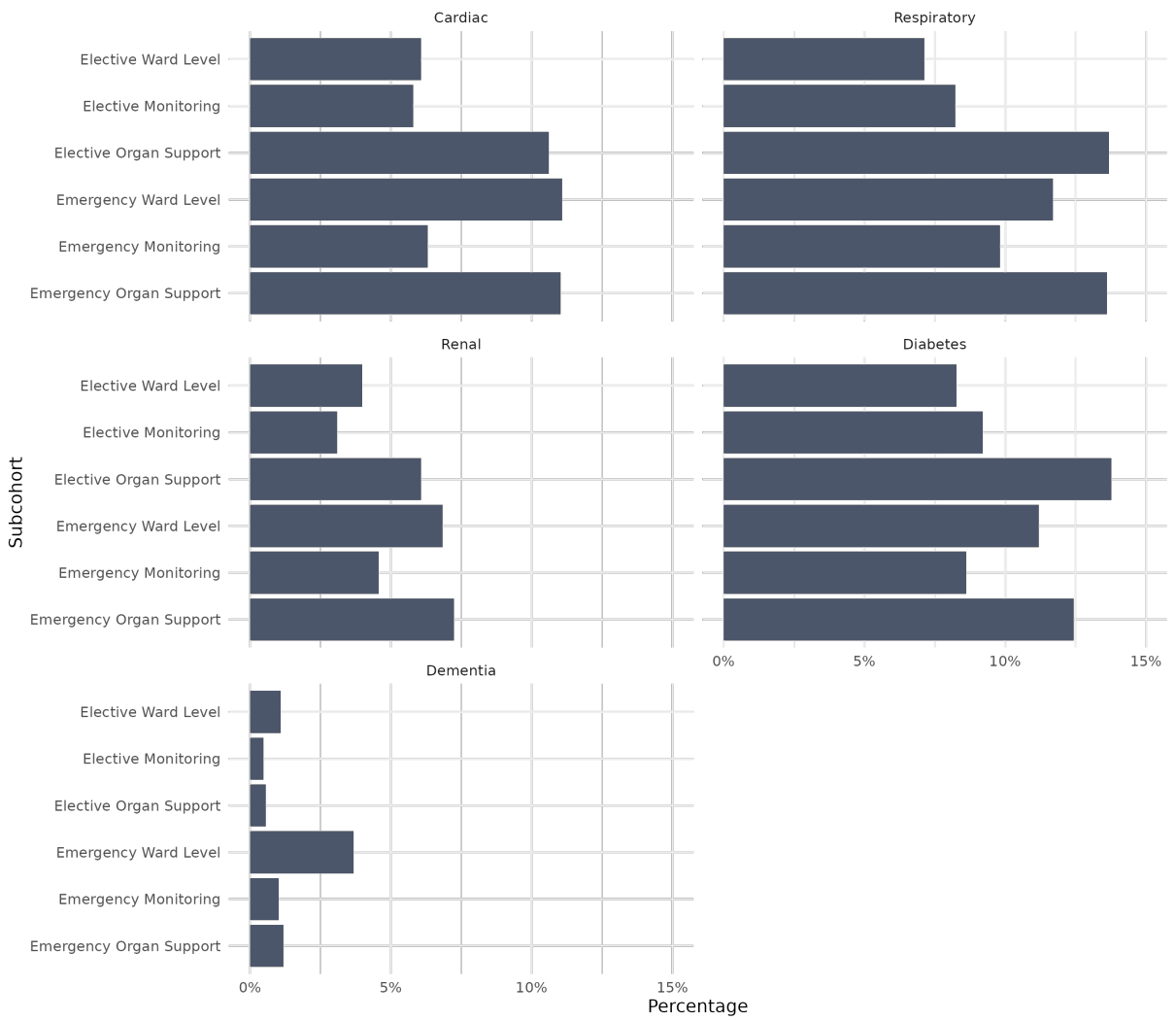


Figure 4.4: Prevalence of comorbidities from Charlson Comorbidity Index (cardiac, respiratory, renal, diabetes, dementia) across subcohorts, showing percentage of patients in each subcohort with each condition

4.2.6 Hospital Admission

Among the total population, the majority of patients were admitted under the care of surgical specialties during their index admission (89%). This proportion of patients was similar between five of the six subcohorts, with the exception of the reduction seen in Emergency - Ward Level (61% of patients, BF > 100). This difference between Ward Level and Monitoring was also apparent for elective patients, albeit to a lesser extent, with 88% contrasted against 100%.

Patients admitted to critical care more frequently underwent operations than those treated at a ward level, and patients receiving organ support had a greater proportion of patients undergoing multiple operations when compared against those receiving monitoring in critical care (BF > 100). Emergency - Ward Level had the greatest proportion of patients not undergoing any operation, 77% of the subcohort. These differences are demonstrated in Figure 4.5. Whilst patients treated at a ward level had a smaller proportion undergoing operations, they did have a greater proportion of patients undergoing other procedures, with 20% of Emergency - Ward Level patients and 16% of Elective - Ward Level patients undergoing endoscopy, contrasted against 8.8% of Emergency - Organ Support and 3.2% of Elective - Organ Support patients (BF > 100).

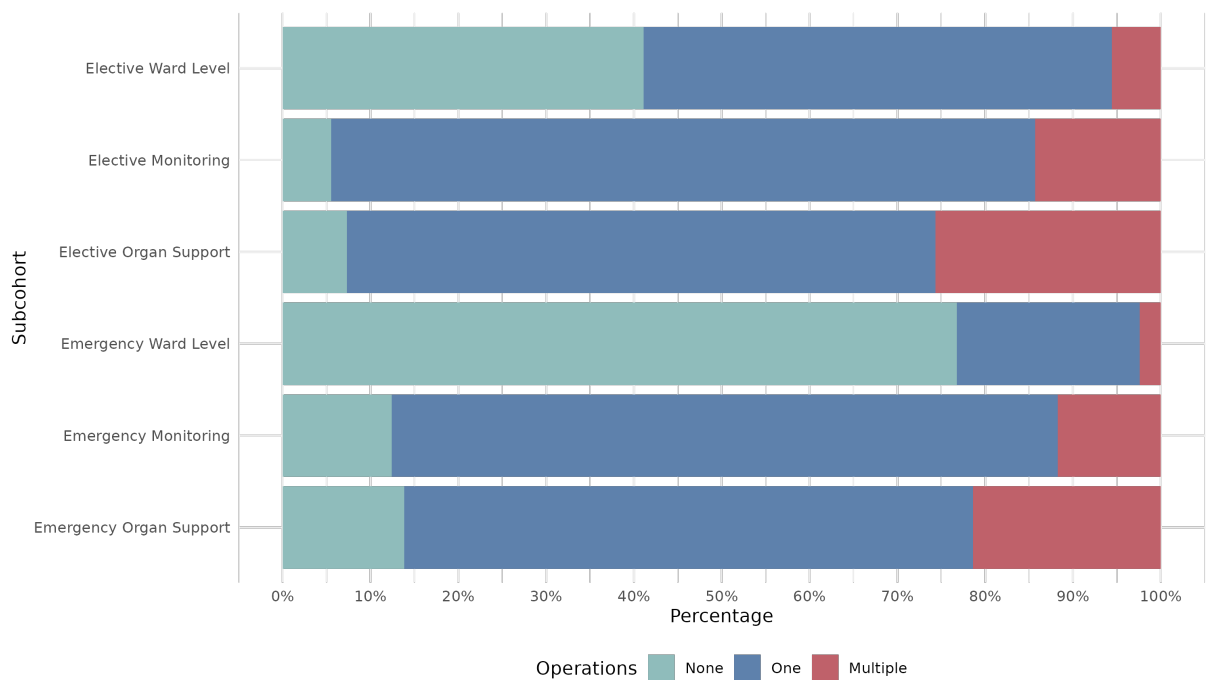


Figure 4.5: Comparison of number of operations during index admission between subcohorts. Demonstrating the greater proportion of ward level patients who received no operation, and the greater proportion of organ support patients who received multiple operations.

Among the total population, diagnosis through screening was 15%. This differed significantly between Elective and Emergency subcohorts ($BF > 100$). Differences are demonstrated in Figure 4.6. Every Emergency subcohort had a proportion of diagnosis through screening of $\leq 5\%$, with a $\geq 90\%$ rate of diagnosis through Clinical Presentation. Every Elective subcohort had a proportion of diagnosis through screening of $\geq 18\%$, with 76-78% diagnosed through Clinical Presentation.

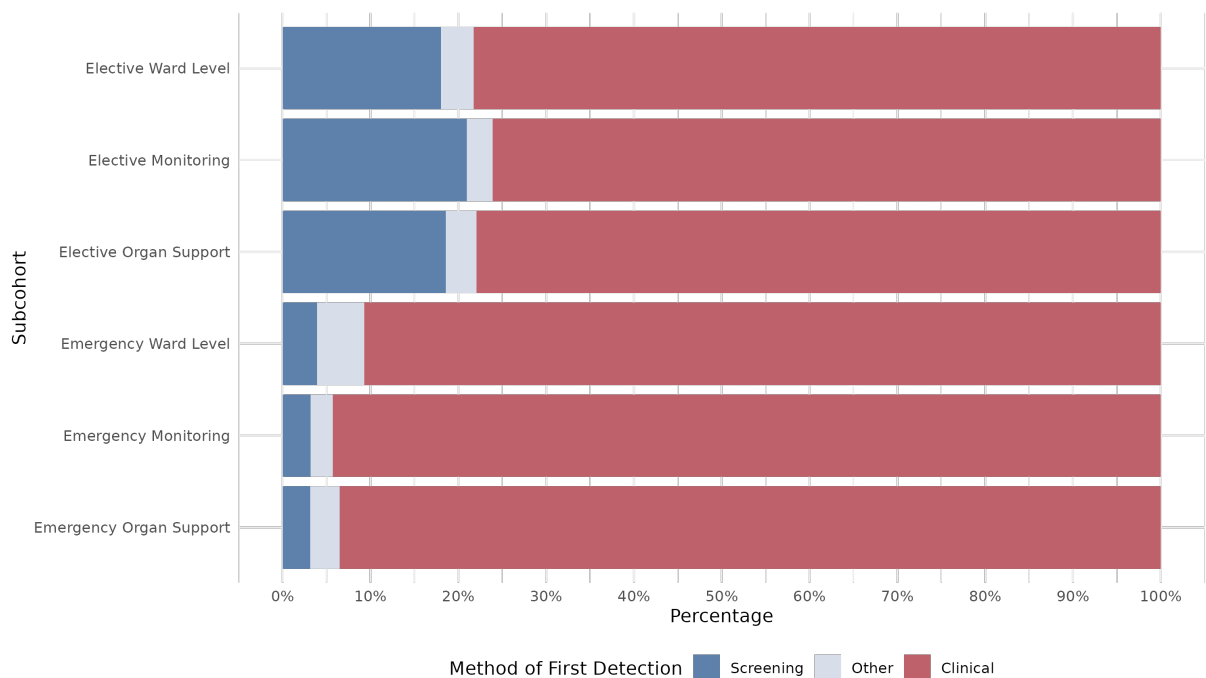


Figure 4.6: Comparison of methods of CRC diagnosis between subcohorts

In linking diagnoses to hospital admissions, “index hospital admissions” included those where diagnosis of CRC was made during inpatient stay. As such all Emergency subcohorts had a median interval between diagnosis and admission of 0 days, whereas all Elective subcohorts had a median interval of a month or greater (BF > 100).

Median length of index hospital admission was 9 days (IQR 5-15) among the total population. Each Emergency subcohort had a greater median length of stay than their Elective counterpart. Among both Elective and Emergency admissions, length of stay increased as you progressed from Ward Level, to Monitoring, to Organ Support. Emergency - Organ Support admissions had a median length of stay of 25 (15-42) days, contrasted against 15 (10-24) days for Emergency - Monitoring. Whilst median length of hospital stay differed by 6 days when comparing Elective - Organ Support and Elective

- Monitoring, and by 10 days when comparing Emergency - Organ Support to Emergency - Monitoring, this difference mostly reflected increased time being treated at a ward level. The difference in critical care median length of stay was only 2 days when contrasting Organ Support against Monitoring subcohorts.

Cardiovascular support was the most commonly occurring form of organ support for both Elective and Emergency groups, followed by respiratory, then renal support, as demonstrated in Figure 4.7. A greater proportion of Emergency - Organ Support patients were ventilated (57% contrasted against Elective 41%, BF > 100). There was no observed difference between Elective and Emergency in the proportions of patients receiving renal support (Elective: 4.5%, Emergency: 6.9%) (BF 0.87).

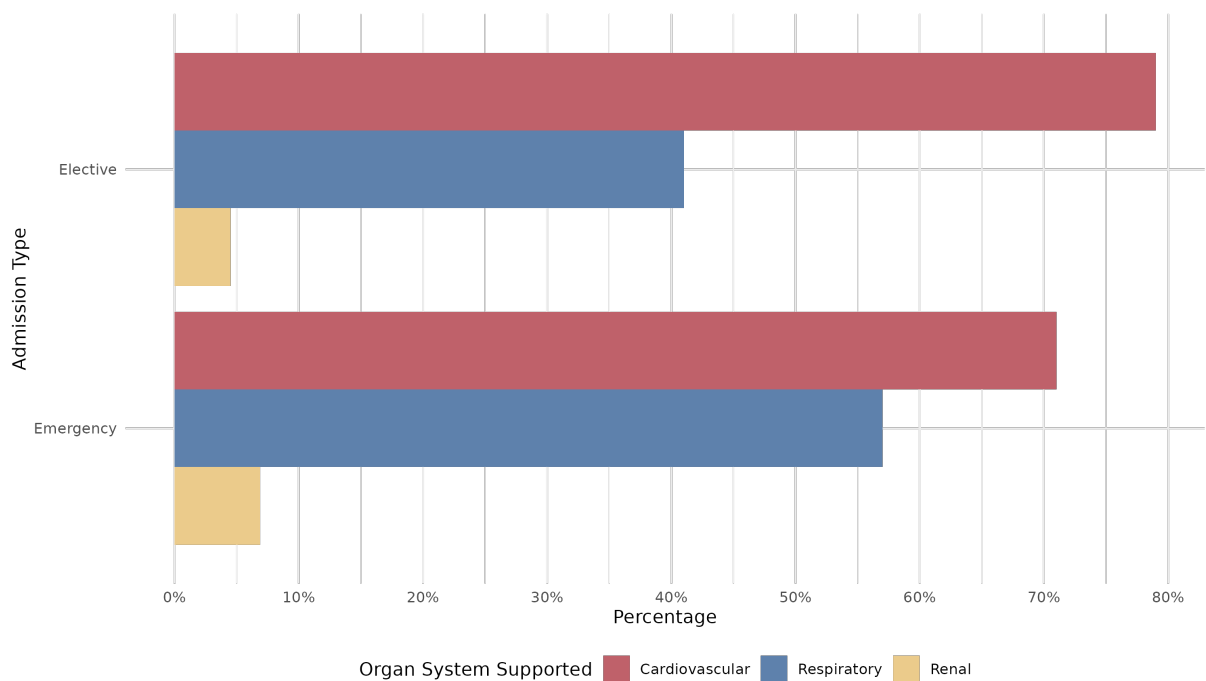


Figure 4.7: Comparison of forms of organ support between admission types

4.2.7 Colorectal Cancer

Reliance on SMR06 records of Anatomic Stage was noted to have significant limitations. 25,938 patients (68%) did not have anatomic stage recorded in SMR06. As one attempt to partially account for missing data, I created a composite “Metastatic Disease” variable. Patients were recorded as having metastatic disease if Anatomic Stage IV was noted in SMR06, or if SMR01 records of comorbidity made reference to metastatic disease prior to index admission. These SMR01 records were based on admission coding, similar to the creation of the Cardiac-Dementia variables. As such this metastatic disease variable may also include patients with metastatic disease that originated from other primary tumours (although all patients also have CRC), and like the other comorbidities is still dependent on accuracy of admission coding.

Details of anatomic stage where available, proportion of patients with missing data, and comparison between the total population percentages of patients with “Metastatic disease” (the composite measure including SMR01 and SMR06 data) and Stage IV disease (measure solely dependent on anatomic stage recorded within SMR06) recorded are shown in Figure 4.8.

Staging data was missing from SMR06 for the majority of patients in all subcohorts (ranging from 60% to 69%), commented on further in the Discussion section of this chapter. although a greater proportion of Organ Support patients had complete Anatomic Stage. The creation of the Metastatic disease variable identified a substantial proportion of patients with metastatic disease in all subcohorts. Among the total population the composite measure identified 9,516 patients (25%) with “Metastatic disease”, contrasted against the 2,453 identified with Stage IV disease in SMR06 (6% of total population, 20% of patients who had anatomic stage recorded). General trends in proportion appeared similar between Stage IV and Metastatic disease, with all Emergency subcohorts having a greater proportion of Metastatic disease than their

Elective counterpart (as seen for Stage IV disease). However the order of subcohorts by proportion of patients with Metastatic disease does differ than the order seen when using Stage IV disease. There were no cases in the cohort where Stage IV disease was noted in SMR06, and Metastatic disease was not found in SMR01.

With these limitations noted, differences are apparent between those admitted electively and those admitted emergently. There were also differences between those admitted to ward level and those admitted to critical care.

The following comparisons make use of anatomic stage as recorded in SMR06, rather than the composite metastatic disease variable. A larger percentage of Ward Level patients had stage IV colorectal cancer than seen in those admitted to critical care. Among elective patients, 19% of Ward Level patients with anatomic stage recorded had stage IV disease, contrasted against 7.5% of Monitoring patients. Among emergency patients, 48% of Ward Level patients with anatomic stage recorded had stage IV disease, contrasted against 23% of Monitoring. Each Emergency subcohort had a greater proportion of patients with Stage IV disease recorded than their elective counterpart (BF > 100).

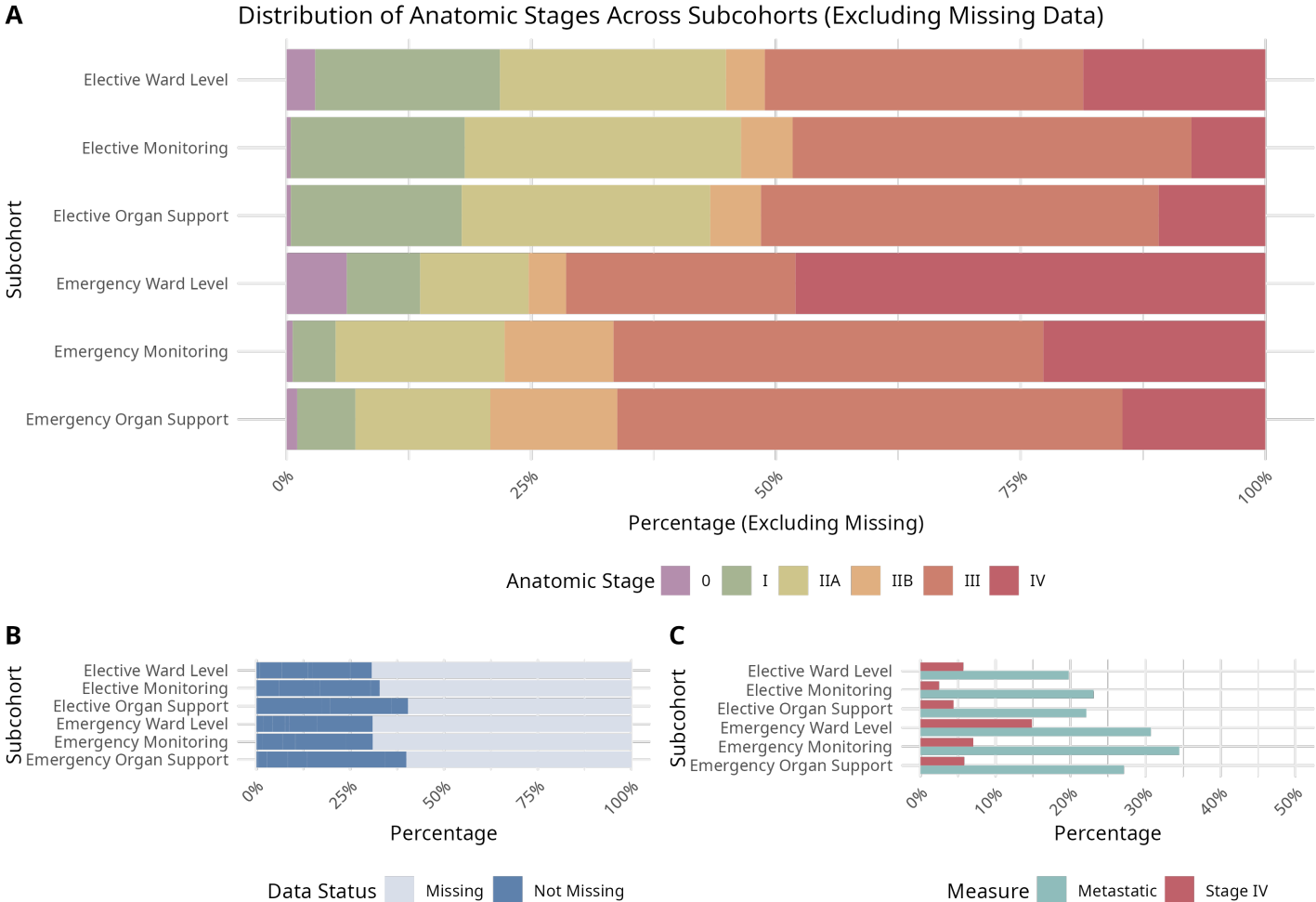


Figure 4.8: Distribution of anatomic stage data across subcohorts. (A) Stage distribution excluding missing data. (B) Proportion of missing stage data. (C) Comparison of metastatic disease prevalence and Stage IV disease among patients with recorded staging.

Among the total population, 66% of patients had treatment planned as having curative intent. The proportion of patients with treatment with curative intent differed between the 6 subcohorts, as noted in Figure 4.9. Each Elective subcohort had a greater proportion of patients treated with curative intent than their emergency counterpart (BF > 100). Organ Support and Monitoring patients had similar proportions of patients treated with curative intent (Elective - Organ Support 84% vs Elective - Monitoring 83%, Emergency - Organ Support 68% vs Emergency - Monitoring 64%). Ward Level patients had the smallest proportion treated with curative intent (Elective Ward 64%, Emergency Ward 32%).

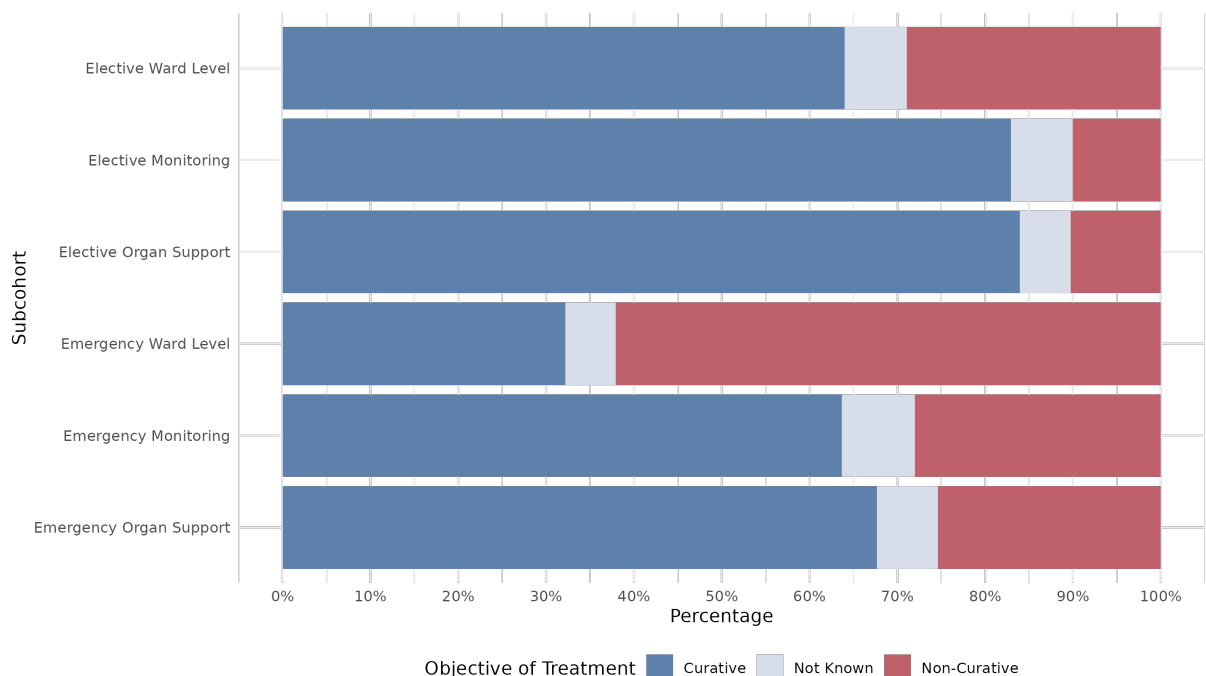


Figure 4.9: Comparison of objectives of CRC treatment between subcohorts

4.3 Discussion

Using this stratification of patients into subcohorts, 45% of patients with CRC were treated outside of critical care in their index admission following diagnosis, and 55% were treated within critical care.

One in twelve patients in the total cohort (8.5%) received organ support in critical care, this accounts for 16% of all critical care admissions. CRC patients admitted to hospital electively were most commonly treated in critical care with monitoring only. In contrast, those patients admitted as an emergency were most commonly managed at ward level. The overall proportion of patients receiving organ support was similar in elective and emergency admissions, with the main difference appearing to be the number of patients admitted to critical care for monitoring only.

Acknowledging that the most common form of admission was an Elective Admission to Critical Care for Monitoring, my primary goals were to compare:

- Patients treated with organ support against those with monitoring only in critical care
- Patients admitted electively against those admitted emergently
- Patients treated at a ward level against those monitored in critical care

Contrasting patients receiving organ support against those monitored in critical care: Patients undergoing organ support tend to be slightly older, with a median difference in age of 2 years, and are more comorbid, with a 60-100% increase in patients with multiple comorbidities. Patients experiencing organ support also undergo a greater number of operations during their hospital stay, with a 75-85% increase in the proportion of patients undergoing multiple operations. Patients with organ support stay in critical care and hospital longer, with a 66% greater median length of stay in critical care, and a 66% greater length of stay in hospital.

There are some factors where differences also appear dependent on the nature of hospital admission. Emergency - Organ Support patients have a 25% increase in the proportion of patients from the most deprived quintile, contrasted against Emergency - Monitoring. No such difference is seen when contrasting the two elective subcohorts.

Among emergency admissions, fewer Organ Support patients have Anatomic Stage IV or known metastatic disease when contrasted against Monitoring. Among elective admissions, the proportions of patients with advanced disease are similar between Organ Support and Monitoring subcohorts.

When comparing emergency and elective admissions more generally: Emergency admissions tend to be older, with a greater proportion of patients in SIMD 1, more comorbid, with a smaller proportion of patients getting any operation during their stay. There is also a greater proportion of patients who are diagnosed during the index hospital admission in the overall emergency cohort, with a later stage of disease, and a smaller proportion being treated with curative intent.

Of those patients treated with Organ Support, respiratory support has a relative increase in proportion of about 50% more for patients during an emergency admission (57%), when compared to elective (41%). This may be expected by some readers, when considering differences such as post operative course for a patient following an emergency laparotomy for CRC, contrasted against elective surgical resection.

Last contrasting Ward Level to Monitoring patients, any difference appears to a greater extent in the Emergency admissions cohorts. Emergency - Ward Level patients are: older, more deprived, more comorbid, with later stages of disease, less likely to be treated by surgeons or with curative intent than those treated with Monitoring in critical care.

Previous work performed in Scotland has described a 16% incidence of Critical Illness amongst patients with colorectal cancer, in the first two years following diagnosis. The population, definitions, and initial findings from this thesis differ. However, when considering the differences in population and definition, as shown below the ultimate findings are consistent. The work from Puxty et al. 2015 investigated all admissions

to Intensive Care Units in the West of Scotland from 2000-2009. My work describes admission to Critical Care, which includes both Intensive Care and High Dependency Units. I investigated all Scottish critical care units rather than one region of Scotland, and a time period approximately a decade later. In the work from Puxty, of those patients with CRC admitted to intensive care, 47.8% received Organ Support. As such 7.6% of their total population of patients with CRC received Organ Support. Acknowledging that Puxty report some missing data on organ support, and did not include patients admitted to High Dependency units; I consider my finding that 8.5% of patients with CRC required organ support to be consistent with theirs.

The observed differences comparing emergency and elective cohorts are unsurprising, emerging as results of the nature of admission. Seeing asymptomatic patients, diagnosed earlier through screening, being admitted electively more frequently is what would be expected and is the aim of Public Health screening initiatives (Jahan and SM-Rahman 2025). Similarly, the resulting earlier diagnosis would be expected to correspond with a greater proportion of patients treated with curative intent.

The differences noted between Ward Level, Monitoring, and Organ Support subcohorts, reflect the fact it is unlikely that these cohorts can be described simply as increasing severity of illness. As noted in Chapter 1, the decision to admit a patient to critical care, and secondarily the decision to embark on organ support, is one that is made through balancing the physiological requirements of the patient against the appropriateness of such a treatment. Noting that Ward Level patients, particularly in the Emergency setting, are older, more comorbid and with later stages of disease; likely reflects decisions being made about inappropriateness of more burdensome treatments. The identification of greater proportions of ward patients receiving non-surgical interventions like endoscopy, may appear to be in conflict with the idea that ward patients account for a group where burdensome interventions are not undertaken. However there is a selection bias occurring here, the decision to admit a patient to hospital in the first place. Each patient admitted to hospital has to have a

reason for admission. If ward level patients do not have an operative reason for admission, then it makes sense to see an apparent rise in another reason for admission (such as requiring endoscopy). Additionally in some cases it may be that the decision to undertake endoscopy, was selected as a less burdensome option than surgical intervention. To investigate any relationship fully here between level of support and intervention would require more in-depth regression modelling. This particular question is not the primary focus of this thesis, and so instead I choose simply to note the difference, and provide some description as to why this shouldn't automatically be taken on face value.

Among Elective patients, for Cardiac, Respiratory, Renal, and Diabetes, these comorbidities occur more frequently in the Organ Support subcohort than in Monitoring. This may reflect that patients who are more unwell with such comorbidities are more likely to require organ support. However this pattern is not seen for patients with Dementia, where patients are disproportionately treated at a Ward Level, and likely reflects decisions being made in appropriateness of admission to critical care. Similar patterns are observed in patients with more advanced CRC, where those with Stage IV disease are much more frequently treated at a Ward Level, rather than in Critical Care.

As noted in Chapter 1, socio-economic factors impact both uptake of CRC screening, and ultimately CRC treatment outcomes. There is a larger than expected proportion of patients in SIMD 1, the most socioeconomically deprived quintile, (24%) in the Emergency - Organ Support subcohort, and a smaller than expected proportion of patients from SIMD 5, the most affluent (15%).

Several limitations already emerge in my initial description of the six subcohorts. Some of these limitations reflect the nature of registry data, and some reflect decisions I have made with cohort stratification. As noted in the Introduction chapter and above, there are several key patient and disease related factors that are not consistently available. Clinical frailty is likely to play a significant role in determining who receives what forms of treatment and where such a treatment is administered, impacting decisions for Oncologists, Surgeons, and Intensivists. However whilst it is now routinely captured for all critical care admissions from 2020 onwards, it is not routinely recorded in SMR01 or other datasets for hospital admissions more broadly. Similarly above I have observed differences between patient groups, such as the proportion of patients with dementia, and assumed that relates to decisions made by the patients, their families, and the professionals treating them. However without recorded information on factors such as ‘critical care referral considered’, or ‘referral made but determined not for admission’, it cannot be determined if these assumptions are true. Whilst some hospitals in Scotland do record critical care referrals in electronic records, this is certainly not standard practice nationwide. Even if it became standard practice, it would still fail to capture such cases where critical care referral is considered, but there is a recognition that the patient could not benefit, and so referral is not made.

Similarly, I observed overwhelming levels of missing data for cancer stage from SMR06. Missing data for cancer stage in registry data is unfortunately common. Sogaard and Olsen 2012 noted missing data for ‘two-thirds of prostate cancer patients and more than half of bladder cancer patients’. They also note that this missing data is likely not at random (MNAR), where missing data increases for more comorbid and elderly patients (Sogaard and Olsen 2012). My attempt to gain further information on disease stage for some patients shows potential in using other health care records such as SMR01, identifying an additional substantial proportion of patients. However, the degree of clarity in classification is poor. I cannot say with certainty that the ‘Metastatic Disease Known’ variable identifies all patients with Stage IV disease, or that it doesn’t

include patients with other metastatic cancers. As such, the descriptions of differences between groups is the total extent that these variables will be used for in this thesis, and other methods to identify patients with similar disease stages are used in the following chapters.

The last key limitation starting to emerge at this point is the criteria set for Organ Support. Including all patients who received any form of Organ Support in critical care, does not accurately stratify the 'Critically Ill' from those that are not. There will be patients in this cohort who received organ support for less than 24 hours in total, perhaps some metaraminol post operatively, or had delayed extubation following major surgery, or even on their routine renal replacement therapy, and do not meet most intensivists definition of being truly 'critically ill'. As described in the following chapters, despite this limitation, differences in patient outcomes can still be observed. The final analysis chapter (Chapter 8) uses a stricter cohort definition for those with organ support, to explore their outcomes more specifically.

As strengths for this chapter, despite the point that the cohort of 'organ support' could benefit from a stricter definition, this stratification into 'organ support' versus 'monitoring' is still a progression from previous published work investigating CRC outcomes in critical care, where the standard criteria for critically ill remains 'admission to critical care'. As identified in this chapter, such a definition used in other work is likely inadequate for this population, where the majority of elective admissions receive some treatment in critical care, and critical care admission should be almost considered the normal route. Additionally where I have observed interaction between the variables of nature of hospital admission, and levels of support in hospital, this justifies my initial decision to investigate 6 subcohorts in total, rather than solely stratifying by level of support during admission. Use of routinely collected reg-

istry data has allowed identification of almost 40,000 patients with CRC treated in hospital in Scotland, and allowed for stratification by patient demographics, disease-related, and admission-related factors. The majority of variables of interest have no missing data, and can be included within relevant analysis.

4.4 Conclusion

The work in this chapter has allowed me to demonstrate the meaningful differences in patient characteristics, between the six subcohorts defined by this thesis. In noting these differences, this has highlighted the importance in stratifying the patient population in such a way.

Patients presenting to hospital electively appear already to be on a different cancer course than those who present emergently. Whilst elective patients appear slightly younger, and less comorbid than their emergency counterparts; the key differences for elective patients appears to be their route to diagnosis (greater levels of screening), stage of disease (less metastatic disease), treatments (more operations), and treatment intent (more curative intent).

Patients treated at a ward level cannot be considered to be the “well” cohort when compared against those treated in critical care. Unmeasured factors, likely decisions made by patients and clinicians about the appropriateness of treatments, precludes this. Instead for patients with CRC, those treated in critical care who receive monitoring only should be considered our “well” baseline. These are the patients who are youngest, least comorbid, most likely to be diagnosed through screening, and with an earlier stage of disease.

This chapter has allowed demonstration of the benefits of reliance on registry data, identifying all patients with CRC in Scotland, linking 94% of these patients to records of hospital admission, and using these inpatient records plus registry data to provide information on: baseline patient characteristics, comorbidity, cancer specific measures, and details of hospital admissions. This chapter has also demonstrated some of the deficiencies when relying on registry information, highlighted by considerable lack of information on Anatomic Stage for the majority of patients, and lack of other relevant variables such as functional status or clinical frailty.

Noting the differences in patient characteristics between our six subcohorts, in the following chapters I aim to investigate whether differences translate into outcomes both for CRC treatment receipt and quality, as well as patient centred factors such as overall survival. In investigating such differences, in the following chapters I will look at both unadjusted differences between six subcohorts, as well as investigating any specific adjusted impact of “critical illness” itself (whilst acknowledging my relatively inexact definition of critical illness). Noting the significant differences in demographics between the six subcohorts, it is likely that significant adjustment for these differences will need to be made in the following chapters, both through targeted filtering of subcohorts where appropriate (minimising other differences between subcohorts), and accounting for differences with multivariable regression modelling.

The next chapter, Chapter 5 investigates differences in measures of cancer care quality using the national cancer Quality Performance Indicators.

Chapter 5

Quality Performance Indicators

5.1 Introduction

Colorectal cancer (CRC) care in Scotland is assessed annually at the local, regional, and national level. This programme of auditing tumour specific care was established in March 2012, and is known as the Quality Performance Indicators (QPIs) (Healthcare and Healthcare Improvement 2012). Created with the aim to both measure and minimise variations in quality of cancer care in Scotland, QPIs were developed by the National Cancer Quality Steering Group, following recommendations by the Scottish Cancer Taskforce (Healthier Scotland 2008; Scottish Cancer Taskforce 2021). The taskforce themselves had been created following the 2008 Scottish Government Report “Better Cancer Care, An Action Plan” (Healthier Scotland 2008). This Scottish government report noted that Scottish patients had lower survival for some cancer types than other European countries (Healthier Scotland 2008). This difference in survival was also demonstrated in EURO CARE-5, a pan-European assessment of cancer survival using patients diagnosed between 2000 and 2007. In data from EURO CARE-5, Scotland had an age-standardised 5-year survival rate of CRC of 53.9%, compared to the Northern European average of 59% (Holleczek et al. 2015).

To develop QPIs, each measure of care quality selected was required to have three attributes: being clinically important, with evidence that they impacted clinical outcomes, and being straightforward to measure. Version 1.0 of the Colorectal Cancer QPIs was published in December 2012, and there have been several updates following review of priorities and available evidence. The current version (5.0) was published in September 2025 (National Cancer Quality Steering Group 2025). The timeline of CRC QPIs is shown in Figure 1.2 (Chapter 1, page 23).

Not all patients will be eligible for all QPIs, and each QPI is only measured against the eligible population. QPI versioning did change over the time period covered by this dataset. Version 3.4 was the most recent version covering this time period, and had minimal differences with previous versions. As such Version 3.4 was used for analysis in this chapter. The CRC QPIs of version 3.4 are reproduced in Table 5.1. Version 3.4 has 12 QPIs, although six are divided further, giving 21 targets in total (Dawson 2018).

CRC QPIs can be broadly categorised into pre-operative, peri-operative and post-operative. Those QPIs pertaining to pre-operative management include:

- Radiological staging (QPI 1i and 1ii)
- Pre-operative imaging (QPI 2)
- Pre-treatment multi-disciplinary meeting (QPI 3)

The peri-operative QPIs include:

- Anticipatory stoma care (QPI 4)
- Adequate lymph node yield (QPI 5)
- Neo-adjuvant therapy in appropriate patients (QPI 6)
- Adequate surgical margins (QPI 7i and 7ii)
- Re-operation rates (QPI 8)
- Anastomotic dehiscence rates (QPI 9i and 9ii)

The post-operative QPIs include:

- Post-operative mortality rates at 30 and 90 days (QPI 10i Elective, QPI10i Emergency, QPI 10ii Elective and QPI 10ii Emergency)
- Use of adjuvant chemotherapy in appropriate patients (QPI 11-Stage III and QPI 11-High-Risk Stage II)
- Mortality rates at 30 and 90 days post chemo- or radio-therapy (QPI 12i-30, QPI 12i-90 and QPI 12ii-30)

Each QPI has a minimum target for the proportion of the population that should meet it, and this differs for each indicator. Each QPI aims either for the majority of patients to receive the care described, or for the minority of patients to experience the adverse outcome. As illustration: QPI 1i, assessing the level of radiological staging of disease, states that $\geq 95\%$ of eligible patients should have CT Chest, Abdomen, and Pelvis before definitive treatment of their CRC. A population of interest are considered to meet the QPI if the target is met or exceeded.

When undergoing treatment for CRC, patients with CRC are the largest cohort of patients with solid organ malignancies admitted to surgical intensive care units (44%) (Puxty et al. 2018, 2015). Critical illness during cancer treatment may represent a significant disruption, one that impairs the likelihood of receipt of cancer treatment, and of meeting cancer quality indicators. Recovery from critical illness, with the associated increased hospital length of stay and disability, may postpone or even prevent planned cancer treatments.

In this chapter I describe how rates of attainment of QPI targets differ between the subcohorts of the CRC population. The subcohorts are stratified using the same method as the previous chapters: both by nature of admission (elective versus emergency), and level of care during inpatient admission (ward level, critical care with monitoring, critical care with organ support).

After describing overall differences in QPI attainment, I investigate one QPI (QPI 11) in additional detail. QPI 11 is the quality performance indicator that measures receipt of timely adjuvant chemotherapy, following resection of colorectal cancer with curative intent. Timely adjuvant chemotherapy is associated with decreased disease recurrence and increased survival for patients with colorectal cancer. A recently published meta-analysis found that with each four week delay to starting adjuvant chemotherapy for CRC, patient mortality increases, with a hazard ratio of 1.13. (Hanna et al. 2020).

Scottish QPI (up to but not including V5.0) consider timely adjuvant chemotherapy to be adjuvant chemotherapy commenced within 12 weeks of surgical resection. I aimed to determine whether receiving organ support during hospital stay was associated with changes in receipt of adjuvant chemotherapy, as measured by QPI 11. As discussed later, Version 5.0 takes on the findings of Hanna et al. 2020 and other work, and tightens the target to chemotherapy within 8 weeks of surgical resection. In this chapter I assess performance against the target set at the time of care, which was a target of 12 weeks. Another noteworthy point for the patient population assessed by QPI 11, is that the eligible population includes only those between 50 and 74 years of age, excluding a significant proportion of older patients who do receive adjuvant chemotherapy.

I hypothesised that patients receiving organ support would have lower rates of QPI attainment, and that patients admitted as an emergency to hospital would have lower rates of QPI attainment than patients admitted electively. Additionally, I hypothesised that critical illness would be negatively associated with attainment of timely adjuvant chemotherapy (QPI 11).

Table 5.1: Quality Performance Indicators: Titles, Variable Labels, & Descriptions,

QPI 1: Radiological Diagnosis and Staging
QPI1i, QPI1ii
Patients with colorectal cancer should be evaluated with appropriate imaging to detect extent of disease and guide treatment decision making.
Proportion of patients with colorectal cancer who undergo CT chest, abdomen and pelvis (colorectal cancer) plus MRI pelvis (rectal cancer only) before definitive treatment.
i: Colon cancer who undergo CT chest, abdomen and pelvis; and
ii: Rectal cancer who undergo CT chest, abdomen and pelvis, and MRI (pelvis).
QPI 2: Pre-Operative Imaging of the Colon
QPI2
Patients with colorectal cancer undergoing elective surgical resection should have the whole colon visualised pre-operatively.
Proportion of patients with colorectal cancer who undergo elective surgical resection who have the whole colon visualised by colonoscopy or CT Colonography pre-operatively, unless the non-visualised segment of colon is to be removed
QPI 3: Multi-Disciplinary Team (MDT) Meeting
QPI3
Patients should be discussed by a multi-disciplinary team prior to definitive treatment.
Proportion of patients with colorectal cancer who are discussed at MDT meeting before definitive treatment.
QPI 4: Stoma Care
QPI4
Patients with colorectal cancer who require a stoma are assessed and have their stoma site marked pre-operatively by a nurse with expertise in stoma care.
Proportion of patients with colorectal cancer who undergo elective surgical resection which involves stoma creation who are seen and have their stoma site marked pre-operatively by a nurse with expertise in stoma care.
QPI 5: Lymph Node Yield
QPI5
For patients undergoing resection for colorectal cancer the number of lymph nodes examined should be maximised.
Proportion of patients with colorectal cancer who undergo surgical resection where 12 lymph nodes are pathologically examined.
QPI 6: Neo-adjuvant Therapy
QPI6
Patients with locally advanced rectal cancer should receive neo-adjuvant therapy designed to facilitate a margin-negative resection.
Proportion of patients with locally advanced rectal cancer with threatened or involved circumferential resection margin (CRM) on preoperative MRI who receive neo-adjuvant therapy, designed to facilitate a margin-negative resection, defined as:
(i) Long course chemoradiotherapy
(ii) Long course radiotherapy
(iii) Short course radiotherapy with long course intent (delay to surgery*); or
(iv) Neo-adjuvant chemotherapy.
QPI 7: Surgical Margins
QPI7i, QPI7ii
Rectal cancers undergoing surgical resection should be adequately excised.
Proportion of patients with rectal cancer who undergo surgical resection in which the circumferential margin is clear of tumour. Please note:
(i) Primary surgery, or immediate / early**surgery following neo-adjuvant short course radiotherapy; and
(ii) Surgery following neo-adjuvant chemotherapy, long course chemoradiotherapy, long course radiotherapy, or short course radiotherapy with long course intent (delay to surgery*).
QPI 8: Re-operation Rates
QPI8
For patients undergoing surgery for colorectal cancer re-operation should be minimised
Proportion of patients who undergo surgical resection for colorectal cancer who return to theatre to deal with complications related to the index procedure (within 30 days of surgery)
QPI 9: Anastomotic Dehiscence
QPI9i, QPI9ii
For patients who undergo surgical resection for colorectal cancer anastomotic dehiscence should be minimised.
Proportion of patients who undergo surgical resection for colorectal cancer with anastomotic leak as a post operative complication.
(i) Colonic anastomosis; and
(ii) Rectal anastomosis (including anterior resection with total mesorectal excision (TME))
QPI 10: 30 and 90 Day Mortality Following Surgical Resection
QPI10i_elec, QPI10i_emerg, QPI10ii_elec, QPI10ii_emerg
Mortality after surgical resection for colorectal cancer.
Proportion of patients with colorectal cancer who die within 30 or 90 days of emergency or elective surgical resection.
(i) Proportion of patients with colorectal cancer who undergo emergency or elective surgical resection who die within 30 days of surgery.
(ii) Proportion of patients with colorectal cancer who undergo emergency or elective surgical resection who die within 90 days of surgery.
QPI 11: Adjuvant Chemotherapy
QPI11_C, QPI11_B
Patients with Dukes C and high-risk Dukes B colorectal cancer should be considered for adjuvant chemotherapy.
Proportion of patients between 50 and 74 years of age at diagnosis with Dukes C, or high-risk Dukes B†, colorectal cancer who receive adjuvant‡ chemotherapy
† High risk Dukes B colorectal cancer is defined as patients with (pT4a or pT4b disease) with / without extramural venous invasion, or pT3 pN0 M0 with extramural venous invasion. ‡ Adjuvant chemotherapy in this instance is defined as chemotherapy treatment which commences within 12 weeks of surgical resection.
QPI 12: 30 and 90 Day Mortality Following Chemotherapy or Radiotherapy
QPI12i_30, QPI12i_90, QPI12ii_30
Mortality after chemotherapy or radiotherapy treatment for colorectal cancer.
Proportion of patients with colorectal cancer who die within 30 or 90 days of chemotherapy or radiotherapy treatment..
(i) Proportion of patients with colorectal cancer who undergo neo-adjuvant chemoradiotherapy, radiotherapy or adjuvant chemotherapy with curative intent who die within 30 or 90 days of treatment.
(ii) Proportion of patients with colorectal cancer who undergo palliative chemotherapy who die within 30 days of treatment

Adapted from Colorectal Cancer Measurability Criteria v3.4 (Dawson 2018)

5.2 Methods

5.2.1 Data Sources

Data stored on the Scottish National Safe Haven as part of the Colorectal Cancer Repository (CORECT-R) was used for this analysis. This contained information from:

- SMR06 - Scottish Cancer Repository
- SMR01 - Daycase and Inpatient Information
- SICSAAG - Critical Care Admission and Level of Support
- QPI - Quality Performance Indicator Attainment

Patient information was collated and joined as described in Chapter 3.

Analysis in this chapter was dependent on information from the Scottish QPI dataset. As noted in Chapter 4, anatomic stage could not be adequately interpreted using SMR06. Instead, the work of this chapter uses anatomic stage as recorded in the QPI dataset. As a result, the population available for analysis was limited to 15,477 patients as shown in Figure 5.1.

5.2.1.1 Defining Clinically Meaningful Difference

No consensus or recommendations exist in oncology literature regarding clinically meaningful differences for QPI attainment rates. As a result I took a statistical approach to define Minimum Clinical Important Difference (MCID) in this chapter; where the Region of Practical Equivalence (ROPE) is set at the range of -0.1 to 0.1 of a standardised parameter (Makowski et al. 2019a; Kruschke 2018).

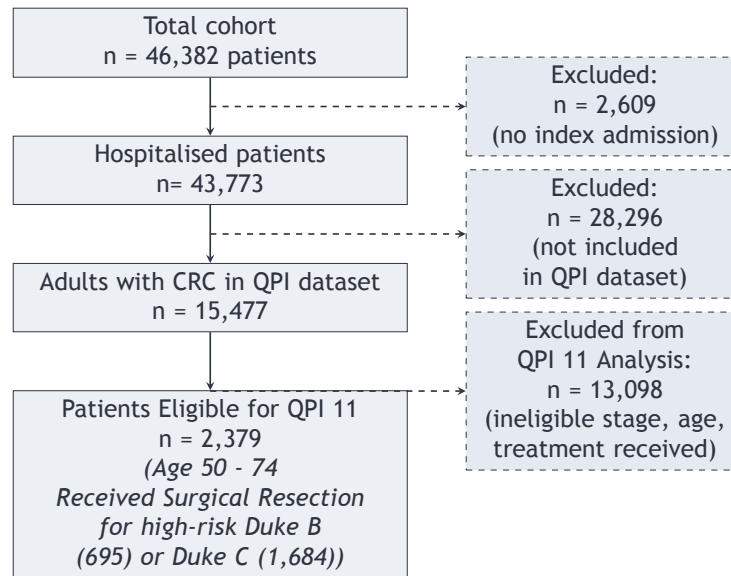


Figure 5.1: CONSORT diagram showing patient selection for QPI analysis. QPI dataset used for demographics and QPI attainment. ‘Patients Eligible for QPI 11’ used for multivariable analysis

I defined ROPE as 10% of the standard deviation from the baseline target (Makowski et al. 2019a). Taking the range of targets from Scottish CRC QPIs, including only those that focused on clinical care, the average target for a measure of cancer care quality was 91%. This 91% target would have a standard deviation of 0.28, with ROPE of 0.028 (2.8%), rounded to 3%.

Using this approach, ROPE for OR of achieving CRC QPI’s was set at range of -0.03 to 0.03. Use of this 3% difference in odds as the threshold for MCID, coincidentally is comparable to estimates for MCID in a range of critical care trials from Yarnell et al. 2021 (Yarnell et al. 2021).

5.2.1.2 Probability of Effect Size

Variable selection for Bayesian multivariable regression was performed through initial univariable analysis, allowing for selection of variables which appeared likely to have an impact on the outcomes of interest. Probability of direction (PD) was used to set the threshold for variable inclusion in multivariable analysis. $PD \geq 95\%$ was selected as the threshold, being analogous to the frequentist threshold of $p \leq 0.1$.

5.2.1.3 Model Creation

Multivariable models were developed repeatedly using differing priors (uninformative, sceptical, optimistic, and pessimistic), with baseline values for each model priors set following the recommendations of Zampieri et al. 2021. Zampieri and colleagues recommend that an uninformative / weakly informative prior should have 95% of the probability distribution sit between OR values of $\frac{1}{2}$ and 2 (i.e. $N(\mu = 0, \sigma = 0.355)$). For a sceptical prior, they recommend that 95% of the probability distribution should sit between OR values of $\frac{1}{1.5}$ and 1.5. For Optimistic, and Pessimistic priors they recommend a distribution centred on the expected OR, that still allows for the opposite to the expected outcome occurring (e.g benefit was expected but harm is observed). See Section 2.3.2.1 for more details on specifying prior beliefs.

Prior distributions' baseline values for Mean and Standard Deviation are provided below:

- **Uninformative** $\sim$ Normal(Mean (μ) = 0, Standard Deviation (σ) = 0.355)
- **Sceptical** $\sim$ Normal($\mu = 0, \sigma = 0.205$)
- **Optimistic** $\sim$ Normal($\mu = 0.15, \sigma = 0.205$)
- **Pessimistic** $\sim$ Normal($\mu = -0.15, \sigma = 0.205$)

Each model included: 10 chains, 1000 burn-in steps, and 5000 total steps.

The nature of admission to hospital (Elective, Emergency) and level of support received in hospital (Ward Level, Monitoring, Organ Support) were considered to be interacting variables. To aid interpretation of this interaction, result summaries are provided as if the combination were a single variable (as opposed to providing a main and interaction effect). In result summaries, the comparator for each of these four groups, are patients with the same nature of admission being monitored in critical care.

- *elective_os* - Elective Admission receiving Organ Support
- *elective_ward* - Elective Admission receiving Ward Care
- *emergency_os* - Emergency Admission receiving Organ Support
- *emergency_ward* - Emergency Admission receiving Ward Care

Where inclusion of variables from single variable models would have introduced duplication, such as the combination of Age At Diagnosis (continuous variable) with Age Group (ordinal factor), or comorbidity specific variables with comorbidity counts, variable selection was made on the basis of model parsimony. Summary of the model used is provided in Table 5.2.

Table 5.2: Summary of Bayesian Models Used in QPI Analysis

Model ID	Outcome of Interest	Model Family	Variables Included
QPI 11	Attaining QPI 11 (Timely Adjuvant Chemotherapy)	Bernoulli	Support In Hospital * Nature of Admission + Age + CRC Stage + Comorbidities (N) + Hospital Length of Stay (Days) + Method of Diagnosis + Sex + SIMD Quintile

5.3 Results

5.3.1 Demographics

15,477 patients were identified and categorised into subcohorts within the QPI dataset. The characteristics of each are shown in Table 5.3, along with results of Bayes Factor testing for differences between subcohorts. An introduction to the use of Bayes Factor in Null Hypothesis Significance Testing is provided in Table 2.1, page 70. As the patients included within the analysis of this chapter are a subset of those included in the total thesis (as noted in Figure 5.1), the following section covers patient demographics for the cohort investigated within this chapter.

5.3.1.1 Patient Characteristics

Among the overall population the median age was 72 years (IQR 63-80), however age distribution differed between the six subcohorts ($BF > 100$). Each Emergency group had a greater median age than their Elective counterpart (increase of 1 to 6 years). Emergency - Ward Level patients were the subcohort with the oldest median age (77 years, 67-84). Elective - Monitoring had the youngest median age (70 years, 61-77).

The overall proportion of female patients was 45%. Most subcohorts had a percentage of female patients within 2% of the population median, however Elective - Organ Support differed, with 39% of the cohort female patients ($BF > 100$).

Within the overall cohort, the proportion of patients in each SIMD quintile sat close to the expected proportion of 20% (Quintile 1 - Most Deprived - 19%, Quintile 5 - Most Affluent - 20%). However there were differences at the extremes of SIMD (BF: Quintile 1: >100, Quintile 5: 22.5). Emergency - Organ Support and Emergency - Ward Level had the greatest proportions of patients from the most deprived quintile (24% and 23% respectively). Elective - Monitoring had the greatest proportion of patients from the most affluent quintile (23%), and the smallest proportion from the most deprived (16%). There was evidence of no difference in proportions of the six subcohorts in the 3 SIMD quintiles in the middle of the distribution (Quintile 2,3,4, BF: <0.01, <0.01, 0.06 respectively).

5.3.1.2 Comorbidities

The overall proportion of patients with no additional comorbidities to cancer was 72%. The subcohorts with the greatest proportion of patients with no additional comorbidities were: Elective - Ward Level (78%) and Elective - Monitoring (77%) (BF >100). The overall proportion of patients with multiple additional comorbidities was 7.3%. The three subcohorts with the greatest proportion of patients with multiple additional comorbidities were: Elective - Organ Support (11%), Emergency - Ward Level (11%), and Emergency - Organ Support (9.7%) (BF >100).

The proportion of patients with named comorbidities differed between the six subcohorts (BF >100). Elective - Organ Support, Emergency - Ward Level, and Emergency - Organ Support had the greatest proportions of patients with each comorbidity. As an example, the population prevalence of Cardiac Disease was 7.8%, but the above three subcohorts had 11%, 11% and 10% (BF > 100). The same was seen for Respiratory Disease, where population prevalence was 10%, and the above three subcohorts had 15%, 13%, and 15% (BF > 100). The only comorbidity where a different pattern

was observed was dementia (overall proportion, 1.6%, BF >100). Ward Level subcohorts had the greatest proportion of patients with dementia in both Elective (1.2%) and Emergency (4%) admissions. Each Emergency subcohort had an equal or greater proportion of patients with dementia, compared to their Elective counterpart.

5.3.1.3 Disease Specific and Admission Characteristics

Looking at the two most common methods of diagnosis: the overall population had 17% diagnosed through screening, 79% through clinical presentation. Patients differed in the proportions diagnosed through screening, clinical presentation, and incidental finding (BF >100). All elective cohorts had $\geq 20\%$ diagnosed through screening (20-26%). All emergency cohorts had $< 5\%$ diagnosed through screening (2.7-4.1%), and all emergency cohorts had $\geq 90\%$ diagnosed through clinical presentation (90-95%).

The median time to diagnosis differed between the six subcohorts (BF >100). With such a majority of emergency patients diagnosed through clinical presentation during their index hospital admission, the median interval between diagnosis and admission in all emergency groups was 0 days. Among elective patients this interval ranged from 44 (21-76) days for Elective - Ward Level, and 67 (40,133) days for Elective - Organ Support patients.

Proportion of patients admitted under surgical specialties differed between subcohorts (BF >100), as did proportion of patients experiencing operations during admission (BF >100). The overall proportion of patients admitted under care of surgical specialties was 85%, and the overall proportion of patients receiving at least one operation during their admission was 68%. Emergency - Ward Level had the smallest proportion of surgical admissions (53%), and operations (16%). Elective - Monitoring

had the greatest proportion of surgical admissions (100%), and operations (95%). The proportion of patients experiencing multiple operations was 10% overall, and the two subcohorts with the greatest proportion of multiple operations were: Elective - Organ Support (25%) and Emergency - Organ Support (22%).

The median hospital length of stay was 8 days. Hospital length of stay increased as the level of support received in hospital increased (BF >100). All emergency subcohorts had longer median lengths of stay than their elective counterpart. As such the subcohort with the longest median length of stay was Emergency - Organ Support (22 days), and the subcohort with the shortest was Elective - Ward Level (5 days).

The overall proportion of patients receiving forms of organ support was similar to the proportions seen within the elective and emergency subcohorts. There was evidence of no difference between elective and emergency organ support patients in regards to the receipt of cardiovascular support (BF 0.099) and renal replacement therapy (BF 0.27). The exception to this was ventilation (BF >100). Among Emergency - Organ Support the proportion of patients receiving ventilation was 51%. Among Elective - Organ Support this proportion was 36%.

Stage IV disease was markedly higher in Emergency - Ward Level (55%) compared to all other groups and overall proportion (23%) (BF >100). Elective critical care groups had the lowest proportion of patients with stage IV disease (Monitoring - 7.5%, Organ Support - 10%) (BF >100). It is worth noting that stage as recorded by QPI is separate to stage as SMR06, and whilst there was missing data (21%, n=3,229), this was not at the same magnitude as the limitations observed with SMR06 recorded values.

Curative intent, as recorded as part of the QPI dataset, was dramatically different between subcohorts (overall proportion 64%, BF >100): greatest in elective critical care subcohorts (Monitoring - 87%, Organ Support - 83%), lesser in emergency critical care (Monitoring - 62%, Organ Support - 62%), and least in Emergency - Ward Level (23%).

5.3.1.4 Summary

The six subcohorts differ between each other in almost all aspects.

Emergency subcohorts tend to be older and more unwell than Elective (both in measures of comorbidity and organ failure during admission); they present with more advanced stages of disease and are less likely to be treated with curative intent. Organ Support patients tend to be more comorbid than patients admitted for monitoring; they are more likely to have multiple admissions and have longer stays in hospital and critical care.

In Elective subcohorts, Ward Level and Monitoring appear to have similar compositions to one another. However, Emergency - Ward Level patients, when contrasted both against Elective - Ward Level, and the other two Emergency subcohorts, have greater levels of patient comorbidity, fewer patients receiving operative intervention, greater proportions of patients with more advanced disease, and a greater proportion of patients treated with non-curative intent.

Table 5.3: Characteristics of Subcohorts Assessed for Quality Performance Indicators

Characteristic	Overall	Elective	Elective	Elective	Emergency	Emergency	Emergency	Bayes Factor
		Ward Level	Monitoring	Organ Support	Ward Level	Monitoring	Organ Support	
	N = 15,477	N = 3,491	N = 5,452	N = 1,182	N = 3,606	N = 1,197	N = 549	
Age At Diagnosis	72 (63, 80)	71 (63, 79)	70 (61, 77)	71 (64, 78)	77 (67, 84)	71 (62, 80)	74 (66, 82)	>100
Female Sex	5,126 (45%)	1,327 (46%)	1,606 (44%)	346 (39%)	1,281 (47%)	392 (47%)	174 (43%)	>100
SIMD (quintile)								-
1	2,911 (19%)	628 (18%)	893 (16%)	219 (19%)	829 (23%)	213 (18%)	129 (24%)	>100
2	3,181 (21%)	681 (20%)	1,086 (20%)	249 (21%)	790 (22%)	260 (22%)	115 (21%)	<0.01
3	3,204 (21%)	725 (21%)	1,143 (21%)	249 (21%)	714 (20%)	262 (22%)	111 (20%)	<0.01
4	3,057 (20%)	751 (22%)	1,100 (20%)	267 (23%)	628 (17%)	214 (18%)	97 (18%)	0.058
5	3,114 (20%)	704 (20%)	1,227 (23%)	198 (17%)	643 (18%)	246 (21%)	96 (18%)	22.5
Comorbidities (N)	-							
None	11,191 (72%)	2,711 (78%)	4,173 (77%)	740 (63%)	2,336 (65%)	879 (73%)	352 (64%)	>100
One	3,152 (20%)	588 (17%)	1,001 (18%)	317 (27%)	871 (24%)	231 (19%)	144 (26%)	>100
Multiple	1,134 (7.3%)	192 (5.5%)	278 (5.1%)	125 (11%)	399 (11%)	87 (7.3%)	53 (9.7%)	>100
Comorbidities (Named)	-							
Cardiac	1,203 (7.8%)	214 (6.1%)	328 (6.0%)	133 (11%)	398 (11%)	73 (6.1%)	57 (10%)	>100
Respiratory	1,587 (10%)	255 (7.3%)	473 (8.7%)	182 (15%)	461 (13%)	135 (11%)	81 (15%)	>100
Renal	970 (6.3%)	202 (5.8%)	215 (3.9%)	83 (7.0%)	342 (9.5%)	80 (6.7%)	48 (8.7%)	>100
Diabetes	1,682 (11%)	302 (8.7%)	561 (10%)	196 (17%)	434 (12%)	117 (9.8%)	72 (13%)	>100
Dementia	242 (1.6%)	43 (1.2%)	27 (0.5%)	5 (0.4%)	143 (4.0%)	14 (1.2%)	10 (1.8%)	>100
Surgical Admission	13,188 (85%)	3,007 (86%)	5,442 (100%)	1,174 (99%)	1,921 (53%)	1,131 (94%)	513 (93%)	>100
Operations	-							
During Admission								
None	5,028 (32%)	1,370 (39%)	285 (5.2%)	98 (8.3%)	3,018 (84%)	176 (15%)	81 (15%)	>100
One	8,887 (57%)	1,922 (55%)	4,407 (81%)	789 (67%)	528 (15%)	894 (75%)	347 (63%)	>100
Multiple	1,562 (10%)	199 (5.7%)	760 (14%)	295 (25%)	60 (1.7%)	127 (11%)	121 (22%)	>100
Diagnosis To Admn (days)	42 (0, 85)	44 (21, 76)	60 (38, 109)	67 (40, 133)	0 (0, 48)	0 (0, 29)	0 (0, 19)	>100
Hospital Duration (days)	8 (5, 15)	5 (2, 9)	8 (6, 12)	14 (8, 24)	8 (3, 19)	14 (9, 22)	22 (12, 39)	>100
Critical Care Duration (days)	1 (0, 3)	NA	2 (1, 4)	5 (3, 7)	NA	3 (2, 4)	5 (3, 9)	>100
Critical Care Planned	5,513 (36%)	NA	4,602 (84%)	674 (57%)	NA	195 (16%)	42 (7.7%)	>100
APACHE II	13.0 (10.0, 17.0)	NA	11.0 (9.0, 13.0)	15.0 (12.0, 19.0)	NA	11.0 (9.0, 15.0)	17.0 (13.0, 22.2)	>100
Organ Support	-							
Vasoactive	1,551 (90%)	NA	NA	1,051 (89%)	NA	NA	500 (91%)	0.099
Ventilated	703 (41%)	NA	NA	425 (36%)	NA	NA	278 (51%)	>100
Renal	105 (6.1%)	NA	NA	62 (5.2%)	NA	NA	43 (7.8%)	0.27
Method of First Detection	-							
Screening	2,678 (17%)	800 (23%)	1,429 (26%)	239 (20%)	146 (4.0%)	49 (4.1%)	15 (2.7%)	>100
Incidental	488 (3.2%)	99 (2.8%)	124 (2.3%)	37 (3.1%)	188 (5.2%)	29 (2.4%)	11 (2.0%)	>100
Clinical	12,225 (79%)	2,561 (73%)	3,864 (71%)	901 (76%)	3,262 (90%)	1,115 (93%)	522 (95%)	>100
Other/Not Known	<0.01							
Not Known	86 (0.6%)	31 (0.9%)	35 (0.6%)	5 (0.4%)	10 (0.3%)	4 (0.3%)	1 (0.2%)	<0.01
Anatomic Stage	-							
0	261 (2.1%)	78 (2.8%)	17 (0.4%)	5 (0.5%)	149 (5.6%)	6 (0.6%)	6 (1.3%)	>100
I	1,709 (14%)	504 (18%)	806 (18%)	171 (17%)	167 (6.2%)	40 (4.1%)	21 (4.6%)	>100
IIA	2,645 (22%)	648 (24%)	1,258 (28%)	247 (25%)	262 (9.8%)	168 (17%)	62 (14%)	>100
IIB	648 (5.3%)	104 (3.8%)	228 (5.1%)	47 (4.8%)	105 (3.9%)	101 (10%)	63 (14%)	>100
III	4,209 (34%)	855 (31%)	1,788 (40%)	412 (42%)	523 (20%)	411 (42%)	220 (49%)	>100
IV	2,776 (23%)	550 (20%)	332 (7.5%)	103 (10%)	1,469 (55%)	242 (25%)	80 (18%)	>100
Unknown	3,229	752	1,023	197	931	229	97	-
Objectives of Treatment	-							
Curative	9,908 (64%)	2,305 (66%)	4,727 (87%)	983 (83%)	814 (23%)	740 (62%)	339 (62%)	>100
Non-curative	5,132 (33%)	1,116 (32%)	540 (9.9%)	160 (14%)	2,729 (76%)	396 (33%)	191 (35%)	>100
Not Known	437 (2.8%)	70 (2.0%)	185 (3.4%)	39 (3.3%)	63 (1.7%)	61 (5.1%)	19 (3.5%)	81.6

Continuous Variables: Mean (IQR). Categorical Variables: N (%). Bayes Factor (BF): Evidence for group differences. Continuous variables analysed using ANOVA Bayes Factor from median and IQR. Categorical variables analysed using contingency table Bayes Factor. $BF \geq 10$ considered strong evidence of difference between groups. $BF \leq 0.1$ considered strong evidence of no difference between groups

5.3.2 QPI Attainment

The six subcohorts differ in rates of QPI attainment (BF 19.6). Table 5.4 reports the number of QPIs achieved, the number missed, and the overall percentage of QPIs achieved, stratified by subcohort. While the overall cohort met 71% (15 of 21) of the QPIs set, Elective - Organ Support had an attainment rate half of this at 33% (7 of 21). Emergency - Organ Support was the lowest performing subcohort, attaining 21% of all QPIs (4 of 19).

Each emergency subcohort achieved a smaller proportion of QPIs than their elective counterpart, and Organ Support subcohorts were the poorest performing subcohorts among elective and emergency admissions. The subcohort meeting the greatest proportion of QPI targets was Monitoring. Elective - Monitoring met 76% (16 of 21) of QPI targets, compared to Elective - Ward meeting 67% (14 of 21). Emergency - Monitoring met 60% (12 of 20) of targets, compared to Emergency - Ward meeting 48% (10 of 21). As noted here, the denominator (the total number of QPIs being assessed against) does change for each subcohort, as subcohorts are excluded when they do not contain any eligible patients.

Table 5.4: Proportion of QPIs Attained By Each Subcohort

	Overall	Elective			Emergency			Bayes Factor
		Ward	Monitoring	Organ Support	Ward	Monitoring	Organ Support	
QPI Met	15	14	16	7	10	12	4	
QPI Failed	6	7	5	14	11	8	15	
Percentage QPI Met (%)	71.4	66.7	76.2	33.3	47.6	60	21.1	19.6

Bayes Factor (BF): Evidence for group differences using contingency table analysis

BF ≥ 10 considered strong evidence of difference. BF ≤ 0.1 considered strong evidence of no difference between groups

Table 5.5 provides detail at the level of each QPI, the target percentage, the percentage achieved by the overall population, and the percentage achieved by each subcohort. When a subcohort achieved the target percentage, the cell in the table has been highlighted in blue. When a subcohort missed the target percentage, the cell has been highlighted in red. Testing for differences between proportions achieving each QPI are reported with Bayes Factors.

Table 5.5: Attainment of Quality Performance Indicators Among Each Subcohort

QPI	Target (%)	Overall N = 15,477	Elective Ward Level N = 3,491	Elective Monitoring N = 5,452	Elective Organ Support N = 1,182	Emergency Ward Level N = 3,606	Emergency Monitoring N = 1,197	Emergency Organ Support N = 549	Bayes Factor
Pre-Operative									
QPI 1i	≥ 95	6,067 (97%)	1,602 (97%)	3,196 (97%)	566 (98%)	504 (92%)	150 (93%)	49 (88%)	>100
Excluded		9,198	1,841	2,164	604	3,061	1,035	493	
QPI 1ii	≥ 95	2,465 (95%)	526 (95%)	1,409 (94%)	345 (95%)	123 (100%)	48 (94%)	14 (82%)	>100
Excluded		12,873	2,936	3,957	819	3,483	1,146	532	
QPI 2	≥ 95	7,581 (91%)	1,955 (94%)	4,317 (91%)	859 (91%)	256 (86%)	153 (79%)	41 (67%)	>100
Excluded		7,144	1,412	691	240	3,309	1,004	488	
QPI 3	≥ 95	12,210 (96%)	3,134 (96%)	5,099 (98%)	1,033 (98%)	2,532 (91%)	305 (91%)	107 (89%)	>100
Excluded		2,711	225	255	128	811	863	429	
Peri-Operative									
QPI 4	≥ 95	2,607 (92%)	538 (94%)	1,412 (92%)	377 (91%)	168 (92%)	87 (93%)	25 (86%)	>100
Excluded		12,658	2,921	3,924	767	3,423	1,103	520	
QPI 5	≥ 90	7,103 (89%)	1,540 (89%)	3,550 (89%)	717 (88%)	440 (89%)	574 (91%)	282 (90%)	>100
Excluded		7,499	1,754	1,456	369	3,114	569	237	
QPI 6	≥ 90	145 (69%)	6 (75%)	105 (67%)	25 (74%)	3 (75%)	6 (100%)	0	>100
Excluded		15,268	3,483	5,295	1,148	3,602	1,191	549	
QPI 7i	≥ 95	1,346 (95%)	308 (94%)	824 (95%)	214 (96%)	0	0	0	>100
Excluded		14,061	3,162	4,587	960	3,606	1,197	549	
QPI 7ii	≥ 85	897 (87%)	169 (91%)	539 (87%)	121 (83%)	42 (89%)	23 (79%)	3 (100%)	>100
Excluded		14,450	3,306	4,835	1,036	3,559	1,168	546	
QPI 8	≤ 10	129 (3.7%)	8 (1.2%)	48 (2.7%)	49 (15%)	7 (3.0%)	6 (1.7%)	11 (7.4%)	>100
Excluded		11,955	2,832	3,648	848	3,375	852	400	
QPI 9i	≤ 5	168 (3.5%)	14 (1.3%)	34 (1.6%)	51 (13%)	11 (2.5%)	22 (4.0%)	36 (18%)	>100
Excluded		10,695	2,435	3,308	789	3,167	649	347	
QPI 9ii	≤ 10	167 (4.9%)	16 (2.1%)	77 (3.8%)	60 (17%)	5 (4.5%)	0 (0%)	9 (17%)	>100
Excluded		12,049	2,718	3,441	833	3,496	1,065	496	
Post-Operative									
QPI 10i	≤ 3	133 (1.5%)	17 (0.8%)	33 (0.7%)	67 (6.7%)	6 (1.8%)	3 (1.3%)	7 (9.1%)	>100
Elective									
Excluded		6,648	1,328	423	179	3,272	974	472	
QPI 10ii	≤ 4	146 (7.6%)	8 (10%)	4 (2.1%)	16 (16%)	27 (6.5%)	23 (3.0%)	68 (17%)	>100
Emergency									
Excluded		13,549	3,414	5,260	1,085	3,191	440	159	
QPI 11i	≤ 15	207 (2.3%)	29 (1.3%)	61 (1.2%)	86 (8.6%)	9 (2.7%)	10 (4.5%)	12 (16%)	>100
Elective									
Excluded		6,648	1,328	423	179	3,272	974	472	
QPI 11ii	≤ 20	223 (12%)	10 (13%)	8 (4.2%)	19 (20%)	41 (9.9%)	53 (7.0%)	92 (24%)	>100
Emergency									
Excluded		13,549	3,414	5,260	1,085	3,191	440	159	
QPI 12i	≤ 1	22 (0.5%)	8 (0.8%)	8 (0.4%)	0 (0%)	1 (0.3%)	4 (1.1%)	1 (1.1%)	<0.01
30d									
Excluded		11,274	2,527	3,382	833	3,228	848	456	
QPI 12ii	≤ 1	55 (1.3%)	18 (1.9%)	16 (0.8%)	5 (1.4%)	6 (1.6%)	7 (2.0%)	3 (3.2%)	<0.01
90d									
Excluded		11,274	2,527	3,382	833	3,228	848	456	
QPI 12iii	≤ 10	123 (8.9%)	26 (7.5%)	8 (3.7%)	1 (2.2%)	78 (13%)	7 (4.9%)	3 (8.6%)	>100
30d									
Excluded		14,101	3,143	5,236	1,136	3,017	1,055	514	
QPI 11	≥ 70	1,339 (80%)	343 (91%)	692 (84%)	87 (58%)	80 (69%)	107 (73%)	30 (41%)	>100
III									
Excluded		13,793	3,114	4,631	1,033	3,490	1,050	475	
High-Risk II	≥ 50	426 (61%)	107 (73%)	199 (65%)	27 (40%)	21 (45%)	62 (70%)	10 (26%)	>100
Excluded		14,782	3,345	5,145	1,114	3,559	1,108	511	
Subcohort achieved QPI target					Subcohort did not achieve QPI target				

Bayes Factor (BF): Evidence for group differences. Categorical variables analysed using contingency table Bayes Factor. BF ≥ 10 considered strong evidence of difference between groups. BF ≤ 0.1 considered strong evidence of no difference between groups

Reviewing each QPI individually in Table 5.5, there were six QPIs where the overall population did not meet the target set:

- QPI 2: Patients undergoing elective resection should have whole colon visualised pre-operatively (Target $\geq 95\%$, Achieved by 91% of the overall cohort)
- QPI 4: Patients who require a stoma should be assessed and have their site marked preoperatively by a stoma nurse (Target $\geq 95\%$, Achieved by 92% of the overall cohort)
- QPI 5: For patients undergoing resection, the number of lymph nodes examined should be maximised (Target $\geq 90\%$, Achieved by 89% of the overall cohort)
- QPI 6: Patients with locally advanced rectal cancer should receive neo-adjuvant therapy, with aim of a margin-negative resection (Target $\geq 90\%$, Achieved by 69% of the overall cohort)
- QPI 10i: Emergency 30 day mortality after emergency surgical resection (Target $\leq 4\%$, Experienced by 7.6%)
- QPI 12i: 90 day mortality after chemotherapy or radiotherapy, given with curative intent (Target $\leq 1\%$, Experienced by 1.3%)

When comparing the six subcohorts, the proportion of patients achieving the standard of care differed for almost all QPIs. Only two of the 21 targets assessed did not show evidence of difference: QPI 12i at 30 days, and 90 days. These targets were the QPI assessing mortality of patients at 30 and 90 days following curative chemotherapy or radiotherapy. In the case of 90 day mortality, there was evidence of no difference as the majority (five of the six) failed to meet the national target.

Pre-operative management QPIs included radiological staging (QPI 1i and 1ii), pre-operative imaging (QPI 2) and pre-treatment multi-disciplinary meeting (QPI 3). The overall population met three (75%) of these four QPI targets with variation demonstrated by sub-cohorts. No sub-cohort met the target for adequate pre-operative

imaging (QPI 2), although elective patients were closer to the 95% target than emergency patients (Ward level 94% vs. 86%; Monitoring 91% vs. 79%; Organ support 91% vs. 67%). Emergency patients managed in critical care with either monitoring or organ support failed to meet any of the pre-operative QPI targets.

Peri-operative QPIs included anticipatory stoma care (QPI 4), adequate lymph node yield (QPI 5), neo-adjuvant therapy in appropriate patients (QPI 6), adequate surgical margins (QPI 7i and 7ii), re-operation rates (QPI 8) and anastomotic dehiscence rates (QPI 9i and 9ii). None of the cohorts met the target threshold for QPIs 4 or 5. Elective patients that received organ support had the poorest performance with only one of the eight peri-operative QPI targets met.

Post-operative QPIs included post-operative mortality rates at 30 and 90 days (QPI 10i Elective, QPI 10i Emergency, QPI 10ii Elective and QPI 10ii Emergency), use of adjuvant chemotherapy in appropriate patients (QPI 11- Stage III and QPI 11- High-Risk Stage II), and mortality rates at 30 and 90 days post chemo- or radio-therapy (QPI 12i_30, QPI 12i_90 and QPI 12ii_30). Post-operative QPI attainment was notably lower in the organ support cohorts when compared to the critical care monitoring groups (Elective 33.3% vs. 76.2%; Emergency 22.2% vs. 88.9%).

Meeting 21% of the total QPI targets, the Emergency - Organ Support subcohort failed to meet national targets for: pre-operative staging and imaging, multidisciplinary decision-making, stoma care, intraoperative lymph node yield, anastomotic dehiscence, mortality post-operatively, receipt of adjuvant chemotherapy, or mortality following chemotherapy and radiotherapy with curative intent.

Increased mortality (QPI 10) was also evident in the Organ Support subcohort. 90-day mortality following elective surgical resection was 1.2% among Elective - Monitoring. Elective - Organ Support had a 90-day mortality 7 times greater, at 8.6%. 90 day mortality following emergency surgical resection was 7% among Emergency - Monitoring. Emergency - Organ Support had a 90-day mortality of 24%.

5.3.3 QPI 11 - Adjuvant Chemotherapy

Access to timely adjuvant chemotherapy (QPI 11), was defined by Scottish QPI programme v3.4 as receipt of adjuvant chemotherapy within 12 weeks of surgical resection, and has different targets for patient percentages depending on anatomic stage. This difference reflects that the evidence for benefit of adjuvant SACT is more clear for patients with Stage III disease (and for patients with more advanced stage III disease) than it is for patients with High Risk Stage II disease (Argilés et al. 2020; Sobrero et al. 2020). As such QPI v3.4 had a target of 70% attainment for patients with Stage III disease, and 50% for patients with High Risk Stage II disease. 1,684 patients (11% of total cohort) were eligible for assessment against QPI 11 - Stage III disease. The overall population of eligible patients met the target, with 80% (n = 1,339) attainment.

There were differences in attaining QPI 11 for Stage III disease between the six subcohorts (BF >100). Three of the six individual subcohorts met the target: Elective - Ward Level (91%, n = 343), Elective - Monitoring (84%, n = 692), and Emergency - Monitoring (73%, n = 107). The remaining three all failed to meet the target: Emergency - Ward Level (69%, n = 80), Elective - Organ Support (58%, n = 87), and Emergency - Organ Support (41%, n = 41).

High-Risk Stage II disease had a QPI target of 50% attainment. 695 patients (4.5% of total population) were eligible for assessment against QPI 11 - High-Risk Stage II disease. The overall population of eligible patients met this target, with 61% (n = 426) attainment. Proportion of patients attaining QPI 11 for High-Risk Stage II disease differed between the six subcohorts (BF >100). As before, the same three subcohorts met this target: Elective - Ward Level (73%, n = 107), Elective - Monitoring (65%, n = 199), and Emergency - Monitoring (70%, n = 62). The remaining three failed to meet the target: Emergency - Ward Level (45%, n = 21), Elective - Organ Support (40%, n = 27), and Emergency - Organ Support (26%, n = 10).

When combining patients with High-Risk Stage II and Stage III disease into a single 'QPI 11' (the actual QPI 11 separates by stage, this composite value has been included for ease of comparison): timely adjuvant chemotherapy was administered to 1765 of 2,379 eligible patients (74.2%). Among Elective - Organ Support only 114 out of 217 eligible patients received timely adjuvant chemotherapy (52%), and for Emergency - Organ Support this dropped further to 40 out of 112 (36%). 47% (n = 154) of all eligible Organ Support patients attained this composite QPI 11, compared to the 74% (n = 1765) of the total patient population.

Organ Support patients consistently demonstrated the lowest QPI 11 attainment rates across all subcohorts. For Stage III disease, Elective - Organ Support patients had a 26 percentage point lower attainment rate (58%) than Elective - Monitoring patients (84%), while Emergency-Organ Support patients had a 32 percentage point lower rate (41%) than Emergency-Monitoring patients (73%).

5.3.3.1 Multivariable Analysis

In subsequent models, due to small patient numbers, QPI 11 Stage III and High-Risk Stage II have been combined into a single QPI 11 variable. A “stage of disease” variable clarifying whether a patient had High-Risk Stage II or Stage III disease has been included in models

Figure 5.2 provides results of the single variable models that were used, ran to determine variable inclusion into multivariable analysis. Posterior probability distributions, estimating each variable’s impact on the Odds Ratio of achieving QPI 11 were generated. Table 5.6 summarises these probability distributions, providing estimates of distribution in central tendency (median), 95% credible intervals, and the probability of direction.

Variables from Table 5.6 that reached the PD threshold of 95% were included in the multivariable model. For the avoidance of collinear variables, and model brevity: age at diagnosis (years) was included rather than the factor variable age grouped by decade. Comorbidity count was included in multivariable analysis rather than the single variables for each individual comorbidity.

Initial single variable analysis reported that the presence of two or more comorbidities was the variable most associated with decreased odds of achieving QPI 11 (Median 0.25, 95% CrI 0.17-0.36). Receipt of organ support (the proxy measure for experiencing critical illness) was the variable with the second greatest negative association with odds of achieving QPI 11 in single variable analysis (Median 0.29, 95% CrI 0.23-0.37). The single variable associated with the greatest increase in odds of achieving QPI 11 was the presence of Stage III disease (contrasted against High-Risk Stage II) (Median 2.3, 95% CrI 1.91-2.77).

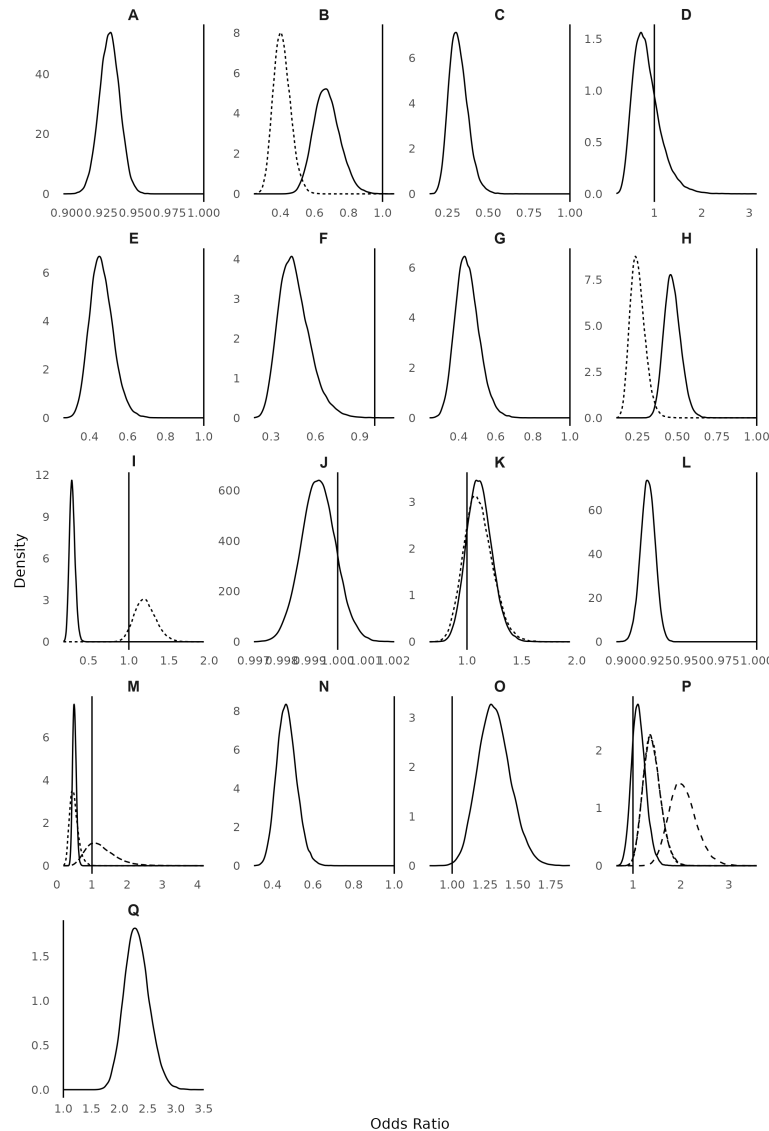


Figure 5.2: Posterior probability distributions of the odds ratio for achieving QPI 11 (timely adjuvant chemotherapy), from univariable logistic regression models fitted to each variable. Vertical line at OR 1 (no effect). Facet key provides title and comparator for each variable

Table 5.6: Summary of posterior probability distributions of the odds ratio for achieving QPI 11 (timely adjuvant chemotherapy), from univariable logistic regression models fitted to each variable.

Variable	Median	95% CrI	PD (%)	Threshold Reached
Age at diagnosis per increase in age by one year	0.93	(0.92 - 0.95)	100.00	TRUE
Age 60-69 vs age <60	0.67	(0.54 - 0.83)	99.98	TRUE
Age 70-79 vs age <60	0.41	(0.32 - 0.52)	100.00	TRUE
Diagnosis-to-admission per increase in interval by one day	1.00	(1 - 1)	86.73	FALSE
Cardiac vs no cardiac comorbidity	0.31	(0.22 - 0.44)	100.00	TRUE
Dementia vs no dementia	0.80	(0.42 - 1.55)	74.68	FALSE
Diabetes vs no diabetes	0.46	(0.36 - 0.59)	100.00	TRUE
Renal vs no renal comorbidity	0.45	(0.29 - 0.7)	99.98	TRUE
Respiratory vs no respiratory comorbidity	0.44	(0.34 - 0.58)	100.00	TRUE
One additional Charlson comorbidity count vs zero	0.47	(0.38 - 0.58)	100.00	TRUE
Two+ additional Charlson comorbidity count vs zero	0.25	(0.17 - 0.36)	100.00	TRUE
Organ Support vs Monitoring	0.29	(0.23 - 0.37)	100.00	TRUE
Ward Level vs Monitoring	1.20	(0.97 - 1.49)	94.97	FALSE
Dx in 2015-2016 vs 2013-2014	1.11	(0.9 - 1.35)	83.98	FALSE
Dx in 2017-2018 vs 2013-2014	1.10	(0.87 - 1.38)	78.59	FALSE
Duration of hospital stay per increase in duration by one day	0.92	(0.91 - 0.93)	100.00	TRUE
Diagnosis clinical presentation vs screening	0.50	(0.41 - 0.61)	100.00	TRUE
Diagnosis incidental finding vs screening	0.47	(0.29 - 0.78)	99.86	TRUE
Diagnosis other/not known vs screening	1.19	(0.62 - 2.28)	70.04	FALSE
Emergency Admission vs Elective	0.47	(0.38 - 0.57)	100.00	TRUE
Female vs Male	1.32	(1.1 - 1.58)	99.84	TRUE
SIMD Quintile 2 vs 1	1.11	(0.86 - 1.44)	79.97	FALSE
SIMD Quintile 3 vs 1	1.39	(1.08 - 1.78)	99.51	TRUE
SIMD Quintile 4 vs 1	1.39	(1.07 - 1.8)	99.39	TRUE
SIMD Quintile 5 vs 1	2.02	(1.55 - 2.66)	100.00	TRUE
Stage III vs High Risk II	2.30	(1.91 - 2.77)	100.00	TRUE
<i>CrI - Credible Interval</i>				
<i>PD - Probability of Direction</i>				
<i>Threshold noted for potential inclusion in subsequent multivariable model $\geq 95\%$</i>				

Outputs from the multivariable model are described in the following section. Figure 5.3 and Table 5.7 provide the results of the multivariable regression analysis using uninformative priors. In the appendix, Table B.1 provides the results of the other variables included in the model. As a point of clarification when interpreting results, nature of admission (elective vs emergency), and level of support were treated as interacting variables in the model. This allowed the impact of level of support to differ depending on the nature of hospital admission. Initial model summaries in R provide

both a “main effect” and an “interaction term”, that can be less intuitive to understand. To aid interpretation these have been converted to provide estimates for the combinations of the variable levels (“conditional effects”), as well as the main effect of nature of admission. This provides an overall estimate of the impact of the nature of admission (the “main effect”), as well as showing estimates for: Elective - Organ Support, Elective - Ward Level, Emergency - Organ Support, and Emergency - Ward Level (the “conditional effects”). For Elective subcohorts the comparator is Elective - Monitoring. For Emergency subcohorts the comparator is Emergency - Monitoring.

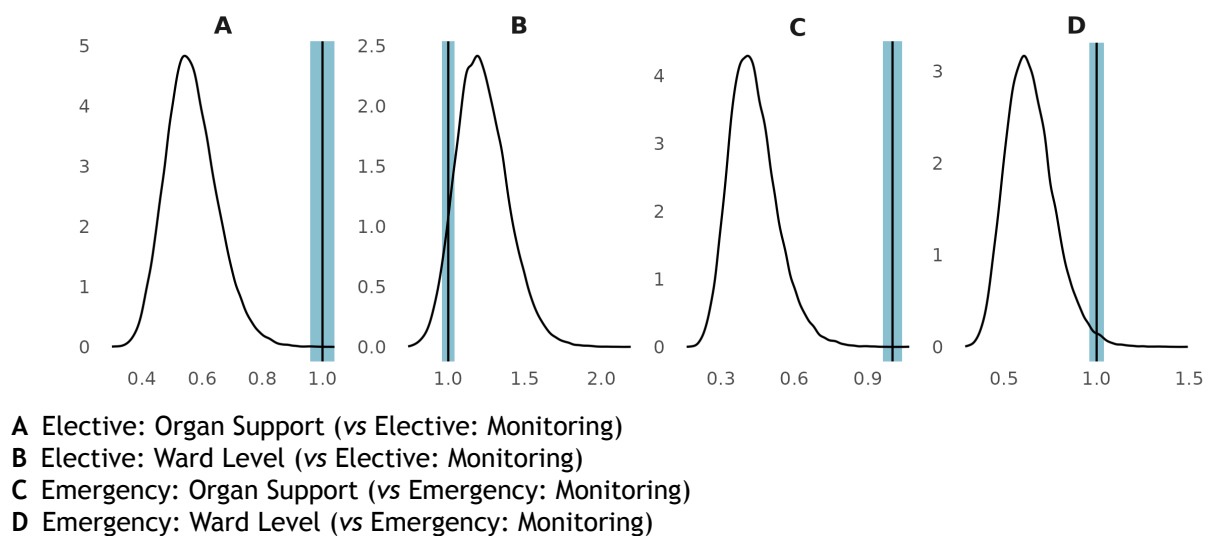


Figure 5.3: Multivariable Analysis Results - Posterior probability distribution of the odds ratio for achieving QPI 11 (timely adjuvant chemotherapy), from multivariable logistic regression model using uninformative priors, for the key variables of interest
 Light blue shaded region indicates region of practical equivalence
 Vertical line indicates OR 1 (no effect)
 Facet key provided for variable names and comparators

Table 5.7: Multivariable Analysis Results - Summary of posterior probability distribution of the odds ratio for achieving QPI 11 (timely adjuvant chemotherapy), from multivariable logistic regression model using uninformative priors, for the key variables of interest, with comparator provided beneath

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease	Percentage Of Largest Effect
Elective: Organ Support <i>vs Elective: Monitoring</i>	0.56	(0.42 - 0.75)	100.00	0.02	0.00	99.98	99.98% chance meaningful reduction
Elective: Ward Level <i>vs Elective: Monitoring</i>	1.21	(0.93 - 1.59)	92.39	8.67	87.17	4.16	87.17% chance meaningful increase
Emergency: Organ Support <i>vs Emergency: Monitoring</i>	0.42	(0.27 - 0.66)	100.00	0.00	0.00	99.99	99.99% chance meaningful reduction
Emergency: Ward Level <i>vs Emergency: Monitoring</i>	0.63	(0.43 - 0.93)	98.90	1.18	0.61	98.20	98.2% chance meaningful reduction
<i>CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease</i>							

5.3.3.2 Level of Support

Receipt of organ support in critical care was associated with a meaningful reduction in the likelihood of patients experiencing timely adjuvant chemotherapy, as measured by QPI 11. This association remains after adjustment for other observed relevant factors. For patients admitted electively, those who received organ support (compared against those monitored in critical care), had a 44% reduction in odds of timely adjuvant chemotherapy (OR 0.56, 95% Credible Interval 0.42-0.75, 99.9% posterior probability). For patients admitted emergently, those who received organ support (compared to those monitored in critical care), had a 58% reduction in odds of timely adjuvant chemotherapy (0.42 0.27-0.66, 99.9%).

Among patients treated at a ward level, impact on the odds of attaining QPI 11 was dependent on the nature of hospital admission. Patients treated at a ward level electively, when compared to those monitored in critical care, may have an estimated 21% increased odds of attaining QPI 11, (OR 1.21, 0.9-1.6, 87% posterior probability). Patients treated in the ward emergently, when compared to those monitored in critical care, had a 39% reduction in odds of attaining QPI 11 (0.63, 0.43-0.93, 98%).

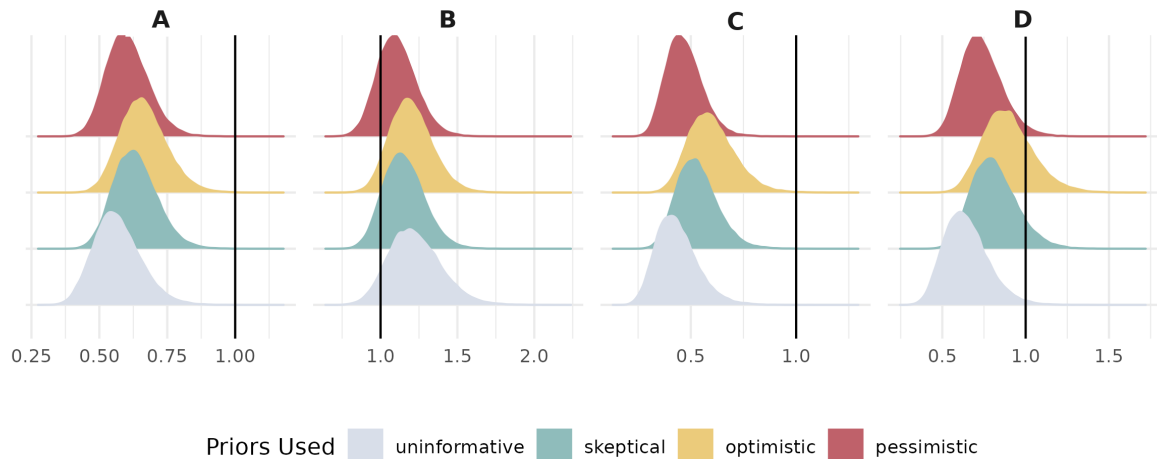
5.3.3.3 Model validity and sensitivity

In addition to reporting results for uninformative priors, sensitivity analysis was undertaken using the sceptical, optimistic and pessimistic priors previously described. Regardless of the choice of priors, posterior estimates for the effect size of organ support still exceeded 97.5% probability of a clinically meaningful difference.

This (arbitrary) threshold for probability of clinically meaningful difference (used to ease comparison between differing priors) was reached in the Emergency - Ward subcohort when using uninformative priors, but was not reached using the other priors. The probability of clinically meaningful difference was least robust in the Emergency - Ward subcohort. Use of all other priors resulted in a greater probability of no clinically meaningful difference. As such the results with the greatest degree of confidence associated with them, are those seen for the relationship between organ support and attainment of QPI 11.

Figure 5.4 demonstrates how estimates of the posterior probability distribution differs for each variable, depending on the priors used (uninformative, sceptical, optimistic, pessimistic). As described above, the likelihood of reaching MCID for the majority of variables is unaffected by choice of model priors. Table 5.8 provides numeric summary for how changing the prior influences the median estimate for Odds Ratio of Attaining

QPI 11, for each of the subcohorts. For Emergency - Organ Support, use of optimistic priors (which assumed receipt of Organ Support would increase likelihood of attaining QPI 11), reduced the estimated impact on Odds Ratio of attaining QPI 11 from: 0.56 to 0.66. For Elective - Organ Support, optimistic priors would reduce the impact of Organ Support on QPI 11 from OR 0.42, to 0.59.



- A Elective: Organ Support (vs Elective: Monitoring)
 B Elective: Ward Level (vs Elective: Monitoring)
 C Emergency: Organ Support (vs Emergency: Monitoring)
 D Emergency: Ward Level (vs Emergency: Monitoring)

Figure 5.4: Sensitivity Analysis - Comparisons of posterior probability distribution of the odds ratio for achieving QPI 11 (timely adjuvant chemotherapy), from multivariable logistic regression models using different prior probability distributions
Facet key provided for variable names and comparators

Table 5.8: Sensitivity Analysis - Summary of comparisons of posterior probability distribution of the odds ratio for achieving QPI 11 (timely adjuvant chemotherapy), from multivariable logistic regression models using different prior probability distributions
Facet key provided for variable names and comparators

[illegible]

Reviewing measures of model validity, the multivariable model chains showed good convergence, with $\hat{R}$ of 1 for each variable. Effective sample size (Bulk ESS), and Tail effective sample size (Tail ESS) were more than adequate for all variables, with the smallest value remaining greater than 30,000. The summary table for model validity is provided in Appendix Table B.2 Posterior predictive check showed good predictive ability of the model when comparing actual values (y), to predicted values (y_{rep}) (Appendix figure B.3). This good fit suggests the model accurately captures relationships in the data, strengthening confidence in the conclusions.

5.4 Discussion

This work is the first to use Colorectal Cancer QPIs to assess quality of cancer care between patient groups, rather than to compare Scottish health boards or national attainment. Rates of QPI attainment differ substantially between the six subcohorts categorised in this thesis. Those who received Organ Support in hospital attained meaningfully fewer QPI targets than those who were treated at the level of Monitoring in Critical Care. Similarly, those who are admitted as an emergency and receive Organ Support achieve fewer targets still.

When assessing the association between the nature of hospital admission and support during admission on cancer care quality: receipt of organ support, is associated with a meaningful decrease in the odds of timely receipt of adjuvant chemotherapy, as measured by CRC QPI 11. Among patients that received organ support there was a reduction in the odds of receiving timely adjuvant chemotherapy of 44% in those admitted electively and 58% in those admitted emergently, when compared to those who received monitoring in critical care. Both of these estimates can be provided along with a >99.9% probability of a clinically meaningful reduction in odds (>3%) of attaining QPI 11.

Compared against patients who received monitoring in critical care, elective ward patients had an estimated 21% increase in odds of receipt of timely adjuvant chemotherapy. The probability of this being a clinically meaningful increase (greater than 3%) was 87%, making this likely, but allowing for approximately a 1 in 7 chance that this observed increase is not present. Emergency ward patients have an estimated 37% reduction in odds of receipt of timely adjuvant chemotherapy, when compared against emergency patients who received monitoring in critical care. The probability of this being a clinically meaningful decrease in odds is 98%.

No previous work published investigates the impact of critical illness on attainment of CRC care quality, as measured by QPIs. Among this cohort of critical illness survivors, the observed rate of receiving timely adjuvant chemotherapy was 47%. This rate appears consistent with other published rates of post-critical care anticancer treatment. Auclin et al. 2017 in their retrospective analysis of 2,327 patients over the age of 65 with solid organ cancers in France; found 52% of all ICU survivors subsequently received anticancer treatment of any form (Auclin et al. 2017). Their cohort did differ to this one, with only 30% of their patients having gastrointestinal cancers, 63% having metastatic disease, and 60% of patients having received chemotherapy prior to critical illness. Their paper did identify rates of anticancer therapy post critical illness higher than other published literature, although their comparisons are to studies of patients with lung cancer specifically. Gheerbrant et al. 2021 in their analysis of adult patients with solid organ cancer and critical illness, found 55% of patients who survived emergency admission to ICU received anticancer treatment at 3 months following hospitalisation. Again their cohort does differ substantially from the cohort used in this analysis. 31% of Gheerbrant's cohort had "digestive" cancers, and 45% had metastatic disease. (Gheerbrant et al. 2021). The lower rate of adjuvant chemotherapy amongst this cohort may be explained by differences observed in cancer site, and cancer stage.

5.4.1 Mechanisms

Several mechanisms could contribute to the reduced level of timely adjuvant chemotherapy observed among patients who experience critical illness. To reiterate, this decreased receipt of timely adjuvant chemotherapy is not related to in-hospital mortality, as patients who died during hospital stay or the first 30 days following discharge are excluded from the analysis. It should not be related to increased rates of patients declining chemotherapy, as such patients are excluded from QPI 11 (however this may not always be accurately recorded).

An increased length of stay following surgical resection could decrease the likelihood of patients receiving adjuvant chemotherapy within 12 weeks following surgery, although hospital length of stay has been adjusted in the models. Patients who experience critical illness are more likely to experience a constellation of physical, cognitive, and psychological impairments known as Post Intensive Care Syndrome (PICS) (Ng et al. 2025; Docherty et al. 2023). With an increased rate of PICS, treating clinicians may feel adjuvant chemotherapy is of increased risk of harm, thus modifying the perceived risk:benefit ratio. Equally, a patient experiencing PICS may be less likely to engage with adjuvant chemotherapy, without declining treatment as such. Last, physical symptoms or ongoing organ dysfunction following critical illness might preclude systemic anti-cancer therapy.

5.4.2 Limitations

This study has several limitations. First as an observational study designed for association it cannot establish causality between organ support and reduced QPI attainment. Secondly it relies on national registry data, putting limitations on the data collected, and on data validity. Whilst I adjusted for measured confounders, several important variables are unmeasured including: clinical decision-making on appropriateness of treatments, clinical frailty, and physical disability. Whilst the dataset included all patients diagnosed with CRC in Scotland over a five year period, when looking at QPI 11 in particular, the sample size was still relatively small, with slightly under 100 patients in the smallest subcohort.

When reviewing QPI definitions (Table 5.1), there are multiple QPIs that may appear incompatible with certain subcohorts. As an example: QPI 2 assesses the population of patients undergoing elective resection, which seems to preclude emergency admission to hospital however my analysis finds several hundred patients with emergency admissions being assessed for QPI 2. As a partial explanation, subcohorts were

defined by the nature of their first hospital admission following diagnosis, not the nature of their surgery. A patient could have an initial emergency admission to hospital, followed by a later elective surgical resection. An alternative explanation may be that this reflects a weakness of national registry information. Nature of hospital admission is recorded in SMR01, where QPI attainment was recorded locally by each treating team. As such there could be errors in coding either nature of hospital admission or eligibility for QPI 2. Considering that greater than 80% of the emergency subcohort patients are excluded from QPI 2 assessment, this suggests that the majority of ineligible patients are correctly excluded. Similarly reassuringly the majority of patients recorded as having Elective admissions are also excluded from Emergency surgery assessment.

With the investigation into timely adjuvant chemotherapy in QPI 11, I used the definition as it existed at the point of patient care, where care was considered timely if received within 12 weeks of surgery. This definition has its weaknesses, in that patients receiving SACT at 11 weeks and 6 days are considered 'timely', whereas those at 12 weeks are considered 'delayed'. Additionally even if such a categorisation were appropriate, it is now outdated as QPI v5 considers receipt within 8 weeks being timely treatment. Other changes in QPI versioning need noting. At the time of patient care, QPI 11 restricted its assessment to patients aged 50-74. This has two issues: it excludes the significant proportion of patients aged greater than 75 who do receive adjuvant SACT, and it excludes the growing number of younger patients being treated for CRC. QPI v5 addresses one of these issues, as now it assesses adult patients from 18 to 75. In the following chapter, Chapter 6 I attempt to account for these limitations, providing detail on cumulative incidence of Adjuvant SACT (demonstrating when patients receive SACT, rather than solely using a simple cut off), and also use the 8 week limit now in place. I also investigate all adult patients, rather than a subset of ages.

As a wider question about the appropriateness of QPIs as a metric of ‘quality care’, in the first half of this chapter I consider QPIs as something akin to a ‘care bundle’, where to achieve a QPI is to meet a measure of cancer care quality, something that should be considered to improve cancer care outcomes. However, there is a gap in the literature here, with no published evidence that attaining CRC QPIs improves patient outcomes. Individual measures such as QPI 11 may be informed by current evidence, however as a package, long term outcomes have not been assessed. This limitation has been recognised by other work. Mariappan et al. 2024 has published evidence that attainment of QPIs for Bladder Cancer is associated with reduced disease recurrence and progression. In Chapter 7, I investigate the association between receipt of Organ Support and a clearly patient centred outcome, long term overall survival.

5.5 Conclusion

Patients who survive critical illness receive poorer quality colorectal cancer care, when using the benchmark of the Scottish Colorectal Cancer QPIs. Patients admitted as an emergency who receive organ support receive care that is even poorer, failing to meet targets on: pre-operative staging and imaging, MDT decision-making, stoma care, intraoperative care and postoperative complications, timely adjuvant chemotherapy, and postoperative mortality.

When investigating receipt of timely adjuvant chemotherapy, even when taking into account the significant differences in: Age, Stage, Comorbidities, Hospital Length of Stay, Method of Diagnosis, Sex, and Deprivation; patients who receive organ support in hospital are less likely to receive timely adjuvant chemotherapy than those that do not.

These findings have important implications for policy and clinical practice. As national cancer care systems continue to expand the use of quality metrics to drive improvement, it is critical that such frameworks account for the needs of complex patients. Inclusion of recovery trajectories and post-ICU follow-up in cancer pathways may help mitigate treatment delays. It may be useful to consider the small proportion of patients that experience critical illness following CRC resection as a particular cohort at high-risk of missing out on originally planned treatment. In doing so, specific follow-up pathways with oncology and critical care may be required for patients who have experienced critical illness, to increase access to appropriate cancer treatments. Future research would be required to investigate both methods to improve access to timely chemotherapy post critical illness, and the appropriateness of doing so. One important variable that this work was not able to investigate, is the impact on functional status following critical illness after cancer surgery, and how physical function or disability impacts access to subsequent cancer care.

In the following chapter I will investigate the relationship between organ support and adjuvant chemotherapy further; exploring whether patients are less likely to receive any adjuvant chemotherapy, or do receive chemotherapy but with a significant delay.

Chapter 6

Systemic Anti-Cancer Therapy

6.1 Introduction

To understand if (or how) critical illness impacts the subsequent cancer journey of patients with colorectal cancer, multiple aspects of systemic anti-cancer therapy (SACT) require investigation. Provision of SACT for CRC is not a single therapy, each indication for SACT differs in terms of: disease stage, eligible patient population, treatment provided, and the goals of treatment. To allow for an interpretable comparison between our subcohorts, and to provide consistency with previous chapters, I chose to focus on one particular indication: adjuvant SACT following surgical resection with curative intent of colorectal cancer, for patients with High-Risk Stage II or Stage III disease.

Investigating the association between receipt of organ support and metrics of adjuvant SACT, in this chapter I analyse two subsets of the total patient population. First all adult patients eligible for adjuvant SACT for the above indication, and subsequently the analysis is restricted to those that received adjuvant SACT.

In Chapter 5 a similar population of patients were investigated when assessing QPI 11. However, QPI 11 in v3.4 restricted its investigation to patients between the age of 50 and 74 years. In this chapter I investigate all adult patients (18 and older) eligible for adjuvant SACT, without an upper age limit. This choice recognises the sizeable proportion of patients aged over 74 who receive adjuvant SACT (detailed later in this chapter), and includes the growing proportion of younger patients (under 50) being diagnosed and treated for CRC. The six subcohorts investigated remain the same as previous chapters, with the patient population stratified by:

- Nature of Hospital Admission: Elective vs Emergency
- Level of Support in Hospital: Ward / Monitoring in Critical Care / Organ Support in Critical Care

I investigated five metrics of SACT, exploring differences in: access to SACT, quality of treatment, and intensity of treatment.

- Receipt of Adjuvant Chemotherapy (SACT A)
- Delay to Commencement of Adjuvant Chemotherapy (SACT B)
- Regime Choice in Adjuvant Chemotherapy (SACT C)
- Dose Delay Between Cycles of Adjuvant Chemotherapy (SACT D)
- Duration of course in weeks of Adjuvant Chemotherapy (SACT E)

6.1.1 Benefits and Receipt of Adjuvant SACT

The European Society for Medical Oncology (ESMO) publishes clear clinical practice guidelines for the treatment of localised colon cancer. Within this, they describe factors that influence the choice of adjuvant therapy following surgical resection as: risk of recurrence, risk of toxicity, and expected benefits from adjuvant chemotherapy (Argilés et al. 2020). For risk of recurrence, they report five year survival after surgical resection alone as: 68-83% for stage II (lower for High-Risk stage II) and 45-65% for

stage III disease. With regards to expected benefits, they report adjuvant SACT provides: patients with High-Risk Stage II disease a 3-4% absolute reduction in mortality following single agent therapy, patients with Stage III disease a 10-15% absolute reduction in mortality following single agent therapy, patients with Stage III disease an additional 4-5% reduction in mortality with addition of a second agent (Argilés et al. 2020).

This thesis arose from the assumption that patient specific differences would likely impact on a patients' likelihood of long-term survival. Sobrero et al. 2020 started from the same assumption; in particular that differences in TNM within anatomic stage (Stage III) would likely impact any additional gain in survival from addition of adjuvant SACT. In their modelling they generated predictions in estimated disease-free-survival gains for patients, dependent on the form of adjuvant SACT received, with 'surgery alone' as the comparator. Considering the addition of fluoropyrimidines as the least burdensome treatment, then 3 months of oxaliplatin, then a further final 3 months of oxaliplatin, they provide estimates for the cumulative gains in DFS for each form of therapy. In doing so they predict for patients with T1N1a: surgery alone would provide 79.6% 3 year DFS, with a gain of 8.7% 3 year DFS from 6 months of dual agent SACT. This would be a relative gain of 1.1x probability of 3 year DFS. For patients with the highest substage of Stage III disease (T4N2b), they predict surgery alone would provide 13.9% 3 year DFS, with a gain of 20.1% from 6 months of dual agent SACT. This would be a relative gain of 2.4x in probability of 3 year DFS. In providing their results in a such a fashion, an individual patient can use their own values and beliefs about risks and benefit, to determine the treatment course most appropriate for them. Sobrero et al. 2020 imagine dialogue between doctor and patient where the patient can reflect on whether any given percentage gain is 'worth' the associated burdens of toxicity, or provides sufficient chance of time alive and disease free. Their work demonstrates

that the ESMO description of 10-15% from one agent, plus 4-5% for an additional agent, only accurately describes the average patient (who in reality does not exist), and that whilst averages provide a useful starting point for any conversation, a more precise patient orientated value would be of more use (Sobrero et al. 2020).

Despite the reported benefit in absolute mortality, not all patients eligible for adjuvant SACT receive it. Boakye et al. 2021 found in their systematic review and meta-analysis of 33 trials of adjuvant SACT for Stage III disease, that 61% of eligible patients received SACT (Boakye et al. 2021). In the previous chapter, we saw that Scottish QPI targets aim for 70% of eligible patients with Stage III disease, and 50% of patients with High-Risk Stage II disease should receive adjuvant SACT (National Cancer Quality Steering Group 2020).

6.1.2 Regime of SACT

As noted above, patients with High-Risk Stage II disease and Stage III disease are currently considered eligible for adjuvant SACT. For patients with Stage III disease the standard treatment offered is fluoropyrimidines in combination with oxaliplatin (Argilés et al. 2020). These combination regimes (CAPOX, FOLFOX) will be referred to as dual agent therapy within this chapter.

For patients with High-Risk stage II disease, the evidence base (and subsequently the recommendations) are less certain. Whilst ESMO recommend dual agent therapy, citing the results of the IDEA trial (Iveson et al. 2019; Argilés et al. 2020), the American Society of Clinical Oncology (ASCO) are less definite, stating in 2021 that dual

agent therapy is: “not routinely recommended, but may be offered as a result of shared decision-making” (Baxter et al. 2022). The receipt of fluoropyrimidines (5FU, Capecitabine) in isolation will be referred to as single agent therapy within this chapter.

6.1.3 Factors Influencing Receipt

Certain patient groups may be expected to have decreased benefits from adjuvant SACT, or increased risks of toxicity. As such they may be considered to have relative contraindications to adjuvant therapy. ESMO state that the following should be considered as relative contraindications to adjuvant SACT: poor performance status (ECOG > 2), and severe comorbidity (hepatic, renal, heart) (Argilés et al. 2020).

ESMO also note that age influences both the benefit and burdens of treatment. Patients over 70 who receive dual agent therapy appear to receive less benefit than younger patients, as well as greater toxicity (Argilés et al. 2020; McCleary et al. 2013). In meta-analysis of 18 trials of adjuvant SACT, McCleary et al. 2013 found that patients aged 70 and above did not experience any survival benefit from dual agent therapy and recommended that older patients should be offered single agent therapy (McCleary et al. 2013). ESMO do not recommend single agent as standard therapy for older patients, rather stating that the benefits of treatment seem to be “more limited” for older patients, with an increased likelihood of toxicity (Argilés et al. 2020). In a non-CRC population, Prasanna et al. 2018 note that elderly patients are often offered reductions in SACT dose intensity.

Similar to the reduction seen in SACT intensity for patients with increasing age, Boakye et al. 2021 identified that increasing comorbidity was inversely associated with receipt of any adjuvant SACT for CRC. Their meta-analysis of patients with stage III disease found that presence of any comorbidity reduced the odds of SACT receipt by 21% (OR 0.79, 0.72-0.87) and that multiple comorbidities reduced the odds of SACT receipt by greater than 50% (OR 0.49, 0.42-0.56). This relationship between comorbidity and decreased SACT found the following disease states to influence SACT: diabetes, heart failure, stroke, COPD, and dementia, but not myocardial infarction or renal disease. Additionally their meta-analysis found the classification of diseases as used by the Charlson Comorbidity Index (the classification structure used in this thesis), was more successful in identifying the diseases associated with decreased SACT, than other measures such as ACE-27 were. (Piccirillo and Feinstein 1996; Boakye et al. 2021).

As discussed in previous chapters, patient frailty is not routinely recorded by many clinical systems, however identifying patients as frail may allow treating clinicians to make more patient-centred decisions (in recognising the increased risk for frail patients from of certain treatments). Meyers et al. 2017 in their study of treatment decisions for elderly patients with colorectal cancer, blinded clinicians to a validated measure of frailty (Edmonton Frail Scale), whilst allowing access to performance status, age, and comorbidity. Whilst clinicians comment on the importance of frailty in their decision making, in this study there was no correlation between decisions made and the presence of frailty. This suggests that whilst frailty may be important to clinicians, it cannot be identified solely through proxy measures such as comorbidity and age. To take into account this patient characteristic that clinicians report as important, we first need to consistently and accurately test for it (Meyers et al. 2017).

6.1.4 Quality, Intensity and Toxicity of Adjuvant SACT

6.1.4.1 Starting Timely Chemotherapy

Current ESMO recommendations for timing of adjuvant SACT, are that adjuvant SACT should commence within 8 weeks following surgery (Argilés et al. 2020) This interval is based on work showing an increased relative risk of death if SACT is commenced after 8 weeks (RR 1.2 (1.15-1.26)) (Des Guetz et al. 2010). In their guidance, ESMO note the presence of some earlier work that suggested even if adjuvant SACT is commenced late, there may be some overall mortality benefit even when commenced up to 5-6 months following surgery (Turner et al. 2018)

More recently, a 2020 meta-analysis implied that this 8 week window may be too generous. Investigating the relationship between delays commencing therapy and overall survival in a range of cancers; the authors found that for patients with colorectal cancer each four-week interval between surgery and starting chemotherapy was associated with a hazard ratio of 1.13 (1.09 to 1.17). The authors of this analysis also specifically noted that their use of a unit of 4 weeks should not imply that a delay of less than that should be considered safe (Hanna et al. 2020).

In Chapter 5, where QPI 11 also investigates a measure of timely access to adjuvant SACT, it is worth noting that the Scottish QPIs at the time of v3.4 considered an interval of greater than 12 weeks to be a delay in starting SACT (National Cancer Quality Steering Group 2020).

6.1.4.2 Dose Delay Between Cycles, Overall Course Duration

Increasing interval between planned doses of adjuvant SACT, reduces one measure of treatment intensity: Relative Dose Intensity (RDI). A premature stop to planned therapy (reducing course length) would also reduce RDI. RDI is the measure of dose provided over a set period of time: $\text{mg}/\text{m}^2/\text{week}$. RDI is considered an important metric, both influencing the potential benefit of SACT, and likelihood of toxicity from therapy (Dale et al. 2003; Lyman 2009; Wonders et al. 2023).

Nielson et al. 2021 performed a series of meta-analyses to investigate the relationship between RDI and overall survival in a range of cancers, including CRC. These meta-analyses investigated work published between 2013 and 2020. They noted a reduction in overall survival from CRC if RDI was less than 80% when compared to $\geq 80\%$ (Nielson et al. 2021).

For overall course length, ESMO currently recommend: Stage III disease either 3-6 months of CAPOX or 6 months of FOLFOX. Stage II disease to be treated as Stage III, or 6 months of single agent therapy (Argilés et al. 2020).

A key trial investigating the question of course length, the Short Course Oncology Treatment (SCOT) trial, published in 2018, indicated that 3 months of dual agent adjuvant therapy (CAPOX/FOLFOX) was non-inferior and less toxic than 6 month treatment for both High-Risk stage II and stage III CRC (Iveson et al. 2018). Work performed by those who developed the Scottish dataset used by this thesis, identified that the publication of the SCOT trial resulted in a significant change in adjuvant SACT prescriptions in Scotland (Hanna et al. 2022). Since then, the final results of SCOT have

been published by Iveson et al. 2026. Whilst these results do not provide new information on toxicity and quality of life, they do confirm the non-inferiority of a 3 month course remains when assessing probability of 5-year disease free and overall survival. (Iveson et al. 2026).

6.1.4.3 Critical Illness and Metrics of Adjuvant SACT

In the above sections I've noted the importance of a diverse range of measures of SACT that impact long term survival (receipt of adjuvant SACT, timely receipt, and relative intensity), and the factors which are likely to impact them (mainly age and comorbidity). What is lacking, is much in the way of evidence for how critical illness is associated with any of these metrics. As noted in Chapter 1, one of the few studies investigating this was the work of Camus et al. 2014. In their single centre study of 65 patients with CRC who survived ICU admission, they identified 31% of patients who were unable to continue with their planned SACT following discharge. Whilst this provides some information, their study does not report whether changes to planned SACT means: no SACT at all, delayed SACT, or less intense SACT (each of which would be associated with a different impact on long term survival). A different study from 2014 does stratify between absence of SACT and modification of SACT amongst intensive care survivors, however unfortunately this reported on patients with lung cancer, a disease process with major differences in prognosis to CRC (Soares et al. 2014). Both Camus et al. 2014 and Soares et al. 2014 report solely on patients admitted to Intensive Care, rather than stratifying by receipt of organ support. At the point of writing, both the above sources are older than 10 years. Similar work has been published more recently, Borcoman et al. 2020 investigated factors associated with one year survival for ICU patients with solid organ cancer. In doing so they identified that 246/470

hospital survivors (52%) were able to receive subsequent oncologic treatment. Like the other studies though, this is limited by use of a range of solid cancer types (20% gastrointestinal) and stages (52% metastatic), with a lack of detail on ‘subsequent oncologic treatment’. (Borcoman et al. 2020).

6.1.5 Summary

Receipt of adjuvant SACT following resection with curative intent for CRC, is associated with improved long term overall survival. As well as omission of adjuvant SACT being associated with increased mortality, delays in commencing SACT, and decreased treatment intensity are also associated with increased mortality. Whilst some work has identified relevant factors in decreased SACT, there is little to clarify how SACT receipt changes for critical illness survivors. In this chapter I assess how receipt of organ support is associated with the likelihood of receiving adjuvant SACT at all, and the likelihood receiving SACT in a timely fashion. I also assess how receipt of organ support is associated with several measures of reduced treatment intensity: single agent therapy, dose delays between cycles, and reduced overall course length.

Whilst reduced treatment intensity in several cases may be associated with similar levels of benefit, as demonstrated by the SCOT trial, such a reduction may also reflect either a clinician’s perception of increased risk of burdens from treatment, or an experience of toxicity from treatment. As such, my chosen measures of intensity (whilst relevant clinically in their own right) may be considered crude proxy measures for more patient centred outcomes such as increasing frailty following critical illness, or patient experience of treatment toxicity.

6.2 Methods

As documented in more detail in Chapter 3, I used registry level and prescription information stored on the Scottish National Safe Haven as part of the Colorectal Cancer Repository (CORECT-R). Regional prescription data (Chemocare) was available on EPCC servers in raw form; as such it required substantial cleaning and categorisation (for SACT regime, therapeutic agents, course duration) prior to use in this work.

In the previous chapter, Chapter 5, a potential limitation was raised. Definitions for patient inclusion were deliberately kept identical to inclusion criteria used by the QPI programme, to allow for meaningful comparison between the results and the QPI programme more broadly. However, any QPI may make reference to treatments that occurred in a separate hospital stay than an index admission. This could result in my description of a patient as an ‘emergency’ (as they initially present to hospital in that manner), only for them to be readmitted at a later point for elective surgical resection. In this chapter, to strengthen against this difficulty, whilst I still used the same definitions as QPI to identify those patients eligible for adjuvant curative SACT, I imposed additional filtering on which hospital admissions were included. Linking SMR01 records of surgical resection to QPI records of surgical resection, I included only those patients who are noted both in the QPI dataset, and SMR01 (record of hospital admissions), to have received curative surgical resection during their index hospital admission. To clarify, in the previous chapter the requirement was solely that the patient received curative surgical resection at some point (as recorded on QPI) in this chapter there is an additional requirement that the surgical resection occurred during this index hospital admission (as recorded on QPI and SMR01).

In addition to the differences in age range, and hospital admissions included, the other key difference with measures investigated in this chapter relates to what is considered a delay starting adjuvant SACT. In Chapter 5, the 12 week time limit used by QPI v3.4 is used. In this chapter I use the more appropriate target set by ESMO, and used by QPI v5, that a delay in adjuvant SACT is when interval between resection and SACT is greater than 8 weeks (Argilés et al. 2020; Healthcare Improvement Scotland 2025).

The questions of interest in this chapter relied on information from:

- SMR06 - Scottish Cancer Repository
- SMR01 - Day-case and Inpatient Information
- SICSAAG - Critical Care Admission and Level of Support
- SACT - Systemic Anti-Cancer Therapy Prescription Records (Chemocare)
- QPI - Scottish Colorectal Cancer QPI Dataset

The questions of interest detailed above are relevant to a subset of patients with CRC who are eligible for adjuvant SACT. These are patients with High-Risk stage II or stage III disease, who received curative surgical resection. The study population consisted of patients with colorectal cancer (with Stage High-Risk II or III disease) who received surgical resection and survived both their hospital stay and the 30 days following discharge. Figure 6.1 provides an overview of the population stratification. To identify these I filtered our previously created dataset to patients with relevant staging, then used the Scottish QPI dataset to identify those noted as receiving curative resection, excluding those who refused adjuvant chemotherapy or received neoadjuvant therapy, and additionally used SMR-01 to include only the hospital admissions where surgical resection was noted to take place.

In the introduction I note that Relative Dose Intensity ($mg/m^2/week$) is a recognised important measure. In this chapter, due to limitations with RDI, I use different proxy measures for dose intensity: delays during course, dual versus single agent therapy, and course length. RDI in this context would rely on multiple sources of unvalidated information (dose received, body surface area, true course length), and require either splitting the subcohorts further at the drug level (causing limitations from sample size), or combining RDIs for different drugs into a normalised value. In this thesis I have attempted to have measures that are meaningful both to clinicians and patients. A difference in percentage of a normalised RDI appears less clear and less easy to interpret than: ‘one chemotherapy drug or two?’, ‘were there delays during chemotherapy?’, or ‘did chemotherapy get stopped early?’. Additionally, a normalised RDI would pose difficulties when defining a clinically meaningful difference.

As noted in Figure 6.1, different questions of interest require different patient populations, either due to population definitions, or limitations of data availability. As a result the following are used:

- SACT A - Receipt of Adjuvant SACT - Includes all patients eligible for SACT by nature of disease stage and surgical resection as described above (n = 3,427)
- SACT B - Delay In Starting Adjuvant SACT - Includes all patients who received adjuvant SACT for above indication (n = 1,988)
- SACT C-E - Delays During, Single Agent versus Dual, Course Length - Required additional chemocare prescription data (n = 1,582)

Variable selection for multivariable regression was performed through initial univariable analysis, allowing selection of variables which appeared likely to have an impact on the outcomes of interest. Variables which had a PD of $\geq 95\%$ were included in multivariable analysis.

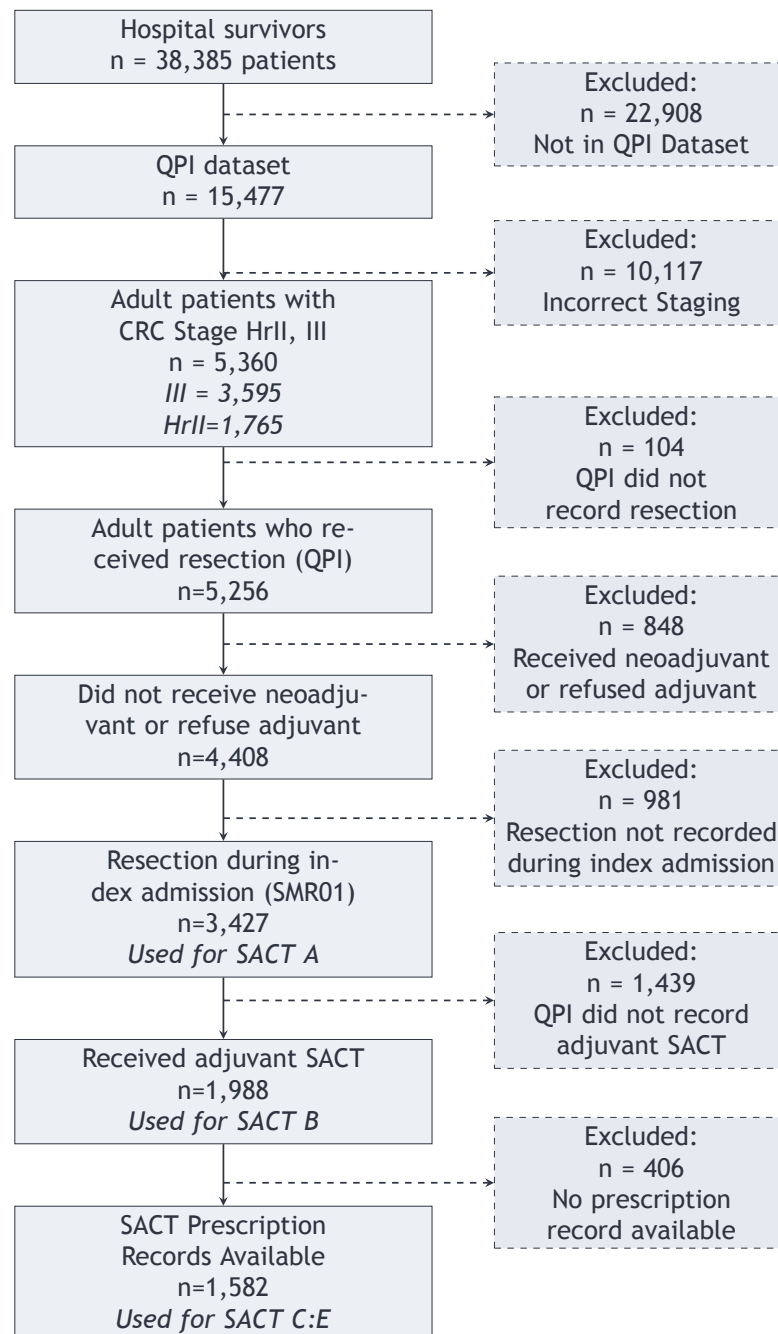


Figure 6.1: CONSORT diagram showing patient selection for subgroup SACT analysis

As in Chapter 5, I used a working definition for 'meaningful clinically important difference' in odds (MCID) of 3%, based on 10% of the standard deviation from the baseline target of cancer care quality. This statistical approach to thresholds for MCID was taken due the lack of published MCIDs (either expert opinion or evidence based) for this context.

6.2.1 Models

Each of the five questions asked in this chapter is described and subsequently investigated with their own Bayesian Multivariable Regression model. Details of these models is included in Table 6.1.

Table 6.1: Summary of Bayesian Models Used in SACT Analysis

Model ID	Outcome of Interest	Model Family	Variables Included
SACT A	Receipt of Adjuvant SACT	Bernoulli	Support In Hospital * Nature of Admn + Age + Dx To Admn (days) + CRC Stage + Comorbidities (Number) + Hospital LOS (Days) + Method Diagnosis + Operations (Number) + SIMD Quintile
SACT B	Delay Commencing Adjuvant SACT	Bernoulli	Support In Hospital * Nature of Admn + Hospital LOS (Days) + Method Diagnosis + Operations (Number)
SACT C	Single Agent or Dual Agent SACT	Bernoulli	Support In Hospital * Nature of Admn + Age + Dx To Admn (days) + CRC Stage + Comorbidities (Number) + Hospital LOS (Days) + Method Diagnosis + Surgery To SACT (days)
SACT D	Dose Delay Between Cycles of SACT	Bernoulli	Support In Hospital * Nature of Admn + SACT Regime
SACT E	Course Length of Adjuvant SACT	Cumulative	Support In Hospital * Nature of Admn + Age + Dx To Admn (days) + CRC Stage + Hospital LOS (Days) + PRE_SCOT + SACT Regime + Sex + SIMD Quintile

Each model was run four times with differing prior distributions for use in later sensitivity analysis, following the recommendations from Zampieri et al. 2021:

- Uninformative $\sim \text{Normal}(\mu = 0, \sigma = 0.355)$
- Sceptical $\sim \text{Normal}(\mu = 0, \sigma = 0.205)$
- Optimistic $\sim \text{Normal}(\mu = 0.15, \sigma = 0.205)$
- Pessimistic $\sim \text{Normal}(\mu = -0.15, \sigma = 0.205)$ (Zampieri et al. 2021)

Each model was performed with 5000 steps total, 1000 steps burn-in and 10 chains. Validity analysis was performed for each model with: sensitivity analysis between choice of priors, effective sample size, R-hat, and posterior predictive checks

6.3 Results

6.3.1 Demographics of Patients Eligible for Curative Adjuvant SACT

3,427 patients were identified as being eligible for receipt of adjuvant SACT (Figure 6.1). The demographic characteristics of this subset are shown in Table 6.2, with additional detail provided in Table C.3 in the appendix.

Table 6.2: Demographic Characteristics - Receipt of Adjuvant Chemotherapy (SACT A)

Characteristic	Overall	Elective	Elective	Elective	Emergency	Emergency	Emergency	Bayes Factor
		Ward Level	Monitoring	Organ Support	Ward Level	Monitoring	Organ Support	
	N = 3,427	N = 650	N = 1,695	N = 326	N = 170	N = 416	N = 170	
Age At Diagnosis	71 (62, 79)	69 (61, 76)	70 (62, 78)	73 (65, 79)	72 (58, 80)	72 (63, 80)	73 (64, 80)	>100
Female Sex	1,567 (46%)	305 (47%)	753 (44%)	127 (39%)	95 (56%)	218 (52%)	69 (41%)	0.40
SIMD (quintile)								-
1	604 (18%)	93 (14%)	285 (17%)	67 (21%)	36 (21%)	72 (17%)	51 (30%)	0.20
5	739 (22%)	140 (22%)	393 (23%)	52 (16%)	37 (22%)	88 (21%)	29 (17%)	<0.01
Additional Charlson Co-morbidities Known								-
None	2,621 (76%)	551 (85%)	1,300 (77%)	211 (65%)	131 (77%)	303 (73%)	125 (74%)	>100
One	608 (18%)	82 (13%)	303 (18%)	77 (24%)	32 (19%)	82 (20%)	32 (19%)	0.031
Multiple	198 (5.8%)	17 (2.6%)	92 (5.4%)	38 (12%)	7 (4.1%)	31 (7.5%)	13 (7.6%)	2.96
Cardiac Disease (Charlson)	200 (5.8%)	23 (3.5%)	101 (6.0%)	31 (9.5%)	9 (5.3%)	25 (6.0%)	11 (6.5%)	<0.01
Respiratory Disease (Charlson)	292 (8.5%)	30 (4.6%)	130 (7.7%)	50 (15%)	11 (6.5%)	52 (13%)	19 (11%)	>100
Renal Disease (Charlson)	172 (5.0%)	20 (3.1%)	71 (4.2%)	30 (9.2%)	9 (5.3%)	28 (6.7%)	14 (8.2%)	<0.01
Surgical Admission	3,421 (100%)	650 (100%)	1,694 (100%)	325 (100%)	167 (98%)	416 (100%)	169 (99%)	<0.01
Operations During Admission								-
One	2,954 (86%)	586 (90%)	1,483 (87%)	242 (74%)	152 (89%)	367 (88%)	124 (73%)	>100
Multiple	473 (14%)	64 (9.8%)	212 (13%)	84 (26%)	18 (11%)	49 (12%)	46 (27%)	>100
Diagnosis To Admission (days)	41 (16, 66)	46 (32, 66)	50 (34, 75)	53 (34, 76)	0 (0, 1)	0 (0, 10)	0 (0, 13)	>100
Duration Hospital Stay (days)	9 (6, 15)	7 (5, 10)	8 (6, 12)	14 (9, 26)	14 (10, 25)	14 (10, 22)	23 (14, 41)	>100
Duration Critical Care Stay (days)	2.00 (1.00, 4.00)	0.00 (0.00, 0.00)	2.00 (1.00, 4.00)	5.00 (3.00, 8.00)	0.00 (0.00, 0.00)	3.00 (2.00, 4.00)	5.00 (3.00, 10.00)	>100
Critical Care Admission Was Planned	1,717 (50%)	0	1,433 (85%)	196 (60%)	0	76 (18%)	12 (7.1%)	>100
APACHE II Score	13.0 (10.0, 16.0)	NA	11.0 (9.0, 13.0)	14.0 (11.0, 18.0)	NA	11.0 (9.0, 13.5)	16.0 (12.0, 19.0)	>100
Vasoactive Support	444 (90%)	-	-	294 (90%)	-	-	150 (88%)	0.093
Ventilated	183 (37%)	-	-	97 (30%)	-	-	86 (51%)	>100
Renal Replacement Therapy	22 (4.4%)	-	-	14 (4.3%)	-	-	8 (4.7%)	0.051
Method of First Detection								-
Clinical presentation	2,630 (77%)	442 (68%)	1,222 (72%)	241 (74%)	161 (95%)	404 (97%)	160 (94%)	>100
Screening examination	711 (21%)	192 (30%)	426 (25%)	73 (22%)		8 (1.9%)		>100
Duke								-
High-Risk II	1,113 (32%)	201 (31%)	534 (32%)	105 (32%)	58 (34%)	164 (39%)	51 (30%)	<0.01
III	2,314 (68%)	449 (69%)	1,161 (68%)	221 (68%)	112 (66%)	252 (61%)	119 (70%)	<0.01

6.3.1.1 Patient Characteristics

Despite filtering to a more comparable disease state and level of treatment, the six subcohorts continue to have some notable differences in demographic characteristics, as seen previously in chapters 4 and 5.

Differences in age are apparent between our subcohorts ($BF > 100$). The overall median age of the cohort was 71, patients admitted as an emergency tended to have an increased median age than those admitted electively (increase of 0 to 3 years).

Bayes Factor contingency table analysis suggests moderate evidence of no difference between subcohorts in proportion of female patients ($BF 0.4$). SIMD Quintiles are established so that 20% of the Scottish population sits within each strata. The overall cohort's proportions sit close to this (Quintile 1 - 18%, $n = 604$ | Quintile 5 - 22% $n = 739$). While Emergency - Organ Support has a larger proportion of patients within the most deprived level, Quintile 1 (30% $n = 51$), BF suggest moderate evidence of no difference between subcohorts in SIMD 1 ($BF 0.2$), and strong evidence of no difference between subcohorts in SIMD 5 ($BF < 0.01$).

6.3.1.2 Comorbidities

There is strong evidence of difference between the subcohorts, of proportions of patients with No Comorbidities ($BF > 100$). The overall proportion of patients with No Comorbidities Additional To Cancer was 76% ($n = 2,621$). Elective - Ward Level patients had a notably higher proportion (85%, $n = 551$), and Elective - Organ Support notably lower (65%, $n = 211$) There was anecdotal evidence (used to mean low level of statistical support, see Table 2.1) that there were differences for Multiple Additional

Comorbidities (BF 2.96). The overall proportion of patients with Multiple Comorbidities was 5.8% (n = 198). Organ Support patients had the highest proportion of patients with multiple comorbidities in both the Elective and Emergency subcohort (12%, n = 38 | 7.6%, n = 13 respectively).

Elective - Organ Support also had the highest proportion of patients with specific comorbidities; Cardiac Disease (9.5% n = 31, Overall 5.8% n = 200), Respiratory Disease (15% n = 50, Overall 8.5% n = 292), and Renal Disease (9.2% n = 30, Overall 5% n = 172). Rates of comorbidity differed between Elective - Organ Support and Elective - Monitoring, whereas in Emergency admissions comorbidity tended to be similar between Organ Support and Monitoring. Of the named comorbidities studied, difference in proportions between subcohorts was only seen for those with Respiratory Disease (BF > 100).

6.3.1.3 Disease Specific and Admission Characteristics

For inclusion into the population of interest, all patients underwent surgical resection during the index hospital admission. The majority of patients underwent one operation during their admission (86% n = 2954), with a minority receiving multiple operations (14% n = 473). The proportion of patients with multiple operations was greatest in the two Organ Support subcohorts (Elective 26% n = 84, Emergency 27% n = 46). There was strong evidence of differences in numbers of operations undertaken between subcohorts (BF > 100).

With regards to method of diagnosis, overall proportion of patients diagnosed through screening was 21% ($n = 711$), and through clinical presentation was 77% ($n = 2630$). Emergency patients had a $\sim 95\%$ proportion diagnosed through clinical presentation in all 3 subcohorts. There was strong evidence of differences in method of diagnosis between subcohorts ($BF > 100$).

The overall median interval between CRC diagnosis and admission was 41 days. Among Emergency patients this was much lower (median 0 days in all subcohorts, $BF > 100$), reflecting the high proportion of patients being diagnosed during their hospital admission.

The overall median hospital length of stay was slightly greater than one week (9 days). There was strong evidence of difference between our six subcohorts ($BF > 100$). Each Emergency subcohort had a duration in hospital approximately one week longer than their Elective counterpart. Each Organ Support subcohort had a hospital duration approximately one week longer than the subcohorts of Ward Level and Monitoring. As such Emergency - Organ Support had a hospital duration 2 weeks longer than the overall median (23 days).

APACHE II scores were calculated only for patients in Critical Care. Overall median APACHE II score was 13. As expected, Organ Support patients had greater APACHE II scores than Monitoring Patients ($BF > 100$). Emergency - Organ Support subcohort had the highest median APACHE II score of 16.

Among Organ Support patients, the overall proportion experiencing each form of support was: Vasoactive (90% $n = 444$), Ventilation (37% $n = 183$), and Renal Replacement Therapy (RRT) (4.4% $n = 22$). Rates of vasoactive support ($BF < 0.1$) and RRT ($BF < 0.1$) were similar between Elective and Emergency subcohorts, however Emergency - Organ Support had a greater proportion receiving ventilation ($BF > 100$: Emergency 51% $n = 86$, Elective 30% $n = 97$).

The overall population had 32% ($n = 1113$) patients with High-Risk Stage II, and 68% ($n = 2314$) patients with Stage III disease. There was evidence of no difference in the split between High-Risk II and Stage III disease among the six subcohorts ($BF < 0.01$).

6.3.2 Receipt of Adjuvant Chemotherapy (SACT A)

With an upper limit of 6 months following surgical resection, the overall proportion of patients eventually receiving adjuvant SACT was 58%. There was strong evidence of differences in adjuvant chemotherapy receipt between the six subcohorts ($BF > 100$). Elective - Ward Level patients were the subcohort with the highest proportion of SACT receipt (71%, $n = 1988$). Within each form of admission, Organ Support patients had the lowest proportion of SACT attainment: Elective - Organ Support (43%, $n = 141$), Emergency - Organ Support (35%, $n = 59$). Table 6.3 highlights these clear differences in the receipt of adjuvant SACT between these six subcohorts. Each Elective subcohort had a higher proportion of receipt of SACT than their Emergency counterpart. Figure 6.2 demonstrates the cumulative incidence of adjuvant SACT receipt for patients following surgical resection. In this figure a clear plateau in SACT receipt occurs at approximately 12 weeks post surgical resection for the six subcohorts (although it appears this plateau may occur later for patients in the Emergency - Organ Support subcohort). Whilst SACT A reports on total adjuvant SACT receipt up to 6 months, the majority of receipt has occurred for most patients by 12 weeks, detailed more in SACT B below.

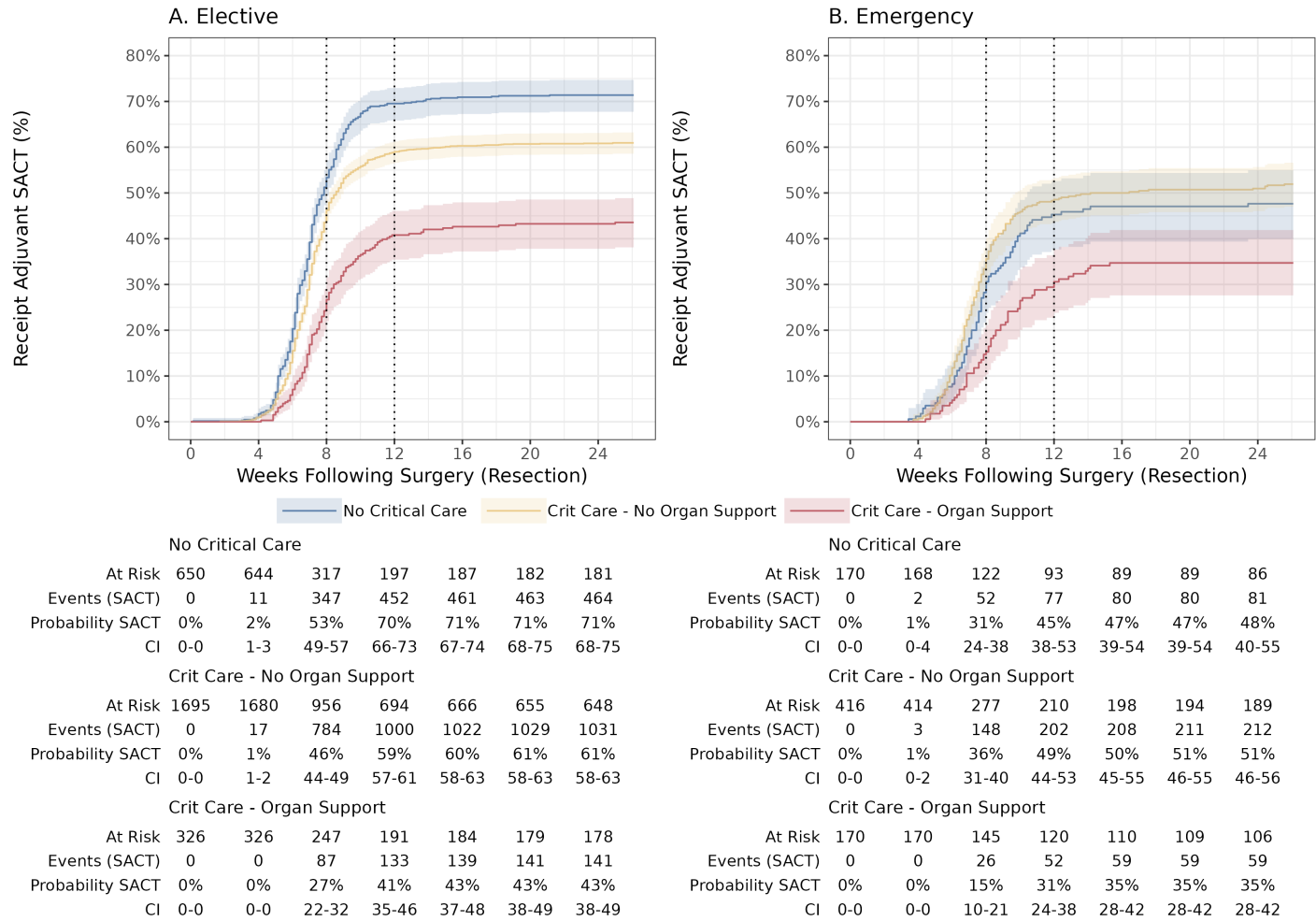


Figure 6.2: Cumulative Incidence Plot and Risk Table - Receipt of Adjuvant SACT Following Curative Surgical Resection for Patients With High Risk Stage II and Stage III CRC
Stratified by nature of hospital admission and level of support during admission - Risk table provides counts of number at risk and events, as well as probability estimates and 95% confidence intervals for SACT receipt

Table 6.3: Proportion of Patients Receiving Adjuvant Chemotherapy (SACT A)

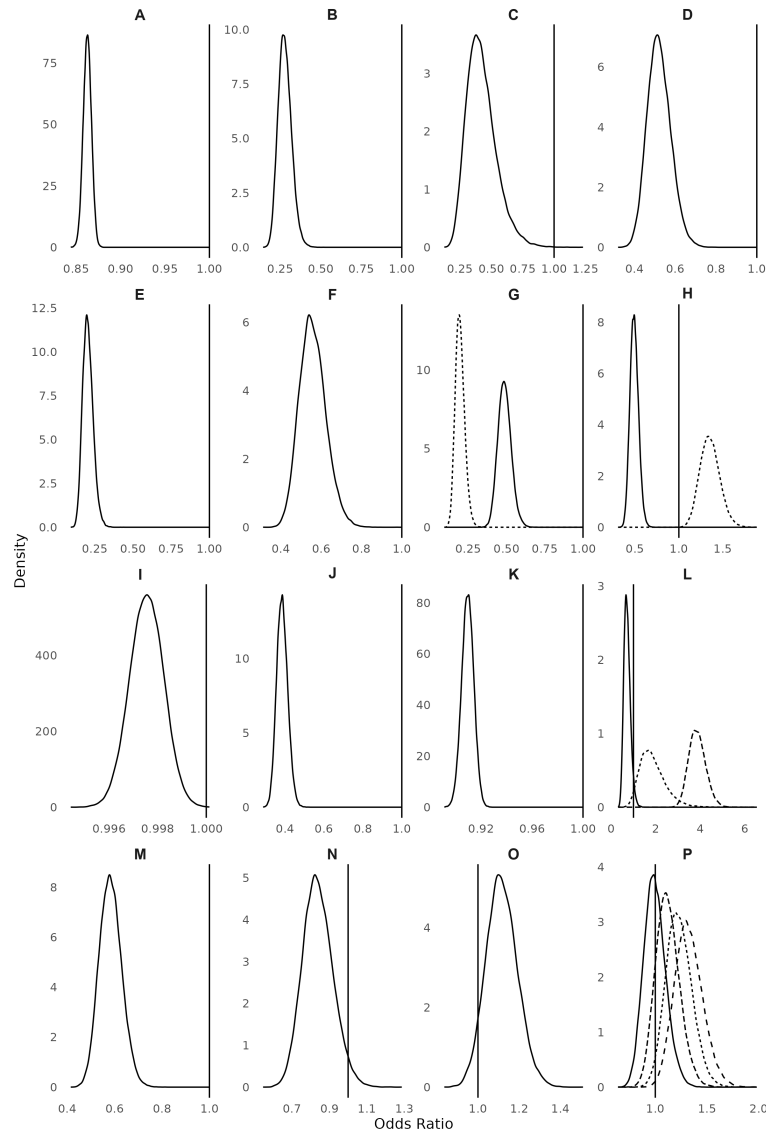
Overall	Elective	Elective	Elective	Emergency	Emergency	Emergency	Bayes
	Ward	Monitoring	Organ	Ward	Monitoring	Organ	Factor
N = 3,427	N = 650	N = 1,695	N = 326	N = 170	N = 416	N = 170	
1,988 (58%)	464 (71%)	1,031 (61%)	141 (43%)	81 (48%)	212 (51%)	59 (35%)	> 100

6.3.2.1 Variable Selection - Univariable Analysis

A series of single variable models were performed to identify variables suitable for inclusion in a later multivariable model. Figure 6.3 displays each of these model's posterior probability distributions of the Odds Ratio of eventual receipt of adjuvant SACT. Table 6.4 provides detailed results of the univariable analysis, including probability of direction, and whether this reaches pre-specified magnitude for inclusion in the multivariable model.

Of the single variable models, the factor most strongly associated with an increased odds of adjuvant chemotherapy receipt was diagnosis through Screening (OR 3.85 (3.19-4.67)). The factor most strongly associated with decreased odds of adjuvant chemotherapy receipt was the presence of multiple additional comorbidities (OR 0.19 (0.14-0.26)).

Of the variables of interest, receipt of organ support was associated with a decreased odds of adjuvant chemotherapy receipt (OR 0.49 (0.4 - 0.59)) in this unadjusted analysis.



- A** Age at diagnosis (*per* increase in age by one year)
B Cardiac comorbidity (vs No cardiac comorbidity)
C Dementia (vs No dementia)
D Diabetes (vs No diabetes)
E Renal comorbidity (vs No renal comorbidity)
F Respiratory comorbidity (vs No respiratory comorbidity)
G Charlson comorbidity count (vs Zero additional comorbidity); solid = One additional, dotted = Two plus
H Support in Hospital (vs Monitoring); solid = Organ Support, dotted = Ward Level
I Diagnosis-to-admission interval (*per* increase in interval by one day)
J Anatomic Stage High Risk II (vs Anatomic Stage III)
K Duration of hospital stay (*per* increase in admission duration by one day)
L Method of first detection (vs Clinical Presentation); dotted = Other/Not Known, solid = Incidental Finding, dashed = Screening
M Non-elective admission (vs Elective admission)
N Multiple operations (vs Single operation)
O Female Sex (vs Male)
P Deprivation quintile (SIMD) (vs Q1); solid = Q2, dashed = Q3, dotted = Q4, dashed = Q5

Figure 6.3: Posterior probability distributions of the odds ratio for receipt of adjuvant chemotherapy (SACT A), from univariable logistic regression models fitted to each variable. Vertical line at OR 1 (no effect). Facet key provides title and comparator for each variable

Table 6.4: Summary of posterior probability distributions of the odds ratio for receipt of adjuvant chemotherapy (SACT A), from univariable logistic regression models fitted to each variable.

Variable	Median	CrI	PD (%)	Threshold Reached
Age at diagnosis per increase in age by one year	0.86	(0.85 - 0.87)	100.00	TRUE
Diagnosis-to-admission per increase in interval by one day	1.00	(1 - 1)	99.99	TRUE
Anatomic Stage High Risk II vs Anatomic Stage III	0.38	(0.33 - 0.44)	100.00	TRUE
Cardiac vs no cardiac comorbidity	0.28	(0.21 - 0.37)	100.00	TRUE
Dementia vs no dementia	0.41	(0.24 - 0.7)	99.96	TRUE
Diabetes vs no diabetes	0.52	(0.42 - 0.64)	100.00	TRUE
Renal vs no renal comorbidity	0.20	(0.15 - 0.28)	100.00	TRUE
Respiratory vs no respiratory comorbidity	0.55	(0.44 - 0.7)	100.00	TRUE
One additional Charlson comorbidity vs zero additional comorbidity	0.49	(0.41 - 0.58)	100.00	TRUE
Two plus additional Charlson comorbidity vs zero additional comorbidity	0.19	(0.14 - 0.26)	100.00	TRUE
Organ Support vs Monitoring	0.49	(0.4 - 0.59)	100.00	TRUE
Ward Level vs Monitoring	1.35	(1.15 - 1.59)	99.99	TRUE
Hospital duration per increase in duration by one day	0.91	(0.9 - 0.92)	100.00	TRUE
Diagnosis incidental finding vs clinical presentation	0.70	(0.47 - 1.03)	96.22	TRUE
Diagnosis other/not known vs clinical presentation	1.78	(0.99 - 3.21)	97.25	TRUE
Diagnosis screening vs clinical presentation	3.85	(3.19 - 4.67)	100.00	TRUE
Emergency admission vs elective admission	0.58	(0.5 - 0.68)	100.00	TRUE
Multiple operations vs single operation	0.83	(0.69 - 1.01)	97.04	TRUE
Female sex vs male	1.11	(0.97 - 1.27)	94.15	FALSE
SIMD Quintile 2 vs 1	0.99	(0.81 - 1.22)	53.68	FALSE
SIMD Quintile 3 vs 1	1.22	(1 - 1.49)	97.59	TRUE
SIMD Quintile 4 vs 1	1.11	(0.91 - 1.37)	85.26	FALSE
SIMD Quintile 5 vs 1	1.32	(1.08 - 1.61)	99.64	TRUE
<i>CrI - 95% Credible Interval</i>				
<i>PD - Probability of Direction</i>				
<i>Threshold noted for potential inclusion in subsequent multivariable model $\geq 95\%$</i>				

6.3.2.2 Results of Multivariable Analysis

Results from the multivariable model ran with uninformative priors are shown in Figure 6.4 and Table 6.5. Results of the remainder of the variables included in this model are in the appendix in Table C.5.

Regarding the primary variable of interest: Receipt of Organ Support, both Emergency and Elective Organ Support patients were likely associated with reduced odds of eventual SACT receipt, when compared to patients receiving Monitoring in critical care.

Emergency - Organ Support was likely to be associated with reduction in odds of SACT receipt (median OR 0.8, 95% CrI 0.52-1.24). The probability of clinically meaningful decrease in odds of SACT receipt was 79%, with 9% probability of no clinically meaningful difference, and 12% probability of clinically meaningful increase in odds of SACT receipt. The median estimate for the association between Emergency - Organ Support and SACT receipt was 20% lower odds of eventual SACT receipt.

Elective - Organ Support was more likely than not to be associated with reduction in odds of SACT receipt (median OR 0.9, 95% CrI 0.68-1.2). The probability of clinically meaningful decrease in odds of SACT receipt was 67%, with 17% probability of no clinically meaningful difference, and 16% probability of clinically meaningful increase in odds of SACT receipt. The median estimate for the association between Elective - Organ Support and SACT receipt was 10% lower odds of eventual SACT receipt.

Compared against Elective - Monitoring patients, Elective - Ward was very likely to be associated with increased odds of SACT receipt (median OR 1.23, 95% CrI 0.98-1.56). The probability of clinically meaningful increase in odds of SACT receipt was 92%, with 6% probability of no clinically meaningful difference, and 2% probability of clinically meaningful decrease in odds of SACT receipt. The median estimate for the association between Elective - Ward and SACT receipt was 23% higher odds of eventual SACT receipt.

Compared against Emergency - Monitoring patients, Emergency - Ward was likely to be associated with decreased odds of SACT receipt (median OR 0.77, 95% CrI 0.5-1.19). The probability of clinically meaningful decrease in odds of SACT receipt was 83.75%, with 7.55% probability of no clinically meaningful difference, and 8.7% probability of clinically meaningful increase in odds of SACT receipt. The median estimate for the association between Emergency - Ward and SACT receipt was 23% lower odds of eventual SACT receipt.

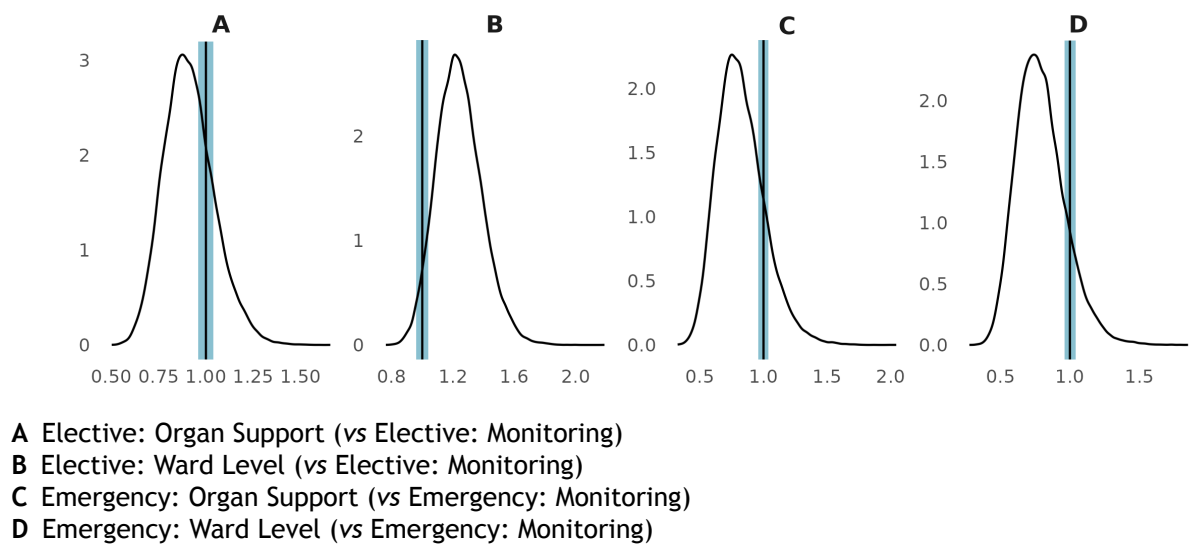


Figure 6.4: Multivariable Analysis Results - Posterior probability distribution of the odds ratio for receipt of adjuvant chemotherapy (SACT A), from multivariable logistic regression model using uninformative priors, for the key variables of interest
 Light blue shaded region indicates region of practical equivalence
 Vertical line indicates OR 1 (no effect)
 Facet key provided for variable names and comparators

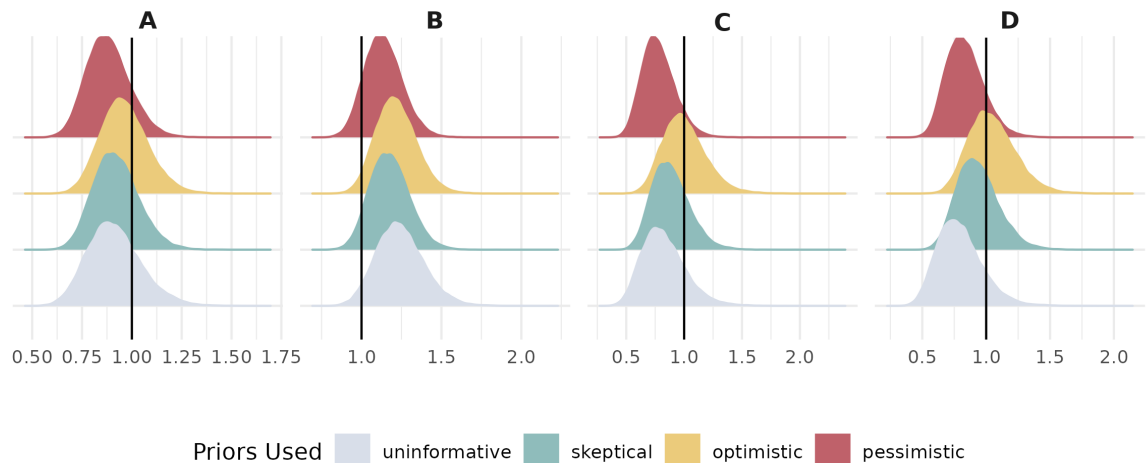
Table 6.5: Multivariable Analysis Results - Summary of posterior probability distribution of the odds ratio for receipt of adjuvant chemotherapy (SACT A), from multivariable logistic regression model using uninformative priors, for the key variables of interest, with comparator provided beneath

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease	Percentage Of Largest Effect
Elective: Organ Support <i>vs Elective: Monitoring</i>	0.90	(0.68-1.2)	76.07	16.99	16.46	66.56	66.56% chance meaningful reduction
Elective: Ward Level <i>vs Elective: Monitoring</i>	1.23	(0.98-1.56)	96.16	5.79	92.51	1.70	92.51% chance meaningful increase
Emergency: Organ Support <i>vs Emergency: Monitoring</i>	0.80	(0.52-1.24)	83.57	9.06	12.31	78.63	78.63% chance meaningful reduction
Emergency: Ward Level <i>vs Emergency: Monitoring</i>	0.77	(0.5-1.19)	88.00	7.55	8.70	83.75	83.75% chance meaningful reduction

CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease

6.3.2.3 Model Validity And Sensitivity

Repeating each model with differing priors (Sceptical, Optimistic, Pessimistic) resulted in similar posterior estimates for each variable, as demonstrated in Figure 6.5, and Table 6.6. Each choice of prior resulted in similar directions of posterior estimates.



- A** Elective: Organ Support (vs Elective: Monitoring)
B Elective: Ward Level (vs Elective: Monitoring)
C Emergency: Organ Support (vs Emergency: Monitoring)
D Emergency: Ward Level (vs Emergency: Monitoring)

Figure 6.5: Sensitivity Analysis - Comparisons of posterior probability distribution of the odds ratio for receipt of adjuvant chemotherapy (SACT A), from multivariable logistic regression models using different prior probability distributions
 Facet key provided for variable names and comparators

Table 6.6: Sensitivity Analysis - Summary of comparisons of posterior probability distribution of the odds ratio for receipt of adjuvant chemotherapy (SACT A), from multivariable logistic regression models using different prior probability distributions
 Facet key provided for variable names and comparators

Variable	Uninf ¹	Skep ¹	Δ Skep ²	Opt ¹	Δ Opt ²	Pess ¹	Δ Pess ²
Elective: Organ Support	0.9	0.91	-0.01	0.96	-0.05	0.87	0.03
Elective: Ward Level	1.23	1.17	0.06	1.21	0.02	1.13	0.1
Emergency: Organ Support	0.8	0.87	-0.06	0.99	-0.18	0.77	0.04
Emergency: Ward Level	0.77	0.92	-0.15	1.03	-0.26	0.82	-0.05
¹ Median Estimate of Odds From Model							
² Median Estimate of Difference Between Uninformative Priors and Model							

Table C.6 (appendix) provides detailed results of the validity analysis. Multivariable model chains showed good convergence, with $\hat{R}$ of < 1.01 for each variable. With the smallest ESS remaining greater than 20,000, there are no concerns about the central estimates or credible intervals.

Figure C.4 (appendix) shows the posterior predictive check for the model, comparing model predictions to actual outcomes. The degree of overlap seen in this suggests that the multivariable model accurately makes predictions in keeping with the observed data.

6.3.3 Delay to Receipt of Adjuvant Chemotherapy (SACT B)

For SACT B and all subsequent sections in this chapter, the population investigated were those who did receive adjuvant SACT, detailed in Figure 6.1. Table C.4 in the appendix describes the characteristics of patients who received adjuvant SACT.

Among the population of patients who received adjuvant SACT following curative surgical resection for High Risk Stage II and Stage III disease, the proportion of patients who experienced delays commencing therapy, with treatment starting greater than 8 weeks after surgical resection, was 27%. There was strong evidence of difference between the six subcohorts ($BF > 100$), detailed in Table 6.7. The majority of Emergency - Organ Support patients who received adjuvant SACT, experienced delays commencing therapy (56% experienced a delay, $n = 33$). Elective - Organ Support patients had the greatest proportion of delays amongst those admitted electively (38%, $n = 54$). Elective - Monitoring patients had the smallest proportion of delays of the six subcohorts (24%, $n = 247$).

Table 6.7: Delays In Receiving Adjuvant Chemotherapy

	Overall N = 1,988	Elective Ward Level N = 464	Elective Monitoring N = 1,031	Elective Organ Support N = 141	Emergency Ward Level N = 81	Emergency Monitoring N = 212	Emergency Organ Support N = 59	Bayes Factor
Delay	544 (27.4%)	117 (25.2%)	247 (24.0%)	54 (38.3%)	29 (35.8%)	64 (30.2%)	33 (55.9%)	> 100
No Delay	1,444 (72.6%)	347 (74.8%)	784 (76.0%)	87 (61.7%)	52 (64.2%)	148 (69.8%)	26 (44.1%)	

Noting strong evidence of difference in delays experienced between groups, I stratified these delays further by magnitude. These differences are shown in Figure 6.2, and described and tested in Table 6.8. The majority of patient delays occurred between 9 and 12 weeks ($n = 472$, 87% of delays), the pattern of which group experiencing what

magnitude of delay remained the same as delays overall. Emergency - Organ Support had the largest proportion of delays between 9-12 weeks (78% of delays $n = 26$), and Elective - Organ Support had the largest proportion of delays between 9-12 weeks for Elective admissions (85% of delays, $n = 46$).

Emergency and Elective Organ Support subcohorts contained the largest proportions of patients experiencing more significant delays. 12% ($n = 7$) of Emergency Organ Support patients who eventually received adjuvant SACT, did so at 12 weeks or later. 6% ($n = 8$) of Elective Organ Support patients who eventually received adjuvant SACT, did so at 12 weeks or later. There was strong evidence of no difference in the proportions of delays experienced at these time points or later, with a BF < 0.1.

Table 6.8: Magnitude of Delays In Receiving Adjuvant Chemotherapy

	Overall N = 1,988	Elective Ward Level N = 464	Elective Monitoring N = 1,031	Elective Organ Support N = 141	Emergency Ward Level N = 81	Emergency Monitoring N = 212	Emergency Organ Support N = 59	Bayes Factor
No Delay (≤ 8 weeks)	1,444 (72.6%)	347 (74.8%)	784 (76.0%)	87 (61.7%)	52 (64.2%)	148 (69.8%)	26 (44.1%)	>100
9 - 12 Weeks	472 (23.7%)	105 (22.6%)	216 (21.0%)	46 (32.6%)	25 (30.9%)	54 (25.5%)	26 (44.1%)	50
12 - 16 Weeks	53 (2.7%)	9 (1.9%)	22 (2.1%)	6 (4.3%)	3 (3.7%)	6 (2.8%)	7 (11.9%)	< 0.1*
16 - 24 Weeks	19 (1.0%)	3 (0.6%)	9 (0.9%)	2 (1.4%)	1 (1.2%)	4 (1.9%)	0 (0%)	

BF Contingency Table Analysis comparison made against No Delay group, *12+ weeks consolidated due to groups with values of 0

6.3.3.1 Variable Selection - Univariable Analysis

In single variable analysis few variables were associated with PD > 95%. Results of these are provided in Table 6.9. Figure C.5 in the appendix provides posterior probability distributions for the single variable models.

In single variable models, the factor most strongly associated with increased odds of delay in commencing adjuvant SACT was experiencing organ support in critical care (OR 2.03, 1.52-2.71). The variable associated with the greatest protection from delay commencing adjuvant SACT was diagnosis through clinical screening (OR 0.8, 0.65 - 1).

Variables included in multivariable analysis were: the nature of admission to hospital, level of support during hospital admission, duration of hospital admission, method of CRC diagnosis, and number of operations during admission.

Table 6.9: Summary of posterior probability distributions of the odds ratio for delay to receipt of adjuvant chemotherapy (SACT B), from univariable logistic regression models fitted to each variable.

Variable	median	CrI	PD (%)	PD_great
Age at diagnosis per increase in age by one year	1.00	(0.99 - 1.01)	61.8	FALSE
Diagnosis-to-admission per increase in interval by one day	1.00	(1 - 1)	70.8	FALSE
Anatomic Stage High Risk II vs Stage III	0.85	(0.67 - 1.07)	91.3	FALSE
Cardiac vs no cardiac comorbidity	1.01	(0.62 - 1.63)	51.4	FALSE
Dementia vs no dementia	0.97	(0.49 - 1.9)	53.7	FALSE
Diabetes vs no diabetes	1.10	(0.78 - 1.54)	71.1	FALSE
Renal vs no renal comorbidity	1.01	(0.58 - 1.72)	51.1	FALSE
Respiratory vs no respiratory comorbidity	1.02	(0.71 - 1.46)	55.0	FALSE
One additional Charlson comorbidity vs zero additional comorbidity	1.12	(0.85 - 1.46)	79.8	FALSE
Two plus additional Charlson comorbidity vs zero additional comorbidity	0.92	(0.55 - 1.54)	61.8	FALSE
Organ Support vs Monitoring	2.03	(1.52 - 2.71)	100.00	TRUE
Ward Level vs Monitoring	1.03	(0.83 - 1.29)	61.4	FALSE
Hospital duration per increase in duration by one day	1.07	(1.06 - 1.09)	100.00	TRUE
Diagnosis incidental finding vs clinical presentation	0.95	(0.55 - 1.61)	57.8	FALSE
Diagnosis other/not known vs clinical presentation	0.95	(0.51 - 1.72)	57.2	FALSE
Diagnosis screening vs clinical presentation	0.80	(0.65 - 1)	97.5	TRUE
Emergency admission vs elective admission	1.56	(1.23 - 1.98)	99.9	TRUE
Multiple operations vs single operation	1.31	(1 - 1.7)	97.5	TRUE
Female sex vs male	1.12	(0.92 - 1.36)	86.62	FALSE
SIMD Quintile 2 vs 1	1.20	(0.9 - 1.6)	88.8	FALSE
SIMD Quintile 3 vs 1	1.07	(0.81 - 1.41)	67.1	FALSE
SIMD Quintile 4 vs 1	0.92	(0.69 - 1.22)	72.2	FALSE
SIMD Quintile 5 vs 1	0.84	(0.63 - 1.11)	89.6	FALSE
<i>CrI - Credible Interval</i>				
<i>PD - Probability of Direction</i>				
<i>Threshold noted for potential inclusion in subsequent multivariable model $\geq 95\%$</i>				

6.3.3.2 Results of Multivariable Analysis

Following adjustment in multivariable analysis, organ support is likely to be associated with a clinically meaningful increase in the likelihood of delays commencing SACT.

Emergency - Organ Support, contrasted against Emergency - Monitoring, was extremely likely to be associated with increased odds of delays (median OR 1.82, 95% CrI 1.12-2.95, 99% probability of clinically meaningful increase). The combined estimated probability of no clinically meaningful difference and clinically meaningful decreased odds of delay was 1.4%. The median estimate was that Emergency - Organ Support had 82% increased odds of delays commencing adjuvant SACT.

Elective - Organ Support, when contrasted against Elective - Monitoring, was also extremely likely to be associated with increased odds of delays (median OR 1.5, 95% CrI 1.09-2.07, 98% probability of clinically meaningful difference). The combined estimated probability of no clinically meaningful difference and clinically meaningful decreased odds of delay was 1.5%. The median estimate was that Elective - Organ Support had 50% increased odds of delays commencing adjuvant SACT.

Elective - Ward Level was likely to be associated with increased odds of delay commencing SACT (median OR 1.13, 95% CrI 0.89-1.43). The estimated probability of clinically meaningful increased odds of delay commencing SACT was 73%, the estimated probability of no meaningful difference was 19.6%, the estimated probability of a decrease in delay commencing SACT was 7.8%. Emergency - Ward Level was more likely than not to be associated with increased odds of SACT delay (median OR 1.14, 95% CrI 0.73-1.78). The estimated probability of clinically meaningful increased odds of delay commencing SACT was 64%, the estimated probability of no meaningful difference was 15%, the estimated probability of a decrease in delay commencing SACT was 21%.

Posterior estimates from the multivariable model ran with uninformative priors are shown in Figure 6.6 and Table 6.10.

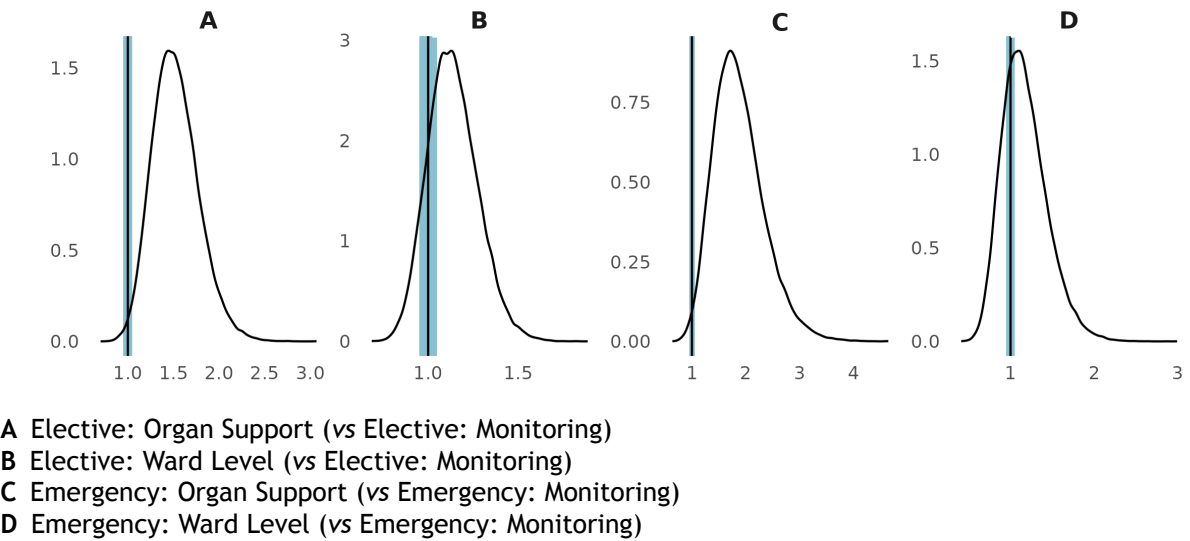


Figure 6.6: Multivariable Analysis Results - Posterior probability distribution of the odds ratio for delay to receipt of adjuvant chemotherapy (SACT B), from multivariable logistic regression model using uninformative priors, for the key variables of interest
 Light blue shaded region indicates region of practical equivalence
 Vertical line indicates OR 1 (no effect)
 Facet key provided for variable names and comparators

Table 6.10: Multivariable Analysis Results - Summary of posterior probability distribution of the odds ratio for delay to receipt of adjuvant chemotherapy (SACT B), from multivariable logistic regression model using uninformative priors, for the key variables of interest, with comparator provided beneath

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease	Percentage Of Largest Effect
Elective Organ Support <i>vs Elective: Monitoring</i>	1.50	(1.09-2.07)	99.26	1.23	98.46	0.32	98.46% chance meaningful increase
Elective Ward <i>vs Elective: Monitoring</i>	1.13	(0.89-1.43)	84.20	19.60	72.61	7.80	72.61% chance meaningful increase
Emergency Organ Support <i>vs Emergency: Monitoring</i>	1.82	(1.12-2.95)	99.14	0.89	98.63	0.48	98.63% chance meaningful increase
Emergency Ward <i>vs Emergency: Monitoring</i>	1.14	(0.73-1.78)	71.39	14.87	63.77	21.36	63.77% chance meaningful increase

CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease

6.3.3.3 Model Validity and Sensitivity

As demonstrated in Figure C.6 (in appendix) and Table 6.11, differing choice of model priors did not meaningfully change posterior probability estimates for the variables of interest.

Estimates of model validity and sensitivity are provided in the appendix, section C.3.1

Table 6.11: Sensitivity Analysis - Summary of comparisons of posterior probability distribution of the odds ratio for delay to receipt of adjuvant chemotherapy (SACT B), from multivariable logistic regression models using different prior probability distributions

Facet key provided for variable names and comparators

Variable	Uninf¹	Skep¹	ΔSkep²	Opt¹	ΔOpt²	Pess¹	ΔPess²
Elective: Organ Support	1.5	1.35	0.15	1.42	0.08	1.28	0.22
Elective: Ward Level	1.13	1.09	0.04	1.13	-0.01	1.05	0.08
Emergency: Organ Support	1.82	1.54	0.27	1.77	0.05	1.35	0.47
Emergency: Ward Level	1.14	1.1	0.04	1.24	-0.1	0.98	0.16

¹ Median Estimate of Odds From Model
² Median Estimate of Difference Between Uninformative Priors and Model

6.3.4 Regime Choice In Adjuvant Chemotherapy (SACT C)

In the following questions (SACT C to E), proxy measures for dose intensity are investigated. To do so, additional information from chemocare is required, resulting in some patient exclusion as noted in Figure 6.1.

In the first of these questions I aimed to assess for differences in receipt of Single Agent vs Dual Agent therapy, The overall proportion of patients receiving single agent therapy was 35% (n = 550). There was strong evidence no difference in proportion of patients receiving Dual versus Single Agent therapy between the six subcohorts (BF < 0.01). Elective - Organ Support had the greatest proportion of patients receiving single agent therapy (44%, n = 47). Emergency - Organ Support had the next greatest proportion of the six subcohorts (39%, n = 18). All four other subcohorts had close to identical proportions receiving single agent therapy (34-35%). There was also evidence of no difference between our six subcohorts in the proportions of patients when stratifying by specific regimens (BF 0.25 - < 0.01). Table 6.12 demonstrates the proportions observed between the six subcohorts.

Table 6.12: Results Summary - Regime Choice In Adjuvant Chemotherapy (SACT C)

	Overall N = 1,582	Elective Ward Level N = 369	Elective Monitoring N = 829	Elective Organ Support N = 107	Emergency Ward Level N = 65	Emergency Monitoring N = 166	Emergency Organ Support N = 46	Bayes Factor
Regime:								
CAPOX	871 (55%)	199 (54%)	479 (58%)	48 (45%)	33 (51%)	90 (54%)	22 (48%)	< 0.01
FOLFOX	161 (10%)	46 (12%)	69 (8.3%)	12 (11%)	9 (14%)	19 (11%)	6 (13%)	< 0.01
5FU	54 (3.4%)	19 (5.1%)	12 (1.4%)	10 (9.3%)	3 (4.6%)	9 (5.4%)	1 (2%)	0.25
Capecitabine	496 (31%)	105 (28%)	269 (32%)	37 (35%)	20 (31%)	48 (29%)	17 (37%)	< 0.01
Dual Agent	1,032 (65%)	245 (66%)	548 (66%)	60 (56%)	42 (65%)	109 (66%)	28 (61%)	< 0.01
Single Agent	550 (35%)	124 (34%)	281 (34%)	47 (44%)	23 (35%)	57 (34%)	18 (39%)	

6.3.4.1 Variable Selection - Univariable Analysis

In single variable analysis, patients with High-Risk Stage II disease had the greatest association with increased likelihood of single agent therapy (OR 5.63, 95% CrI 4.46-7.13). Patients diagnosed through screening had the greatest association with decreased likelihood of single agent therapy (OR 0.67, 95% CrI 0.54 - 0.84). In univariable analysis Organ Support was associated with increased likelihood of single agent therapy (1.34, 95% CrI 0.98-1.82 Probability of Direction of 96.6%). Full results of single variable analysis are included in Table 6.13 and Figure C.8.

Table 6.13: Summary of posterior probability distributions of the odds ratio for receipt of single agent adjuvant chemotherapy (SACT C), from univariable logistic regression models fitted to each variable.

Variable	median	CrI	PD (%)	PD_great
Age at diagnosis per increase in age by one year	1.08	(1.07 - 1.1)	100.00	TRUE
Diagnosis-to-admission per increase in interval by one day	1.00	(1 - 1)	96.30	TRUE
Anatomic Stage High Risk II vs Stage III	5.63	(4.46 - 7.13)	100.00	TRUE
Cardiac vs no cardiac comorbidity	1.12	(0.68 - 1.86)	67.45	FALSE
Dementia vs no dementia	0.96	(0.48 - 1.91)	55.11	FALSE
Diabetes vs no diabetes	1.44	(1.03 - 2.01)	98.35	TRUE
Renal vs no renal comorbidity	1.19	(0.67 - 2.09)	72.40	FALSE
Respiratory vs no respiratory comorbidity	1.25	(0.87 - 1.79)	88.91	FALSE
One additional Charlson comorbidity vs zero additional comorbidity	1.23	(0.93 - 1.63)	92.70	FALSE
Two plus additional Charlson comorbidity vs zero additional comorbidity	1.57	(0.94 - 2.59)	95.96	TRUE
Organ Support vs Monitoring	1.34	(0.98 - 1.82)	96.57	TRUE
Ward Level vs Monitoring	0.99	(0.79 - 1.24)	54.42	FALSE
Hospital duration per increase in admission duration by one day	1.01	(1 - 1.03)	97.30	TRUE
Diagnosis incidental finding vs clinical presentation	1.25	(0.73 - 2.11)	79.19	FALSE
Diagnosis other/not known vs clinical presentation	0.90	(0.49 - 1.64)	63.64	FALSE
Diagnosis screening vs clinical presentation	0.67	(0.54 - 0.84)	99.98	TRUE
Non-elective admission vs elective admission	1.03	(0.8 - 1.32)	58.40	FALSE
Multiple operations vs single operation	0.91	(0.68 - 1.2)	75.24	FALSE
Female sex vs male	1.15	(0.95 - 1.4)	91.71	FALSE
SIMD Quintile 2 vs 1	0.95	(0.71 - 1.27)	63.50	FALSE
SIMD Quintile 3 vs 1	0.90	(0.68 - 1.2)	76.24	FALSE
SIMD Quintile 4 vs 1	0.95	(0.72 - 1.27)	62.72	FALSE
SIMD Quintile 5 vs 1	0.95	(0.72 - 1.26)	62.82	FALSE
Surgery-to-chemotherapy interval per increase in interval by one day	0.94	(0.89 - 1)	98.08	TRUE
<i>CrI - Credible Interval</i>				
<i>PD - Probability of Direction</i>				
<i>Threshold noted for potential inclusion in subsequent multivariable model $\geq 95\%$</i>				

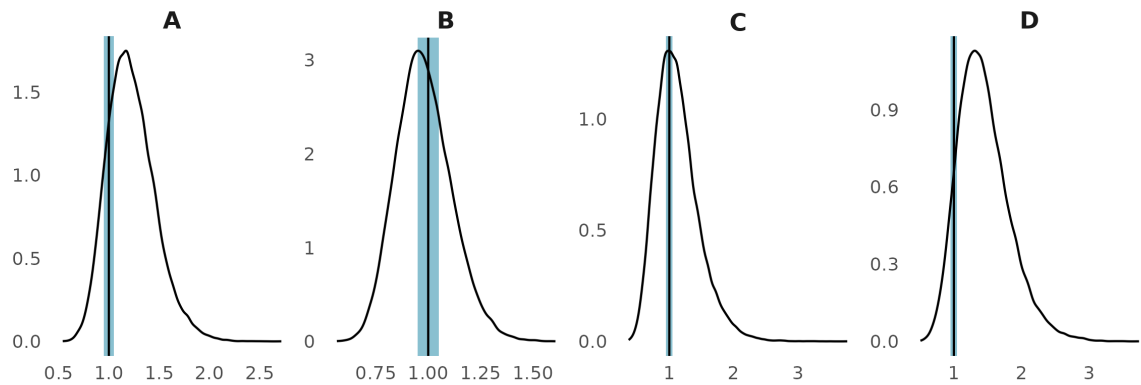
6.3.4.2 Results of Multivariable Analysis

In multivariable analysis, Elective - Organ Support was likely associated with a clinically meaningful increase in single agent therapy (a decreased intensity of SACT) (median OR 1.2, 95% CrI 0.83-1.76). The probability of a clinically meaningful increase in single agent therapy was 76%, with a median estimate 20% higher odds. This estimate allows for 13% probability of no clinically meaningful difference, and 11% probability of meaningful decrease in single agent therapy (increased SACT intensity).

For Emergency - Organ Support, any association is less clear. Reviewing the graphical distribution of the posterior distribution in Figure 6.7, the distribution appears centred close to null effect. Tabulating the distribution provides a 54% probability of meaningful increase in single agent therapy, a 32% probability of meaningful decrease in single agent therapy, and a 13% probability of no clinically meaningful difference (median OR 1.08, 95% CrI 0.61-1.91).

Emergency - Ward, was likely associated with a clinically meaningful increase in single agent therapy (median OR 1.4, 95% CrI 0.8-2.3, 86% probability of clinically meaningful increase); with a median increase in odds of 40%. This estimate had a 6.5% probability of no clinically meaningful difference, and a 6.9% probability of clinically meaningful decrease. Elective - Ward Level patients had a distribution of OR for single agent therapy centred on 1 (OR 0.97, 95% CrI 0.75-1.26).

Full results from the multivariable model ran with uninformative priors are shown in Figure 6.7 and in Table 6.14.



- A** Elective: Organ Support (vs Elective: Monitoring)
B Elective: Ward Level (vs Elective: Monitoring)
C Emergency: Organ Support (vs Emergency: Monitoring)
D Emergency: Ward Level (vs Emergency: Monitoring)

Figure 6.7: Multivariable Analysis Results - Posterior probability distribution of the odds ratio for receipt of single agent adjuvant chemotherapy (SACT C), from multivariable logistic regression model using uninformative priors, for the key variables of interest
 Light blue shaded region indicates region of practical equivalence
 Vertical line indicates OR 1 (no effect)
 Facet key provided for variable names and comparators

Table 6.14: Multivariable Analysis Results - Summary of posterior probability distribution of the odds ratio for receipt of single agent adjuvant chemotherapy (SACT C), from multivariable logistic regression model using uninformative priors, for the key variables of interest, with comparator provided beneath

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease	Percentage Of Largest Effect Explained
Elective: Organ Support <i>vs Elective: Monitoring</i>	1.20	(0.83-1.76)	83.04	13.12	75.82	11.06	75.82% chance meaningful increase
Elective: Ward Level <i>vs Elective: Monitoring</i>	0.97	(0.75-1.26)	58.31	28.59	28.28	43.13	43.13% chance meaningful reduction
Emergency: Organ Support <i>vs Emergency: Monitoring</i>	1.08	(0.61-1.91)	60.90	13.15	54.37	32.48	54.37% chance meaningful increase
Emergency: Ward Level <i>vs Emergency: Monitoring</i>	1.40	(0.84-2.32)	90.11	6.53	86.54	6.93	86.54% chance meaningful increase

CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease

6.3.4.3 Model Validity And Sensitivity

Repeating each model with differing priors (Sceptical, Optimistic, Pessimistic) resulted in similar posterior estimates for each variable, as demonstrated in Figure C.9 (appendix) and Table 6.15. Emergency - Organ Support appeared susceptible to choice of priors; pessimistic priors for Emergency - Organ Support shifted median estimate of OR from 1.08 to 0.9. Estimates of model validity and sensitivity are provided in the appendix, in Table 6.13, where all model chains achieved convergence and ESS was adequate.

Posterior predictive check for the model is provided in the appendix in Figure C.10 (appendix), where we see good agreement between model predictions and patient outcomes.

Table 6.15: Sensitivity Analysis - Summary of comparisons of posterior probability distribution of the odds ratio for receipt of single agent adjuvant chemotherapy (SACT C), from multivariable logistic regression models using different prior probability distributions
Facet key provided for variable names and comparators

[illegible]

6.3.5 Dose Delay in Adjuvant Chemotherapy (SACT D)

In keeping with other published work on dose delays, a dose delay was considered to occur when the cycle interval was one week greater than the recommended interval at any point during therapy, e.g. if a cycle interval was 14 days, an interval of 21 days or greater would be considered a delay (Wonders et al. 2023; Lyman et al. 2003, 2004). Recommended cycle intervals were:

- Oral Capecitabine: 21 Days (Haller et al. 2011)
- CAPOX: 21 Days (Haller et al. 2011)
- 5FU: 14 Days (André et al. 2004)
- FOLFOX: 14 Days (André et al. 2004)

The overall proportion of patients who experienced dose delays between SACT cycles was 42% (n = 1,582). There was strong evidence of no difference between subcohorts, in the proportion of patients experiencing delays during adjuvant SACT (BF < 0.01). Emergency - Organ Support had the highest proportion of patients experiencing dose delays (50%). However, this subcohort was small, consisting of 46 patients, 3% of the overall population receiving SACT. Table 6.16 details differences in proportions of patients experiencing delays between cycles, between the six subcohorts.

Stratifying subcohorts by the number of delays during each course of SACT, there did appear to be a difference observed when investigating patients who experienced ≥ 2 Delays (BF 9.6) and ≥ 3 Delays. The results are detailed in Table 6.17.

Table 6.16: Regime Choice In Adjuvant Chemotherapy

	Overall N = 1,582	Elective Ward Level N = 369	Elective Monitoring N = 829	Elective Organ Support N = 107	Emergency Ward Level N = 65	Emergency Monitoring N = 166	Emergency Organ Support N = 46	Bayes Factor
Any Dose Delay								
FALSE	924 (58%)	230 (62%)	471 (57%)	61 (57%)	41 (63%)	98 (59%)	23 (50%)	< 0.01
TRUE	658 (42%)	139 (38%)	358 (43%)	46 (43%)	24 (37%)	68 (41%)	23 (50%)	

Table 6.17: Magnitude of Delays Between Cycles of Adjuvant SACT

	Overall N = 1,582	Elective Ward Level N = 369	Elective Monitoring N = 829	Elective Organ Support N = 107	Emergency Ward Level N = 65	Emergency Monitoring N = 166	Emergency Organ Support N = 46	Bayes Factor
No Delay	924 (58%)	230 (62%)	471 (57%)	61 (57%)	41 (63%)	98 (59%)	23 (50%)	
1 Delay	461 (29%)	88 (24%)	254 (31%)	36 (34%)	18 (28%)	52 (31%)	13 (28%)	<0.01 ¹
2 Delays	139 (8.8%)	35 (9.5%)	72 (8.7%)	7 (6.5%)	5 (7.7%)	12 (7.2%)	8 (17%)	9.6 ²
3 Delays +	58 (3.7%)	16 (4.3%)	32 (3.9%)	3 (2.8%)	1 (1.5%)	4 (2.4%)	2 (4.3%)	5.7 ³

*BF Contingency Table Analysis, details of comparison: 1 - No Delay vs Any Delay
2 - <2 Delays vs ≥2 Delays, 3 - <3 Delays vs ≥3 Delays*

6.3.5.1 Variable Selection - Univariable Analysis

In univariable analysis, only one factor was associated with an altered likelihood of any dose delays. Receipt of 5FU compared to CAPOX was associated with a reduction in likelihood of experiencing delays (OR 0.54, 0.34-0.85, PD 99.7%). Results of single variable analysis are provided in Table 6.18, and in the appendix in Figure C.11

Table 6.18: Summary of posterior probability distributions of the odds ratio for dose delay in adjuvant chemotherapy (SACT D), from univariable logistic regression models fitted to each variable.

Variable	median	CrI	PD (%)	PD_great
Age at diagnosis per increase in age by one year	1.00	(0.99 - 1.01)	51.65	FALSE
Diagnosis-to-admission per increase in interval by one day	1.00	(1 - 1)	76.59	FALSE
Anatomic Stage High Risk II vs Stage III	0.96	(0.76 - 1.2)	64.86	FALSE
Cardiac vs no cardiac comorbidity	1.19	(0.72 - 1.95)	74.97	FALSE
Dementia vs no dementia	0.95	(0.48 - 1.89)	56.09	FALSE
Diabetes vs no diabetes	1.20	(0.86 - 1.68)	85.67	FALSE
Renal vs no renal comorbidity	0.99	(0.56 - 1.74)	51.05	FALSE
Respiratory vs no respiratory comorbidity	1.31	(0.92 - 1.85)	92.99	FALSE
One additional Charlson comorbidity vs zero additional comorbidity	1.11	(0.84 - 1.46)	76.98	FALSE
Two plus additional Charlson comorbidity vs zero additional comorbidity	1.44	(0.87 - 2.38)	92.41	FALSE
Organ Support vs Monitoring	1.08	(0.79 - 1.47)	69.38	FALSE
Ward Level vs Monitoring	0.82	(0.66 - 1.02)	96.42	TRUE
Duration of hospital stay per increase in admission duration by one day	1.01	(0.99 - 1.02)	80.82	FALSE
Diagnosis incidental finding vs clinical presentation	0.81	(0.47 - 1.38)	77.70	FALSE
Diagnosis other/not known vs clinical presentation	1.27	(0.69 - 2.32)	77.53	FALSE
Diagnosis screening vs clinical presentation	1.12	(0.91 - 1.37)	85.74	FALSE
Emergency admission vs elective admission	1.00	(0.78 - 1.27)	51.24	FALSE
Multiple operations vs single operation	0.88	(0.67 - 1.15)	82.39	FALSE
FOLFOX regime vs CAPOX	1.23	(0.91 - 1.67)	91.17	FALSE
5FU regime vs CAPOX	0.54	(0.34 - 0.85)	99.67	TRUE
Capecitabine regime vs CAPOX	1.07	(0.87 - 1.32)	72.83	FALSE
Female sex vs male	1.05	(0.87 - 1.27)	68.86	FALSE
SIMD Quintile 2 vs 1	0.92	(0.69 - 1.23)	70.75	FALSE
SIMD Quintile 3 vs 1	1.08	(0.82 - 1.42)	69.65	FALSE
SIMD Quintile 4 vs 1	0.84	(0.63 - 1.11)	88.91	FALSE
SIMD Quintile 5 vs 1	0.86	(0.65 - 1.12)	86.44	FALSE
Surgery-to-chemotherapy interval per increase in interval by one day	1.03	(0.98 - 1.09)	87.22	FALSE
<i>CrI - Credible Interval</i>				
<i>PD - Probability of Direction</i>				
<i>Threshold noted for potential inclusion in subsequent multivariable model $\geq 95\%$</i>				

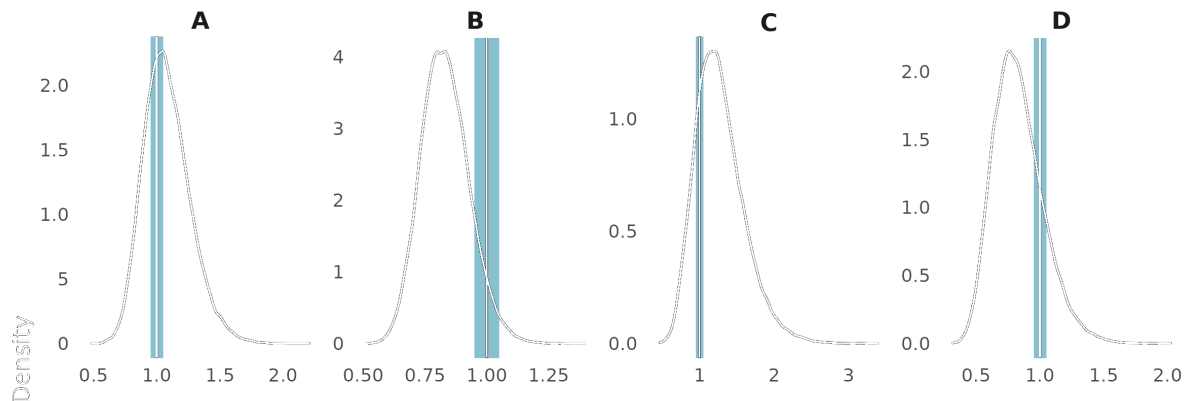
6.3.5.2 Results of Multivariable Analysis

In multivariable analysis, Emergency - Organ Support was more likely than not associated with a clinically meaningful increase in delay between doses (Median OR 1.23, 95% CrI 0.75-2.03). The probability of clinical meaningful increase in delays was 73%, allowing for 15% probability of a meaningful decrease, and 11% probability of no clinically meaningful difference.

The estimates of association between Elective - Organ Support and delays between doses was centred close to OR 1 (Median OR 1.06, 95% CrI 0.77-1.49), with a 53% probability of increased delays, 22% probability of no clinically meaningful difference, and 25% probability of decreased number of delays.

Elective - Ward was more likely than not associated with a reduced odds of dose delays (Median OR 0.83, 95% CrI 0.66-1.04, 88% probability decreased number delays).

Results from the multivariable model ran with uninformative priors are shown in Figure 6.8 and Table 6.19.



- A** Elective: Organ Support (vs Elective: Monitoring)
B Elective: Ward Level (vs Elective: Monitoring)
C Emergency: Organ Support (vs Emergency: Monitoring)
D Emergency: Ward Level (vs Emergency: Monitoring)

Figure 6.8: Multivariable Analysis Results - Posterior probability distribution of the odds ratio for dose delay in adjuvant chemotherapy (SACT D), from multivariable logistic regression model using uninformative priors, for the key variables of interest
 Light blue shaded region indicates region of practical equivalence
 Vertical line indicates OR 1 (no effect)
 Facet key provided for variable names and comparators

Table 6.19: Multivariable Analysis Results - Summary of posterior probability distribution of the odds ratio for dose delay in adjuvant chemotherapy (SACT D), from multivariable logistic regression model using uninformative priors, for the key variables of interest, with comparator provided beneath

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease	Percentage Of Largest Effect Explained
Elective: Organ Support vs Elective: Monitoring	1.06	(0.77-1.49)	64.42	21.83	53.18	25.00	53.18% chance meaningful increase
Elective: Ward Level vs Elective: Monitoring	0.83	(0.66-1.04)	95.00	9.62	1.94	88.44	88.44% chance meaningful reduction
Emergency: Organ Support vs Emergency: Monitoring	1.23	(0.75-2.03)	79.56	11.41	73.54	15.05	73.54% chance meaningful increase
Emergency: Ward Level vs Emergency: Monitoring	0.81	(0.51-1.28)	81.42	11.48	13.53	74.99	74.99% chance meaningful reduction

CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease

6.3.6 Duration of Adjuvant Chemotherapy in Weeks (SACT E)

The overall cohort median course duration was 15 weeks (3.75 months). There was strong evidence of no difference in course duration in weeks between the six subcohorts (BF < 0.01). This is detailed in table 6.21

Table 6.21: Regime Choice In Adjuvant Chemotherapy

	Overall N = 1,582	Elective Ward Level N = 369	Elective Monitoring N = 829	Elective Organ Support N = 107	Emergency Ward Level N = 65	Emergency Monitoring N = 166	Emergency Organ Support N = 46	Bayes Factor
Regime								
CAPOX	871 (55%)	199 (54%)	479 (58%)	48 (45%)	33 (51%)	90 (54%)	22 (48%)	< 0.01
FOLFOX	161 (10%)	46 (12%)	69 (8.3%)	12 (11%)	9 (14%)	19 (11%)	6 (13%)	< 0.01
5FU	54 (3.4%)	19 (5.1%)	12 (1.4%)	10 (9.3%)	3 (4.6%)	9 (5.4%)	1 (2%)	< 0.01
Capecitabine	496 (31%)	105 (28%)	269 (32%)	37 (35%)	20 (31%)	48 (29%)	17 (37%)	< 0.01
Weeks (median, IQR)	15 (9,21)	15 (9,21)	15 (9,21)	15 (9,21)	11 (9, 21)	15 (9, 21)	14 (9,21)	< 0.01

6.3.6.1 Variable Selection - Univariable Analysis

In univariable analysis, the greatest magnitude association with increased course duration was patients receiving Capecitabine in contrast to CAPOX (median OR 2.11, 95% CrI 1.76-2.51). The second greatest magnitude association was patients receiving their treatment prior to the results of the SCOT trial (median OR 1.82, 95% CrI 1.5-2.22).

Female sex was associated with decreased odds of a longer course (median OR 0.89, 95% CrI 0.76-1.04). Details of the results from single variable models are provided in Table 6.22 and in the appendix in Figure C.14.

Table 6.22: Summary of posterior probability distributions of the odds ratio for course duration of adjuvant chemotherapy (SACT E), from univariable logistic regression models fitted to each variable.

Variable	median	CrI	PD (%)	PD_great
Age at diagnosis per increase in age by one year	1.01	(1 - 1.02)	96.24	TRUE
Age 40-49 vs age under 40	1.14	(0.75 - 1.73)	71.84	FALSE
Age 50-59 vs age under 40	1.09	(0.83 - 1.43)	73.28	FALSE
Age 60-69 vs age under 40	1.06	(0.81 - 1.36)	65.50	FALSE
Age 70-79 vs age under 40	1.28	(0.98 - 1.67)	96.53	TRUE
Age 80+ vs age under 40	1.33	(0.83 - 2.14)	89.42	FALSE
Diagnosis-to-admission interval per increase in interval by one day	1.00	(1 - 1)	98.49	TRUE
Anatomic Stage High Risk II vs Stage III	1.32	(1.1 - 1.58)	99.91	TRUE
Cardiac vs no cardiac comorbidity	1.24	(0.8 - 1.92)	82.40	FALSE
Dementia vs no dementia	1.05	(0.54 - 2.03)	55.45	FALSE
Diabetes vs no diabetes	1.17	(0.89 - 1.53)	86.16	FALSE
Renal vs no renal comorbidity	0.98	(0.58 - 1.64)	52.68	FALSE
Respiratory vs no respiratory comorbidity	1.01	(0.75 - 1.36)	52.15	FALSE
One additional Charlson comorbidity vs zero additional comorbidity	1.08	(0.87 - 1.36)	75.38	FALSE
Two plus additional Charlson comorbidity vs zero additional comorbidity	1.19	(0.75 - 1.9)	78.24	FALSE
Organ Support vs Monitoring	0.96	(0.74 - 1.23)	62.55	FALSE
Ward Level vs Monitoring	0.91	(0.76 - 1.09)	85.25	FALSE
Duration of hospital stay per increase in admission duration by one day	1.01	(1 - 1.02)	90.51	FALSE
Diagnosis incidental finding vs clinical presentation	0.89	(0.54 - 1.46)	68.09	FALSE
Diagnosis other/not known vs clinical presentation	0.97	(0.55 - 1.69)	54.95	FALSE
Diagnosis screening vs clinical presentation	0.98	(0.83 - 1.15)	61.09	FALSE
Emergency admission vs elective admission	0.92	(0.75 - 1.13)	79.06	FALSE
Multiple operations vs single operation	1.00	(0.8 - 1.25)	50.41	FALSE
Diagnosis pre-SCOT trial results vs post trial publication	1.82	(1.5 - 2.22)	100.00	TRUE
FOLFOX regime vs CAPOX	1.29	(1 - 1.66)	97.67	TRUE
5FU regime vs CAPOX	0.75	(0.52 - 1.07)	94.73	FALSE
Capecitabine regime vs CAPOX	2.11	(1.76 - 2.51)	100.00	TRUE
Female sex vs male	0.89	(0.76 - 1.04)	93.46	FALSE
SIMD Quintile 2 vs 1	0.96	(0.76 - 1.23)	61.11	FALSE
SIMD Quintile 3 vs 1	0.86	(0.68 - 1.09)	88.62	FALSE
SIMD Quintile 4 vs 1	0.81	(0.64 - 1.03)	95.89	TRUE
SIMD Quintile 5 vs 1	0.88	(0.7 - 1.11)	86.60	FALSE
Surgery-to-chemotherapy interval per increase in interval by one day	0.97	(0.93 - 1.01)	90.62	FALSE
<i>CrI - Credible Interval</i>				
<i>PD - Probability of Direction</i>				
<i>Threshold noted for potential inclusion in subsequent multivariable model $\geq 95\%$</i>				

6.3.6.2 Results of Multivariable Analysis

In multivariable analysis, Organ Support was about as likely as not to be associated with any alteration in course length. For both Elective - Organ Support (median OR 0.97, 95% CrI 0.72-1.29) and Emergency - Organ Support (median OR 0.95, 95% CrI 0.68-1.68), posterior estimates of Organ Support's association with course duration were centred around no effect.

Results from the multivariable model ran with uninformative priors are shown in Figure 6.9 and Table 6.23.

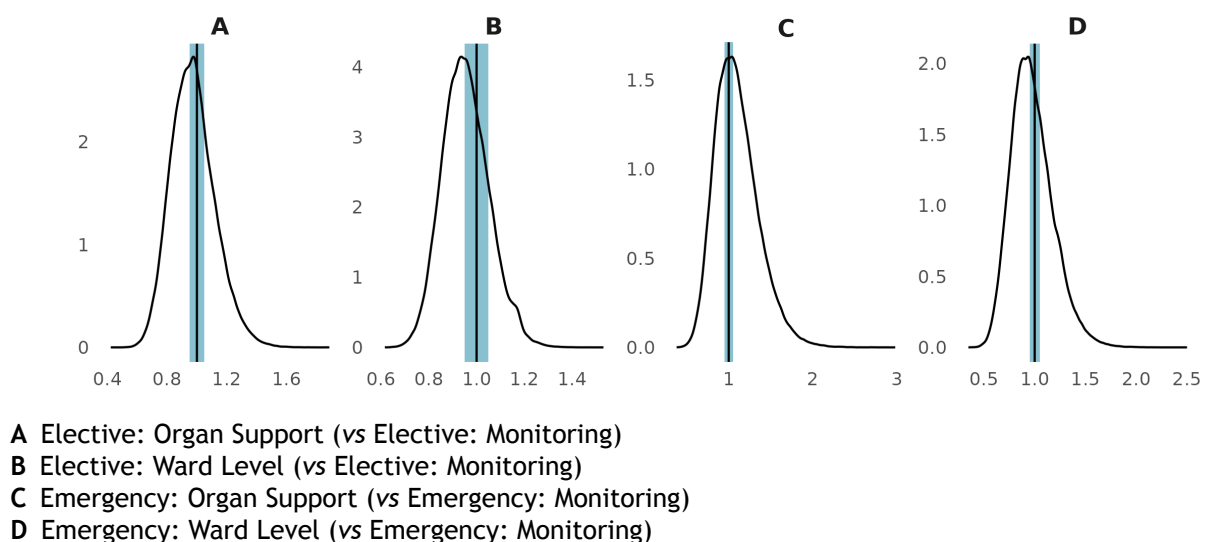


Figure 6.9: Multivariable Analysis Results - Posterior probability distribution of the odds ratio for course duration of adjuvant chemotherapy (SACT E), from multivariable logistic regression model using uninformative priors, for the key variables of interest
 Light blue shaded region indicates region of practical equivalence
 Vertical line indicates OR 1 (no effect)
 Facet key provided for variable names and comparators

Table 6.23: Multivariable Analysis Results - Summary of posterior probability distribution of the odds ratio for course duration of adjuvant chemotherapy (SACT E), from multivariable logistic regression model using uninformative priors, for the key variables of interest, with comparator provided beneath

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease
Elective: Organ Support <i>vs Elective: Monitoring</i>	0.97	(0.72-1.29)	59.79	26.19	28.08	45.73
Elective: Ward Level <i>vs Elective: Monitoring</i>	0.95	(0.78-1.16)	69.29	33.58	16.37	50.05
Emergency: Organ Support <i>vs Emergency: Monitoring</i>	1.07	(0.68-1.68)	60.83	16.29	52.69	31.02
Emergency: Ward Level <i>vs Emergency: Monitoring</i>	0.95	(0.63-1.44)	58.74	18.32	32.66	49.02
<i>CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease</i>						

6.3.6.3 Model Validity and Sensitivity

Repeating each model with differing priors (Sceptical, Optimistic, Pessimistic) resulted in similar posterior estimates for each variable, as demonstrated in Table 6.24 and in the appendix in Figure C.15. In the case of this analysis, median estimates appear identical for each choice of prior, although the 95% CrI differ. No choice of prior meaningfully impacted the estimated probability of reaching MCID. Estimates of model validity and sensitivity are provided in the appendix, in Table C.12, where all model chains achieved convergence and ESS was adequate.

Posterior predictive check for the model is provided in the appendix in Figure C.16, where there was good agreement between model predictions and patient outcomes.

Table 6.24: Sensitivity Analysis - Summary of comparisons of posterior probability distribution of the odds ratio for course duration of adjuvant chemotherapy (SACT E), from multivariable logistic regression models using different prior probability distributions

Facet key provided for variable names and comparators

Variable	Uninf ¹	Skep ¹	Δ Skep ²	Opt ¹	Δ Opt ²	Pess ¹	Δ Pess ²
Elective: Organ Support	0.97	0.97	0	0.97	0	0.97	0
Elective: Ward Level	0.95	0.95	0	0.95	0	0.95	0
Emergency: Organ Support	1.07	1.07	0	1.07	0	1.07	0
Emergency: Ward Level	0.95	0.95	0	0.95	0	0.95	0
¹ Median Estimate of Odds From Model							
² Median Estimate of Difference Between Uninformative Priors and Model							

Estimates of model validity and sensitivity are provided in the appendix, section C.6.2

6.3.7 Summary of Results

A visual summary of the association of critical illness (receipt of organ support) with the odds ratios for our questions of interest is shown below in table 6.25. Cells within this table are highlighted based on the estimated magnitude of impact, and the estimated probability of this impact. The greatest probability of meaningful difference (> 98%) is seen when observing that critical illness is associated with delays in commencement of SACT for elective and emergency patients.

Table 6.25: Summary Of Impact of Critical Illness on Questions of Interest (Odds Ratios)
Probabilities rounded to 0.5%, OR rounded to .1

Factor of Interest	Estimated Impact: Elective	Probability Of Meaningful Impact	Estimated Impact: Emergency	Probability Of Meaningful Impact
SACT Receipt	0.9 (0.7-1.2)	66.5%	0.8 (0.5-1.2)	84.0%
Delayed SACT Start	1.5 (1.1-2.1)	98.0%	1.8 (1.1-3.0)	99.0%
Single Agent Therapy	1.2 (0.8-1.8)	76.0%	1.1 (0.6-1.9)	54.0%
Delays Between Cycles	1.1 (0.8-1.5)	53.0%	1.2 (0.8-2.0)	74.0%
Reduced Course Length	0.97 (0.7-1.3)	46%	1.1 (0.7-1.7)	53%

6.4 Discussion

6.4.1 Critical Illness and Adjuvant SACT

This chapter aimed to investigate factors that influenced the likelihood of adjuvant SACT receipt among eligible CRC patients, as well as factors influencing likelihood of: delays starting adjuvant SACT, single agent therapy rather than dual agent therapy, delays between planned cycles of SACT, and shorter overall course lengths of SACT.

6.4.1.1 SACT Receipt

In Chapter 5 I noted an association between receipt of organ support and a reduced likelihood of achieving timely adjuvant chemotherapy. In this chapter I have separated this into two questions for adult hospital survivors, first do eligible patients receive adjuvant SACT at all? and second if they do receive it, does it commence within a sensible timescale?

SACT A investigates the question of patients receiving adjuvant SACT at all. Unadjusted analysis demonstrated strong evidence of a difference between the six sub-cohorts in the proportions of eligible survivors receiving adjuvant SACT, with those receiving Organ Support having the lowest proportions of adjuvant SACT receipt.

Adjuvant SACT was received by 57% of total eligible patients, comparable to the results of the meta-analysis by Boakye et al. 2021, where 61% of eligible patients received adjuvant SACT. The finding that 43% (n = 141) of eligible Elective - Organ Support survivors, and 35% (n = 59) of Emergency - Organ Support survivors eventually received adjuvant SACT, is substantially lower than the 69% finding by Camus et al. 2014 in a population of patients with CRC who survived ICU admission.

The population studied by Camus et al. 2014 was small (n = 65 survivors), and the majority of patients within that population were not being treated with curative intent. Additionally Camus et al. 2014 did not stratify beyond admission to critical care. The largest subgroup of critical care admissions in this analysis (Elective Critical Care - Monitoring), had 61% of patients eventually receive adjuvant SACT, a result more close to the findings of Camus et al. 2014 and Boakye et al. 2021.

Ultimately the work of this section of the thesis, demonstrates with a larger and more clearly defined patient population than seen in previous work, that the unadjusted cohort of patients who experience organ support in critical care, has a smaller proportion of patients who eventually receive adjuvant SACT for CRC, than previous studies have indicated.

Attempting to investigate the association of organ support receipt in isolation, after adjustment with multivariable regression, I noted a 79% posterior probability, considered likely, that Emergency - Organ Support is associated with a clinically meaningful reduction in odds of adjuvant SACT receipt, with a median estimate of a 20% reduction in odds. I noted a 67% posterior probability, considered more likely than not that Elective - Organ Support is associated with a clinically meaningful reduction in odds, with a median estimate of a 10% reduction. Both of these estimates allowed for at least 20% probability of Organ Support not being associated with a reduced odds of SACT receipt; both had estimates of odds ratio that included both practi-

cal equivalence and even increased likelihood of SACT receipt. The model provided an estimate of approximately 1 in 6 (16.5%) that Elective - Organ Support patients had an increased likelihood of SACT receipt, and an estimate of approximately 1 in 8 (12.3%) that Emergency - Organ Support patients had an increased likelihood of SACT receipt. As such, the likely association between organ support receipt and reduced subsequent adjuvant SACT should be considered as suggestive but not definitive. As noted, a limitation is that these regression models have not been structured in a manner that allows for comment on a causal relationship, as they were designed using univariable screening. In Chapter 8 I attempt to specifically investigate the causal relationship between receipt of organ support and eventual SACT receipt, and also use a stricter definition of critical illness (requiring greater than 24 hours of organ support for inclusion). This stricter definition of critical illness addresses the likely heterogeneity within the Organ Support subcohorts, where some patients meet any definition of critical illness, but others likely receive minimal support during their recovery from surgical resection.

Remaining factors were included in the analysis to allow for adjustment to investigate the association between Organ Support receipt and eventual Adjuvant SACT. However the associations between other factors and adjuvant SACT receipt remain useful for interpreting face validity of the dataset. The univariable association between increasing Age, High Risk Stage II Disease compared against Stage III disease, and increasing comorbidity with decreased eventual SACT receipt, is consistent with the relationships previously observed by Prasanna et al. 2018, and Boakye et al. 2021. Additionally SIMD Quintile 5 (most affluent) was associated with a 30% increased likelihood of adjuvant SACT receipt (OR 1.3, 1.1-1.6, 99% probability), when compared to the least affluent quintile in univariable analysis. This univariable estimate for SIMD cannot be used as a definitive estimate of the association between affluence and eventual SACT receipt; it does demonstrate that there was a difference between these particular groups, but does not address why a difference exists. This finding is in keeping with results seen among an English cohort, where patients from more de-

prived backgrounds had a lower probability of NICE-recommended treatments (Kells et al. 2025). Whilst Scottish work has demonstrated a relationship between deprivation and death from colorectal cancer, further work would be required to investigate the relationship between deprivation and cancer care quality (Lemmon et al. 2024).

6.4.1.2 Delay Starting SACT

In this second analysis, there is strong evidence of difference in the proportions of patients experiencing delays commencing SACT ($BF > 100$). Stratifying the magnitude of the delay, the difference is noted at the 9 - 12 week time interval ($BF > 50$), with strong evidence of there being no difference at later time points. There is a small minority of patients (4% of those who eventually receive SACT) whose adjuvant treatment is delayed greater than 12 weeks.

Organ Support is extremely likely to be associated with delays in commencing adjuvant SACT. Elective - Organ Support had a median estimate of 50% increased odds of delay commencing SACT (OR 1.5, 1.1-2.1, 99% probability meaningful increase). Emergency - Organ Support had a median estimate of 80% increased odds of delay commencing SACT (OR 1.8, 1.1-2.9, 99% probability). This association remains after adjustment for hospital length of stay. Whilst this study design can only describe association, the association between organ support and delay commencing adjuvant SACT is not explained by increased length of stay in the organ support groups.

For most patients experiencing a delay commencing SACT, this delay appears to be treatment starting up to 4 weeks later than desired. Whilst it is reassuring that there is not a large proportion of patients waiting greater than 12 or 16 weeks, the work of Hanna et al. 2020 has demonstrated that each four week delay starting adjuvant SACT is associated with increased mortality (Hanna et al. 2020). A limitation of this analysis,

is this dataset was collected prior to the publication of the findings from Hanna et al. 2020. As such, the majority of treatment beginning between 8 and 12 weeks was in keeping with Scottish Quality Performance Indicators at the time. A future piece of work demonstrating whether median time to adjuvant SACT has changed following the publication of QPI 5.0, may indicate if the pattern of 12 weeks to treatment was due to clinicians aiming to hit targets, or something more fixed.

6.4.1.3 Relative Intensity of SACT

Across the three proxy measures of adjuvant SACT intensity, Single Agent vs Dual Agent, Delays Between Cycles, Duration of Therapy, evidence for an association with Organ Support was weak. In initial unadjusted comparisons, there was evidence of no difference between subcohorts for each proxy measure, with BF consistently < 0.01. In adjusted multivariable analysis, I observed Elective - Organ Support as likely associated with Single Agent SACT (75.8% probability of increased odds of single agent therapy), and Emergency - Organ Support as about as likely as not (54.0% probability). I observed Emergency - Organ Support as likely associated with Dose Delays during SACT (73.5% probability of increased odds of delay), and Elective - Organ Support as about as likely as not (53.2% probability). Neither Organ Support subcohort was likely to be associated with odds of shorter course lengths of adjuvant SACT. As such, when there was signal for difference in SACT intensity, the relationship was of Organ Support being associated with decreased intensity. However no association with decreased intensity could be considered very likely.

If Organ Support admission does modify SACT intensity, the proxy measures used above may not be sensitive enough to detect it. Further analysis may be appropriate, considering the work of Nielson et al. 2021 which demonstrated a relationship between Relative Dose Intensity (RDI) < 80% and decreased survival for patients with

CRC treated with FOLFOX based chemotherapy regimens. Future work could: validate measures of RDI for each regimen in the chemocare dataset, investigate relationship between RDI and overall survival for this cohort, and use causal methods to investigate any relationship between Organ Support and RDI.

Assessing the proxy measures more broadly, the observed association in unadjusted analyses were in keeping with prior information. High-Risk stage II disease was associated with a greater than 8 times increase in odds of single agent therapy (OR 8.68, 6.6-11.6, 100% probability). Each increase in age by one year was associated with an 11% increased likelihood of single agent therapy (OR 1.11, 1.09-1.13, 100% probability). Both of these findings are as expected, considering the recommendations from McCleary et al. 2013 for this strategy. Similarly the finding of greater odds of single agent therapy for older patients, is in keeping with the findings of Prasanna et al. 2018 that elderly patients are often offered reduced SACT dose intensity.

Observing the association between treatment before publication of the SCOT trial, and increased course lengths (median OR 1.8, 95% CrI 1.5-2.2, 100% probability), is in keeping with the findings of Hanna et al. 2022, where the proportion of patients receiving course lengths greater than 3 months decreased from 75% to 42%.

6.4.2 Strengths

The work of this chapter captures a cohort of all patients with colorectal cancer treated with adjuvant SACT in Scotland over a several year window.

The work in this chapter provides an analysis of a more representative patient population than that undertaken by CRC Quality Performance Indicators. In expanding the range of ages to all adult patients with no upper limit, I include two populations excluded by previous versions of QPI, first the small but growing population of adults aged under 50 with CRC (now included in v5.0), and the large proportion of patients aged greater than 75 being treated with adjuvant SACT (who continue to be excluded in v5.0).

Separating the two questions of QPI 11, of timely adjuvant chemotherapy, into ‘any receipt of adjuvant SACT’, and ‘delays commencing adjuvant SACT’; I demonstrate a likely association between Organ Support and reduced odds of eventual adjuvant SACT, and an extremely likely association between Organ Support and delays commencing adjuvant SACT.

As in previous chapters, the use of Bayesian regression models allows both to estimate the magnitude of the effect of each factor on the question of interest, as well as providing estimates of certainty in that effect being clinically meaningful.

No previous work provides estimates of the impact of Organ Support on subsequent adjuvant SACT intensity.

6.4.3 Limitations

The design of the above analyses does not allow for causal inference. As such any association identified can not be described as the impact of Organ Support on any measure of SACT. The unrecorded measures, considered likely to be confounders, such as frailty prior to hospital admission, and decisions of treating clinicians, remain present here as they did in previous chapters.

Whilst all patients treated with adjuvant SACT for CRC over a several year window were included, with some of the subcohorts this still became a small sample size of less than 100 (46 in Emergency - Organ Support, 65 in Emergency - Ward Level). As a result, relationships between questions of interest and variables in some groups may be underpowered to identify a meaningful association.

The limitations of proxy measures for Relative Dose Intensity are discussed earlier in this discussion. Resulting from these I am unable to comment with any great confidence on how Organ Support may be associated with RDI.

Similarly, whilst delays between cycles, and reduction in course length may reflect patients experiencing toxicity, a measure of toxicity itself would have been more meaningful as a patient-centred outcome. The reliance on registry level and prescription information data in this thesis meant that measures of toxicity were not available. This lack of relevant metrics again highlights one of the key limitations of relying on routinely collected information.

6.5 Conclusion

In this chapter I demonstrate a likely association between Organ Support and reduced odds of eventual adjuvant SACT, and an extremely likely association between Organ Support and delays commencing adjuvant SACT. Clinicians who care for patients with critical illness post surgical resection, and oncologists caring for these patients with CRC post critical illness, should be aware that their patients have decreased odds of receiving subsequent treatments that could improve overall survival.

The relationship between receipt of timely SACT and overall survival in other populations is well documented. Future work should aim to establish; if critical illness has a causal relationship with decreased adjuvant therapy, the mechanisms of any causal relationship, and if the relationship between reduced timely SACT and reduced overall survival is observed amongst survivors of critical illness.

It may be survivors of critical illness should be considered as a population who would benefit from intervention to increase receipt of subsequent timely SACT. If so, specific oncology or rehabilitation input post critical illness may be required. Alternatively, it could be the case that surviving critical illness reduces the likelihood of overall benefit from commencing adjuvant SACT, due to increased risk of toxicity, or deconditioning. If so, aiming to increase access to SACT could be burdensome without merit. Both questions of interest would need to be investigated further before changes to clinical pathways were recommended.

In the next chapter, Chapter 7, I explore differences in long term survival between the six subcohorts.

Chapter 7

Survival

7.1 Introduction

Both colorectal cancer (CRC) and critical illness are understood to meaningfully reduce patients' chances of long-term survival. In this chapter I describe long term survival for hospital survivors with CRC, stratified by level of support received during hospital admission.

I first describe long term survival for all patients (with all stages) of CRC. In keeping with previous chapters, I then investigate the association between Organ Support and long term survival for a more homogenous cohort, those who have undergone surgical resection and adjuvant chemotherapy for High-Risk II or Stage III disease.

7.1.1 Survival from Colorectal Cancer

Survival from cancer can be assessed against a range of measures, each metric providing slightly different information depending on the outcome of interest. Measures of survival may be relatively straight forward, such as *overall survival*, which describes the number of patients with cancer alive at certain time points following diagnosis. Alternatively measures can be more nuanced such as *(age adjusted) net survival*, which aims to describe the probability of not dying due to cancer (adjusting for age and deaths from other causes). Other measures such as *disease-free survival* can be used, if what is important to measure is both not dying and remaining cancer free.

The European Society for Medical Oncology, in their Magnitude of Clinical Benefit Scale (ESMO-MCBS), considers the key patient-centred outcome to be overall survival. They report that measures such as disease-free survival should be considered important “intermediate” or “surrogate” end-points. For patients with CRC, overall survival requires 5 years follow up to be considered a mature measure (Cherny et al. 2025).

The Public Health Scotland report, “Cancer Survival In Scotland”, publishes both estimates of overall and cancer-specific survival. In the 2015-2019 report, overall five-year survival for all cancer types combined was 47.8% (47.5 - 48.1) (Public Health Scotland 2022b). For patients with CRC, five-year overall survival was 46.9% (45.9 - 47.8), similar to the figure for all cancer types. For men five-year survival was 46.4% (45.1 - 47.6), for women was it 47.4% (46.1 - 48.7) (Public Health Scotland 2022b).

Five-year cancer-specific survival (net survival, excluding deaths not due to cancer) was estimated at 60% (57.9 -62.2). (Public Health Scotland 2022b) These cancer-specific values are similar to English data, where five-year age-standardised survival from 2016-2020 was reported at 57.6% (57.2-58.1). (NHS Digital 2023)

In the ESMO guidelines for localised colon cancer, they report five-year survival following surgical resection to be 68-83% for patients with Stage II disease, and 45-65% for patients with Stage III disease. They also report adjuvant SACT to provide a 3-4% absolute reduction in mortality for patients with High-Risk Stage II disease, single agent therapy to provide 10-15% absolute reduction in mortality for patients with Stage III disease, and an additional 4-5% absolute reduction in mortality following addition of a second agent (Argilés et al. 2020).

As already discussed in this thesis, both receipt of adjuvant SACT and time to commence adjuvant SACT appear to impact survival. A recently published meta-analysis reporting that with each four week delay commencing adjuvant chemotherapy, is associated with an increase in patient mortality, with a hazard ratio of 1.13 (Hanna et al. 2020).

7.1.2 Critical Illness Survival

Adults admitted to hospital are at an increased risk of death compared with the general population. Approximately 35% of adult in-patients are estimated to be in their last year of life (Cosgrove et al. 2019). For patients admitted to critical care, the value is similar. A Welsh cohort study of 50,384 patients from 2006-2013 (including those aged 16 and older, only their first critical care stay during that time period), reported in-hospital mortality of 15.5%. Of those who survived to hospital discharge, 81.6% survived to one year follow up (Szakmany et al. 2019). As such, of those ad-

mitted to critical care, 31% of patients had died by the point of one year follow up. Accounting for age, critical care survivors have excess mortality following hospitalisation when compared to an matched cohort; a 2016 Scottish population study identified higher five-year mortality among intensive care survivors (32%) when contrasted against those who had survived a ward-level hospitalisation (22%) (Lone et al. 2016).

Investigating longer term survival, a French cohort study, with in-hospital mortality for patients admitted to intensive care of 19%, found hospital survivors' three-year survival to be 74.2% (Atramont et al. 2019). This resulted in three-year survival for patients who experienced critical illness to be 60%, when we consider those who died in hospital as well as those who died in the three years following discharge.

For longer term survival still, a Canadian cohort study, where in-hospital mortality for patients admitted to intensive care was 16%, followed survivors for a median of 5 years. Survival over this period was 68% for hospital survivors (Hill et al. 2016). 68% survival for the 84% of patients who survived to hospital discharge, results in a five-year survival estimate of 57%, a figure comparable to the estimates for cancer-specific five-year survival for patients with CRC. Another matched cohort study of Scottish patients, found five-year survival among ICU survivors to be the same as the Canadian results, with 68% five-year survival (Lone et al. 2016).

Age as a factor is associated with long term survival following critical illness. Stratifying by age in the French cohort study, those aged under 80 who survived hospital discharge had a three-year survival of 77.5%, whereas those survivors aged 80 and over had a three-year survival of 55.1% (Atramont et al. 2019) . In the multivariable analysis of the Canadian study, Hill and colleagues found that the factor most associated with increased mortality was increasing age (Hill et al. 2016) .

The Canadian study also reported significant burdens amongst survivors; 84% of ICU survivors re-attended hospital during follow up and 65% were readmitted to hospital. Of the total cohort of survivors, 25% were readmitted to intensive care during a subsequent hospital stay (Hill et al. 2016). Scottish estimates for readmission to hospital following critical illness, found 24% of survivors were readmitted to hospital within 90 days of discharge (Lone et al. 2018; Cosgrove et al. 2019). In the Scottish cohort study, ICU survivors had an estimated mean hospital admission rate of 4.8 admissions over five years, greater than the matched cohort rate of 3.3 admissions over five years (Lone et al. 2016).

Previous work has investigated the association between ICU admission and survival for patients with solid organ cancers. However, the bulk of this literature focuses on the heterogenous grouping of solid organ cancers, rather than specific cancer types (Puxty et al. 2014; Zee et al. 2021). Similarly, the majority of the literature looking at survival following ICU admission for patients with cancer continues for one year follow up, with a few studies following patients for four years (Puxty et al. 2014). Currently for patients with CRC and critical illness the long-term outcomes literature is limited in three key respects: survival is rarely reported at the time point recommended by ESMO (5 years), CRC is grouped in with other solid organ cancers with differing prognoses, and critical illness is rarely described beyond admission to critical/intensive care. In this chapter I aim to address these limitations. Using subcohorts of patients stratified by nature of admission and level of support during hospitalisation, I provide additional information beyond the binary of admission to critical care. Focusing solely on CRC I provide disease specific estimates. Following patients for five-year overall survival I use the patient centred measure recommended by ESMO.

7.2 Method

7.2.1 Data Sources

As described in the methods chapters, the cohort was constructed using national level registry information of all patients in Scotland diagnosed with CRC from 2013-2018. Using Scottish Cancer Registry (SMR-06), Scottish Records of Inpatient Admissions (SMR-01), and Scottish Intensive Care Society Audit (SICSAG) information patients diagnosed with CRC were identified, and assigned to one of the six subcohorts. Overall survival following cancer diagnosis was determined using the Scottish Mortality Records. SMR-01, SMR-06, and Scottish Quality Performance Indicators Data (QPI) provide additional data pertaining to:

- Surgical Resection of CRC - During Hospital Stay
- Anatomic Stage of CRC
- Age of Patient At Diagnosis
- Comorbidities, both named and count (classification as Charlson Comorbidity Index)
- Duration of Index Hospital Stay
- Method of Cancer Diagnosis
- Number of Operations During Index Hospital Stay
- Sex of Patient
- Scottish Index of Multiple Deprivation (SIMD) Quintile
- Admitting Specialty During Index Admissions
- Overall Aim of CRC Therapy

In these analyses, the definition of a hospital survivor was a patient who survived both hospital discharge, and the first thirty days following hospital discharge. Using the same approach as previous chapters, the key characteristics of hospital admission assessed were: level of support during hospital admission (Ward Level Care, Monitoring in Critical Care, Organ Support in Critical Care), and the nature of hospital admission (Elective, Emergency) resulting in the same six sub-cohorts used earlier.

Understanding that both the likelihood and impact of critical illness will differ depending on cancer stage, I also analysed the impact on survival amongst a more uniform group of patients. This group of patients have been investigated in Chapter 6: those who should be experiencing treatment with curative intent with High-Risk Stage II or Stage III disease, who received surgical resection during their index admission, who subsequently received adjuvant chemotherapy (SACT).

Selecting patients with High-Risk Stage II and Stage III disease who have undergone surgical resection and adjuvant SACT, ensures the inclusion of only patients considered both as having "curable disease", and who have undergone "curative treatment". If after such filtering, differences in mortality persisted, there may be greater reason to suspect an impact of critical illness itself on long term survival.

A CONSORT diagram of the patient filtering through the study selection criteria for the second analysis is shown in Figure 7.1. Filtering was required based on data availability, staging, the receipt of surgical resection, and the receipt of adjuvant chemotherapy. These steps were performed using the same criteria as the Quality Performance Indicators (QPI) for Colorectal Cancer in Scotland. Additionally for data validity it was also required: that surgical resection occurred during the index admission (recorded in SMR-01), and that prescription data from CHEMOCARE was available.

For this more focused subcohort, whilst some variables were no longer relevant, I did include other potentially relevant variables such as: delay commencing adjuvant SACT, any delay during course of adjuvant SACT, and single agent or dual agent adjuvant SACT.

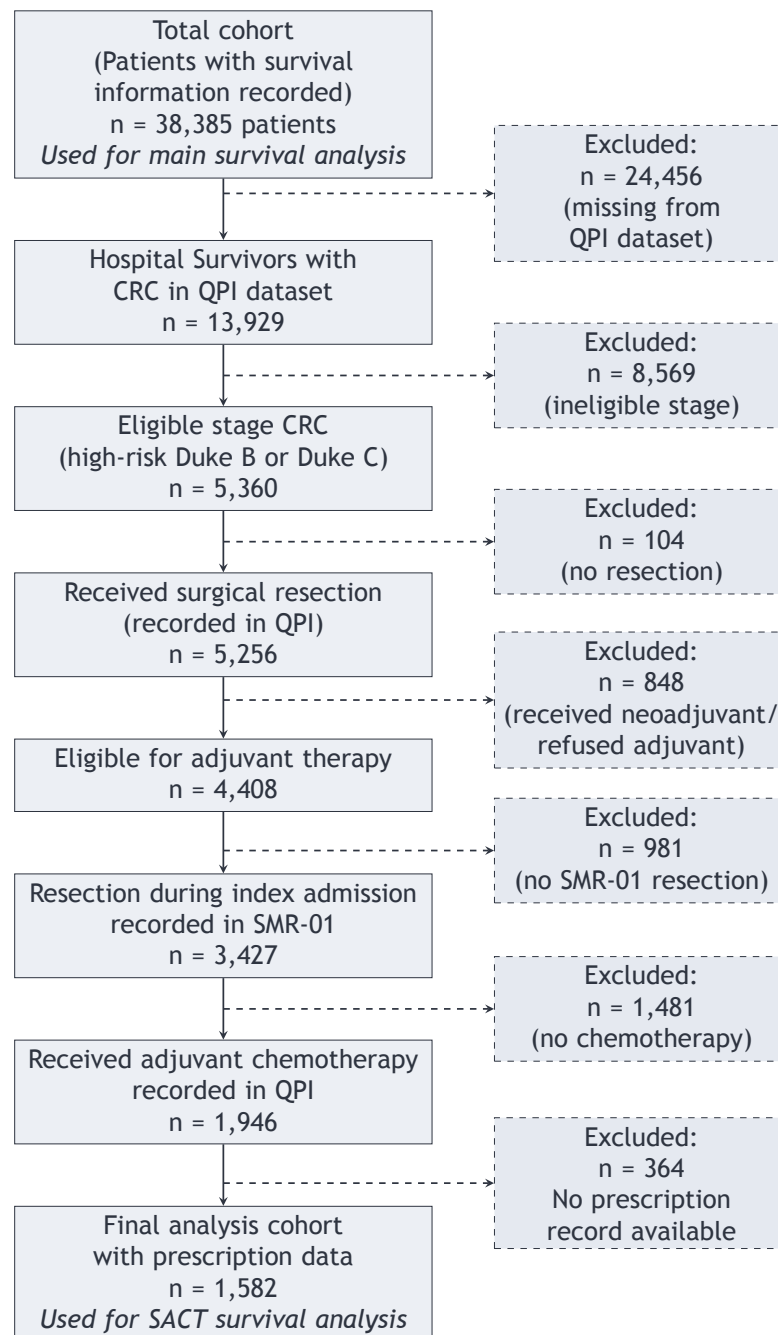


Figure 7.1: CONSORT diagram showing patient selection for main and subgroup survival analysis

7.2.2 Survival Analysis

7.2.2.1 Kaplan Meier

The most common form of time to event, or survival, analysis used in clinical studies would be the use of the Kaplan-Meier method. This accounts for censoring of data, where event outcome information is unavailable either due to loss of patient to follow up, or survival beyond the final follow up time period (Altman and Bland 1998). As terminology: the probability of survival past a certain time point may be called the survival function, the rate of event occurrence during a period of time may be called the hazard rate, and the hazard function represents the instantaneous risk of event occurrence, given the individual has survived up to that time point (Schober and Vetter 2018).

The Kaplan-Meier method estimates the probability of survival beyond a certain time period, using conditional probability, where the condition is that the patient was alive at the start of the time period being assessed. This approach assumes that those who are censored have the same percentage chance of survival as those who are not censored (Bland and Altman 1998). To calculate the probability of survival over time the number of events that occur during an interval is divided by the number of people at risk at the beginning of the interval. Each interval is set at the unique time point an event, in our case death occurs. Patients who have been censored do not influence the number of events, but are subtracted from the number of people at risk (Jager et al. 2008).

A worked example is provided in Table 7.1

Table 7.1: Worked Example of Kaplan-Meier Survival Calculation

Day	At Risk	Deaths	Lost to Censoring	Daily Survival Probability	KM Calculation	Cumulative Survival
0	100	0	0	1	Starting point	100%
1	100	10	0	$1 - (10/100) = 0.9$	$1 \times 0.9 = 0.9$	90%
2	90	10	0	$1 - (10/90) = 0.889$	$0.9 \times 0.889 = 0.8$	80%
3	80	0	10	NA	NA	80%
4	70	10	0	$1 - (10/70) = 0.857$	$0.8 \times 0.857 = 0.686$	69%

Such an analysis allows for a representation of survival of a group over time, and can be stratified to compare subgroups. However it is unable to determine the impact of multiple factors on survival, and for this a different method such as Cox Proportional Hazards is often used.

7.2.2.2 Cox Proportional Hazards

Cox Proportional Hazards (Cox PH) regression, separates both the baseline hazard function for a population, and how each variable (coefficient) adjusts hazard for an individual (Schober and Vetter 2018; Wang et al. 2019). The mechanism for the Cox Proportional Hazards model does not estimate the baseline hazard, only the impact of each coefficient on the hazard. In doing so, Cox PH models allow for the baseline hazard to vary over time, but make the assumption that the impact of any given variable is time-independent. That is to say that the impact of a variable has the same impact on Day 1 that it would on day 100 (Schober and Vetter 2018). This combination of modelling the impact of coefficients and not modelling the baseline hazard means that the Cox PH model is referred to as a “semi-parametric” model.

As such hazard for a patient a at time t can be represented through:

$$h_a(t) = h_0(t) \times \exp(\beta_1 x_{a1} + \beta_2 x_{a2} + \dots)$$

7.2.2.3 Bayesian Modelling

Cox PH models are well established in frequentist analysis of survival data, however their use in Bayesian statistics is less common, with alternative approaches being taken that allow for direct modelling of the baseline hazard. The Bayesian framework adopted in this thesis uses R, the probabilistic programming language Stan, and the popular R package BRMS as an interface from R to compile Stan code. As a result, commonly used tooling for Bayesian statistics is not feature complete for Cox PH models (Bürkner 2020; Hervas 2017).

Alternative approaches are often taken, such as the use of fully parametric models, where the baseline hazard function is modelled along with the impact of each co-variate (Bartoš et al. 2022). Recognising that Cox PH models in the BRMS ecosystem in R would not be able to use standardised tooling for assessing model accuracy, I initially investigated use of fully parametric models, such as Weibull, gamma, and log-normal. These were discarded as options due to having poor fit with the dataset: either through poor predictive accuracy (relating to censoring), or the shape of the parametric baseline hazard not matching well with the observed data.

Fortunately a more appropriate technique is available, one that allows modelling of the baseline hazard for a population in a time varying manner, and also the impact of model coefficients on the hazard function, in a fully compatible way with commonly used Bayesian tools. This gives all the advantages of a Bayesian analysis as described in previous methods chapters, whilst also allowing for predicted survival estimates and survival curves to be generated, as well as being at it's heart methodologically comparable to Cox PH models.

This approach is to use Bayesian Piece-Wise Exponential Additive Mixed Models (PAMMs).

Fundamentally, a PAMM organises survival data into a set number of intervals. For this analysis, intervals set at 3 months, 6 months, 9 months, 12 months, 2 years, 3 years, 4 years and 5 years were selected. This balanced clinical relevance (increased variability in hazard during the first year of follow up) against computational intensity (each additional interval significantly increases size of dataset for analysis). For each patient it is recorded if they experienced an event during that interval. This allows the baseline hazard to vary between intervals. The length of each interval is taken into account as another variable, to allow for differing lengths of intervals. The number of events during an interval can now be modelled as a Poisson regression model. In such a regression model, an event during an interval is the outcome variable, and predictor variables are the variables of interest, as well as the interval length, “offset” coefficient. Results from PAMMs are comparable to those provided by Cox PH analysis (Hervas 2017; Tierens et al. 2019). As seen in previous chapters the use of a Bayesian framework allows us to accurately quantify uncertainty in our predictions, as well as assessing the impact of differing priors on model predictions.

7.2.2.4 ROPE + MCID

As described in previous chapters, thresholds for prior probabilities and minimum clinically important difference (MCID) need to be set for analysis. Fortunately with cancer survival the European Society of Medical Oncology have developed and published the Magnitude of Clinical Benefit Scale (Cherny et al. 2025). This tool had been developed to assess the impact of proposed anticancer treatments, to determine if such treatments have substantial impact on cancer survival and should be promoted and advocated for as treatment options.

Using the minimum value considered to be a significant impact on survival, the MCID for can be set for patients, and as such the range for the Region of Practical Equivalence (ROPE). The values considered to be a substantial positive or negative impact on survival, can be used to centre optimistic and negative priors' probability estimates.

ESMO-MCBS considered a median of five-year follow up to be required for patients with colorectal cancer. For patients with solid organ cancers with curative intent, they determined three thresholds for treatment: A, B, and C, where A and B were considered to reflect "substantial benefit". ESMO report that treatments meeting threshold for A or B would "justify rapid consideration for reimbursement". Grade A, would reflect a therapy that provides a 5% or greater improvement in survival gain. Grade B, reflects a therapy that provides a 3 to 5% improvement in survival gain. Grade C, would reflect a less than 3% improvement in survival gain (Cherny et al. 2025). As such I set MCID at 3% difference in overall survival at five years.

Optimistic and pessimistic priors were set to be centred at a 5% difference in overall survival (either improved or reduced) at 5 years. To calculate the hazard ratio the following was undertaken: The most recent estimate for baseline 5 years survival in all patients with colorectal cancer of 46.9% (Public Health Scotland 2022b) was used to calculate a hazard ratio that would result in a 3% absolute improvement in survival at five years, of 49.9%.

To estimate such a hazard ratio we can take the following steps:

- Baseline Survival at 5 Years: 46.9% (0.469)
- 3% absolute improvement in Baseline Survival at 5 Years: 49.9% (0.499)
- Baseline Hazard Rate (λ) Over 5 Years:

$$\lambda_{\text{baseline}} = \frac{-\ln(\text{survival})}{5} = \frac{-\ln(0.469)}{5} = 0.151 \text{ per year}$$

- Improved Hazard Rate Over 5 Years:

$$\lambda_{\text{improved}} = \frac{-\ln(0.499)}{5} = 0.139 \text{ per year}$$

- Hazard Ratio:

$$\text{HR} = \frac{\lambda_{\text{improved}}}{\lambda_{\text{baseline}}} = \frac{-\ln(0.499)/5}{-\ln(0.469)/5} = \frac{-\ln(0.499)}{-\ln(0.469)} = 0.92$$

Using this approach to convert differences in overall survival to hazard ratio, the ROPE can be set at 0.92 to 1.09. Using the 5% estimate to centre the optimistic and pessimistic priors; provided an estimated mean for the optimistic prior at 0.87, and an estimated mean for the pessimistic prior at 1.15.

With the second cohort of patients, where baseline survival was 77%, I set ROPE at 0.89 - 1.17, optimistic mean at 1.32, and pessimistic mean at 0.80. As seen above, to achieve the same difference in absolute survival, with differing levels of baseline hazard, different hazard ratios were required.

Using the recommendations from Zampieri et al. 2021, as in previous chapters, optimistic and pessimistic priors had standard deviations set so that: optimistic priors allowed for 15% of the prior probability for Hazard Ratio to be 1 or greater. pessimistic priors allowed for 15% of the prior probability for Hazard Ratio to be 1 or less.

7.2.3 Model Predictions

After confirming model validity, and predictive accuracy, the model can be used to make predictions of survival. This allows visualisation of the isolated impact of critical illness and nature of admission on long term survival. In these predictions, a standardised reference population was sampled from the original dataset, predicted survival was computed at 30 day intervals. For each individual at each time point, cumulative survival was calculated from posterior predictions of cumulative hazard. For each subcohort, mean and 95% credible intervals were calculated for each time point, to allow stratified survival curves to be plotted.

7.3 Results: Total Population

7.3.1 Kaplan Meier

Of the total population of patients with CRC who survived their index admission (38,385), five-year kaplan-meier estimate for overall survival was 52% (95% CI 52-53), as shown in Figure 7.2 and Table 7.2.

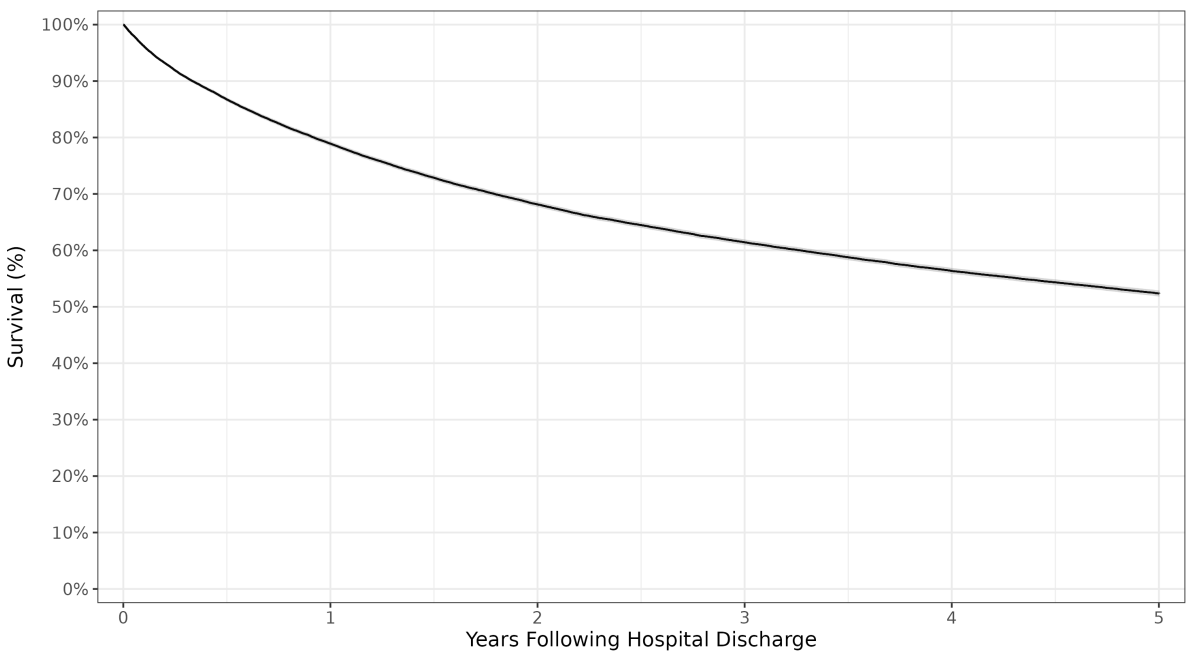


Figure 7.2: Kaplan Meier Overall Survival Curve for Total Population of Patients with CRC
Time zero being discharge alive from hospital, survival being overall survival

Table 7.2: Summary of Kaplan Meier estimates for overall survival for patients with CRC following discharge alive from hospital, including all patients (all stages of disease) discharged alive

Time	At Risk	Cumulative Events	Survival (95% CI)
0	38,385	0	100% (100, 100)
1	29,825	8,084	79% (78, 79)
2	23,803	12,020	68% (68, 69)
3	19,663	14,276	61% (61, 62)
4	16,438	15,831	56% (56, 57)
5	13,701	16,936	52% (52, 53)

Overall survival was markedly different when stratified by treatment intent, as seen in Figure 7.3 and Table 7.3. Patients whose treatment intent was recorded as curative had five-year survival of 71% (95% CI 70-71), those whose treatment intent was recorded as non-curative had 9% (95% CI 8-9). There was a large proportion of patients with unrecorded treatment intent, whose overall five-year survival was 48% (95% CI 46-50).

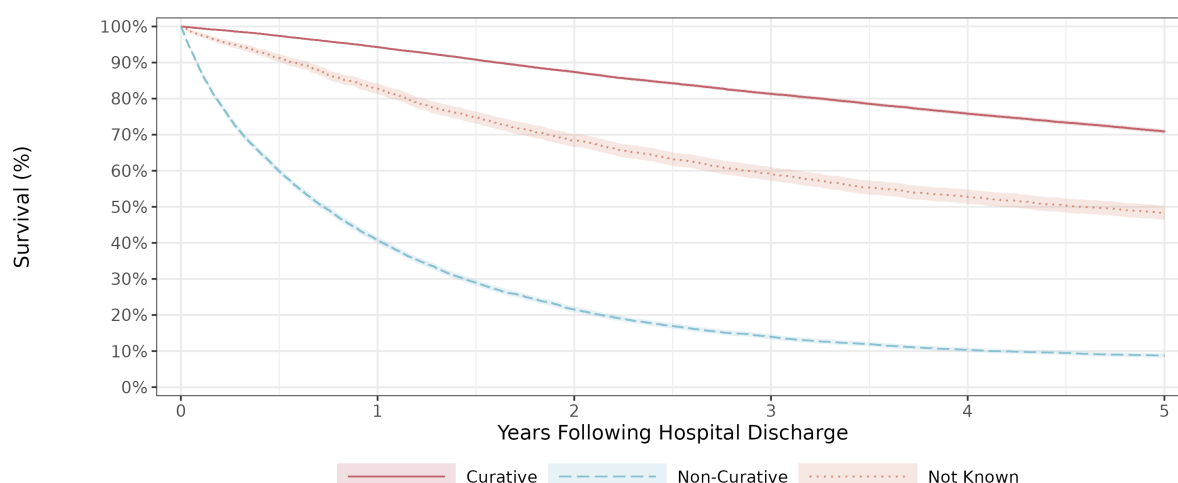


Figure 7.3: Kaplan Meier Overall Survival Curve for Total Population of Patients with CRC, Stratified by Treatment Intent
Time zero being discharge alive from hospital, survival being overall survival

Table 7.3: Risk Table Summarising Kaplan Meier Overall Survival for Total Population of Patients with CRC, Stratified by Treatment Intent
Time zero being discharge alive from hospital, survival being overall survival

Time	Curative		Non-Curative		Not Known	
	At Risk (Cum. Events)	Survival (95% CI)	At Risk (Cum. Events)	Survival (95% CI)	At Risk (Cum. Events)	Survival (95% CI)
0	25,309 (0)	100% (100, 100)	10,460 (0)	100% (100, 100)	2,616 (0)	100% (100, 100)
1	23,483 (1,445)	94% (94, 95)	4,186 (6, 189)	41% (40, 42)	2,156 (450)	83% (81, 84)
2	20,014 (3,098)	87% (87, 88)	2,032 (8,098)	22% (21, 22)	1,757 (824)	68% (67, 70)
3	16,962 (4,429)	81% (81, 82)	1,214 (8,786)	14% (13, 15)	1,487 (1,061)	59% (57, 61)
4	14,334 (5,524)	76% (75, 76)	812 (9,089)	10% (10, 11)	1,292 (1,218)	53% (51, 55)
5	11,976 (6,405)	71% (70, 71)	614 (9,208)	9% (8, 9)	1,111 (1,323)	48% (46, 50)

Stratifying by the nature of admission and support during admission, demonstrates difference in 5 year survival between the six subcohorts, as shown in Figure 7.4. All elective subcohorts had greater five-year survival than all emergency subcohorts. Among elective and emergency admissions, patients treated with monitoring in critical care had the greatest overall survival, followed by those treated with organ support in critical care, and last were those treated at a ward level.

Elective patients that received monitoring in critical care had the greatest five-year survival estimates of 70% (95% CI 69-71). Elective patients that received organ support in critical care had five-year survival estimates of 61% (95% CI 59-63), and those receiving ward level care had 54% (95% CI 53-55). Among emergency patients, those that received monitoring in critical care had five-year survival estimates of 40% (95% CI 37-44), with those treated with organ support in critical care had 34% (95% CI 31-37), and those that received ward level care had 23% (95% CI 22-24).

Noting that the five-year overall survival estimates for the population of CRC hospital survivors of 52%, was greater than the most recently published Scottish estimates of 46.9% (Public Health Scotland 2022b), As a validation check, an adjusted estimate of mortality taking hospital mortality into account was undertaken. With the observed hospital mortality of 12% for all patients, a 52% estimated five year overall survival for hospital survivors, becomes 46% estimated overall survival for all patients admitted to hospital. Adjusted five year mortality rates for all hospital admission subcohorts are provided in the Appendix in Table D.15.

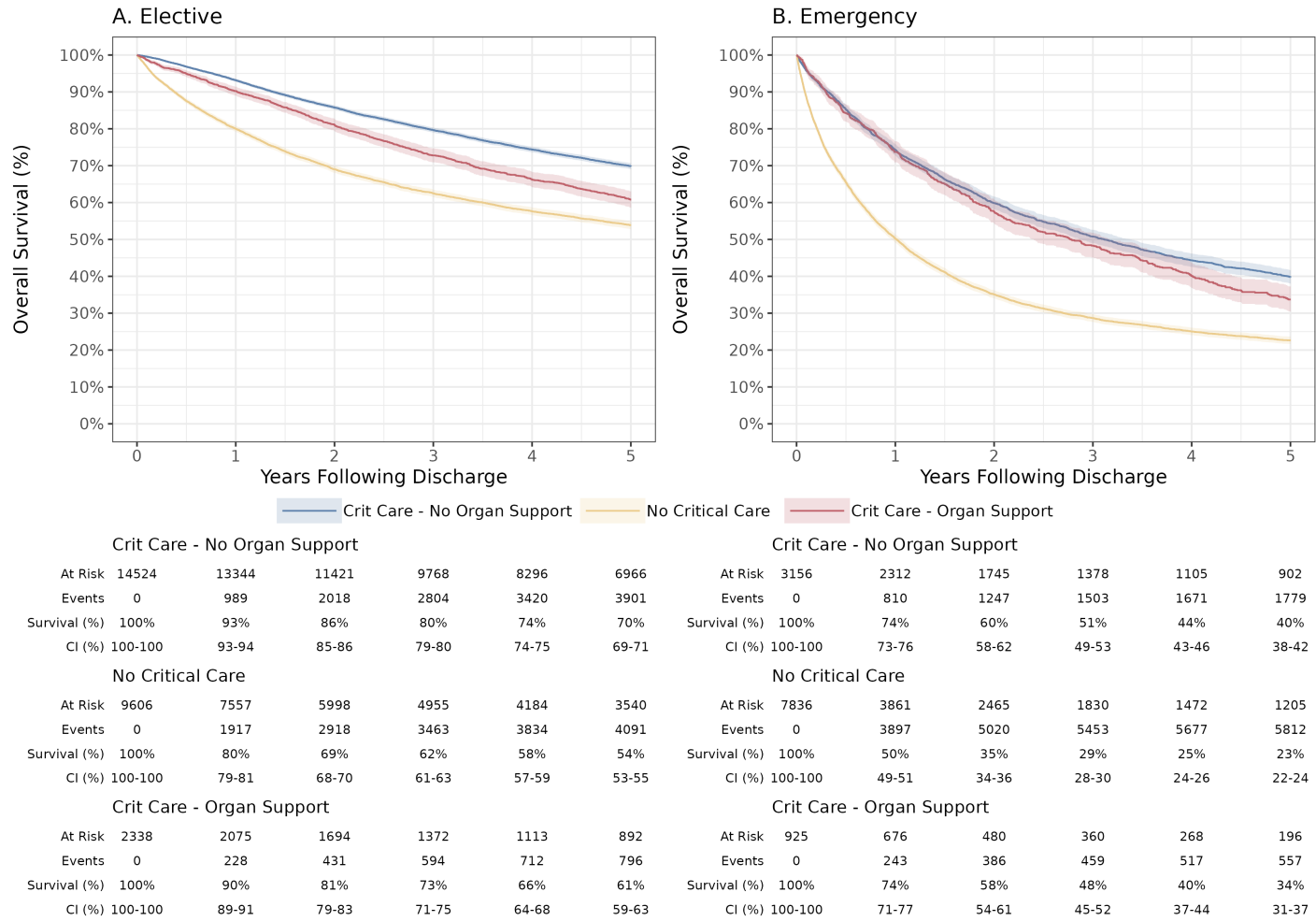


Figure 7.4: Kaplan Meier Plot and Risk Table - Five-Year Overall Survival For Patients With CRC - Stratified by nature of hospital admission and level of support during admission - Risk table provides counts of number at risk and events, as well as probability estimates and 95% confidence intervals for survival

7.3.2 Univariable Analysis

To identify appropriate variables for multivariable analysis, a series of univariable models of overall survival to five years follow up were constructed. Results of these models are shown in Figure 7.5 and Table 7.4. The same methodology of variable screening was used as seen in previous chapters, where variables with a PD > 95% were included in the final model.

Of the single variable models, the following were included in the multivariable analysis:

- Age Decade - Grouped (Factor)
- Surgical Resection of Colorectal Cancer During Admission (Logical)
- Count of Charlson Comorbidities (Factor)
- Level of Support During Hospital Stay (Factor)
- Duration of Hospital Stay Weeks - Grouped (Factor)
- Method of Cancer Detection (Factor)
- Nature of Admission (Factor)
- Number of Operations During Admission (Factor)
- SIMD Quintile (Factor)
- Surgical Admission (Logical)
- Treatment Objectives (Factor)

Of the variables which reached the threshold for probability of direction but were not included: Age was included as a grouped variable rather than numeric, due to an observed non-linear relationship between age and likelihood of death. Comorbidities were included in the grouped “comorbidity count” variable rather than individual named comorbidities, for model brevity. Anatomic stage and metastatic disease were both excluded, due to large amounts of missing data within each variable.

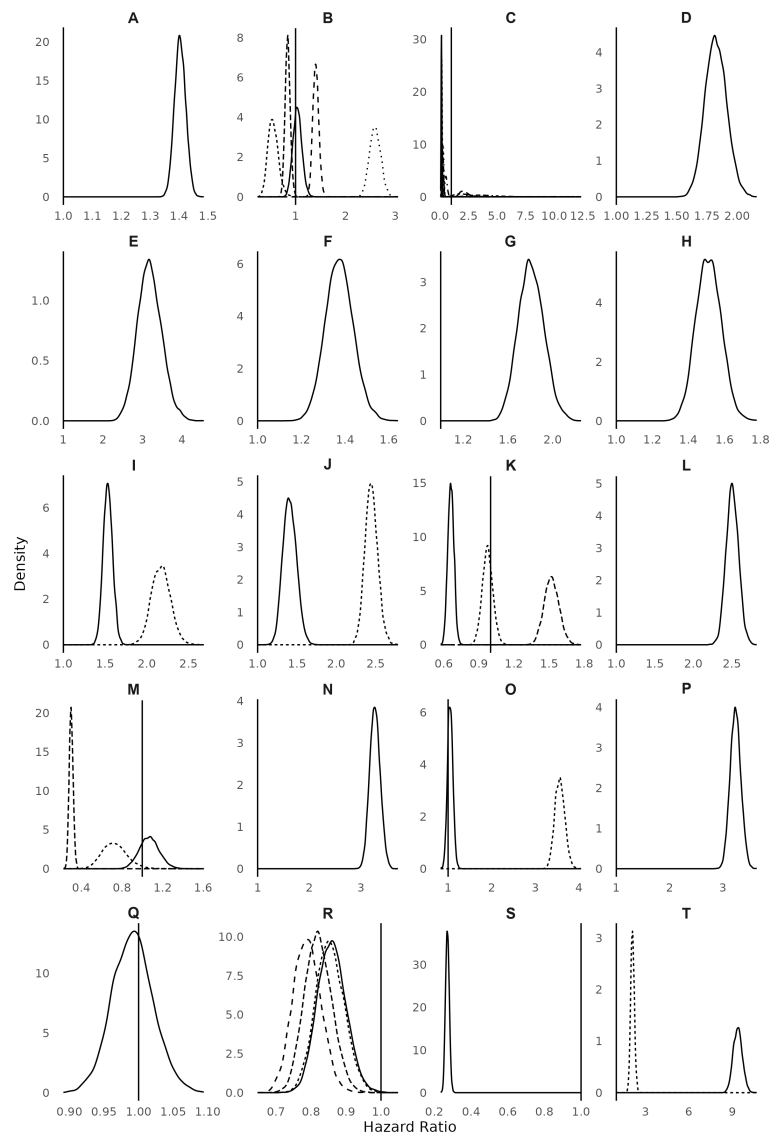
Whilst performed for initial variable screening, univariable analysis does allow for some comment on any unadjusted association with hazard. The following is included for illustration of some aspects within the cohort, but does not attempt to state any association with certainty, as I report on unadjusted analyses.

Therapy with non curative or palliative intent, when compared against those treated with curative intent, provided a median hazard ratio of 9.38 (95% CrI 8.78-9.99). Diagnosis following Screening Examination when compared against those diagnosed following clinical presentation, provided a median hazard ratio of 0.3 (95% CrI 0.26-0.34). Increasing age appeared associated with increasing hazard (median HR 1.4, 95% CrI 1.37-1.44), as did the presence of multiple comorbidities (median HR 2.17 95% CrI 1.95-2.4). Increasing affluence appeared associated with decreasing hazard, when the most affluent quintile (SIMD 5) was compared against the most deprived (SIMD 1) (median HR 0.79, 95% CrI 0.71-0.87).

Of note, age appeared to have a non-linear relationship with hazard of mortality. Whilst in general, increasing age was associated with increased hazard, the youngest cohort (< 40) had a similar hazard of mortality to those aged 60-69 (univariable median HR 1.04, 95% CrI 0.87-1.22). For all other bracketed age cohorts, those younger than 60-69 had reduced hazard, and those older had increased hazard.

Table 7.4: Summary of posterior probability distributions of the hazard ratio for five-year overall survival (total cohort), from univariable survival models fitted to each variable.

Variable	Median	CrI	PD (%)	Threshold Reached
Age at diagnosis per increase in age by one decade	1.40	(1.37 - 1.44)	100.00	TRUE
Age <40 vs age 60-69	1.04	(0.87 - 1.22)	66.02	FALSE
Age 40-49 vs age 60-69	0.54	(0.37 - 0.77)	99.99	TRUE
Age 50-59 vs age 60-69	0.84	(0.75 - 0.95)	99.84	TRUE
Age 70-79 vs age 60-69	1.40	(1.29 - 1.53)	100.00	TRUE
Age 80+ vs age 60-69	2.59	(2.38 - 2.82)	100.00	TRUE
No curative resection in admission vs curative resection	3.24	(3.05 - 3.44)	100.00	TRUE
Anatomic Stage I vs Stage 0	0.14	(0.09 - 0.2)	100.00	TRUE
Anatomic Stage IIA vs Stage 0	0.17	(0.12 - 0.24)	100.00	TRUE
Anatomic Stage IIB vs Stage 0	0.26	(0.17 - 0.4)	100.00	TRUE
Anatomic Stage IIIA vs Stage 0	0.24	(0.14 - 0.39)	100.00	TRUE
Anatomic Stage IIIB vs Stage 0	0.30	(0.21 - 0.42)	100.00	TRUE
Anatomic Stage IIIC vs Stage 0	0.54	(0.38 - 0.78)	99.92	TRUE
Anatomic Stage IVA vs Stage 0	2.08	(1.52 - 2.91)	100.00	TRUE
Anatomic Stage IVB vs Stage 0	1.99	(0.93 - 3.79)	96.04	TRUE
Anatomic Stage IVC vs Stage 0	3.76	(1.87 - 7.09)	99.98	TRUE
Cardiac vs no cardiac comorbidity	1.82	(1.66 - 2)	100.00	TRUE
Dementia vs no dementia	3.17	(2.61 - 3.82)	100.00	TRUE
Diabetes vs no diabetes	1.37	(1.25 - 1.5)	100.00	TRUE
Renal vs no renal comorbidity	1.81	(1.59 - 2.04)	100.00	TRUE
Respiratory vs no respiratory comorbidity	1.51	(1.38 - 1.65)	100.00	TRUE
One additional Charlson comorbidity vs zero additional comorbidity	1.53	(1.43 - 1.64)	100.00	TRUE
Two plus additional Charlson comorbidity vs zero additional comorbidity	2.17	(1.95 - 2.4)	100.00	TRUE
Organ Support vs Monitoring	1.41	(1.25 - 1.58)	100.00	TRUE
Ward Level vs Monitoring	2.44	(2.29 - 2.61)	100.00	TRUE
Admission duration 2-3 weeks vs <1 week	0.66	(0.61 - 0.71)	100.00	TRUE
Admission duration 3-4 weeks vs <1 week	0.97	(0.89 - 1.06)	71.97	FALSE
Admission duration 4+ weeks vs <1 week	1.52	(1.4 - 1.65)	100.00	TRUE
Known metastatic disease vs no known metastatic disease	2.51	(2.35 - 2.67)	100.00	TRUE
Diagnosis incidental finding vs clinical presentation	1.07	(0.88 - 1.27)	76.01	FALSE
Diagnosis other vs clinical presentation	0.72	(0.51 - 0.99)	98.04	TRUE
Diagnosis screening examination vs clinical presentation	0.30	(0.26 - 0.34)	100.00	TRUE
Non-elective admission vs elective admission	3.27	(3.08 - 3.48)	100.00	TRUE
Multiple operations vs one operation	1.05	(0.93 - 1.17)	79.16	FALSE
No operations vs one operation	3.56	(3.35 - 3.79)	100.00	TRUE
Female sex vs male	0.99	(0.93 - 1.05)	61.66	FALSE
SIMD Quintile 2 vs 1	0.86	(0.78 - 0.94)	99.92	TRUE
SIMD Quintile 3 vs 1	0.85	(0.78 - 0.94)	100.00	TRUE
SIMD Quintile 4 vs 1	0.82	(0.75 - 0.9)	99.98	TRUE
SIMD Quintile 5 vs 1	0.79	(0.71 - 0.87)	100.00	TRUE
Surgical admission vs medical admission	0.27	(0.25 - 0.29)	100.00	TRUE
Non curative / palliative intent vs curative intent	9.38	(8.78 - 9.99)	100.00	TRUE
Therapy intent not known vs curative intent	2.12	(1.88 - 2.38)	100.00	TRUE
<i>CrI - Credible Interval</i>				
<i>PD - Probability of Direction</i>				
<i>Threshold noted for potential inclusion in subsequent multivariable model $\geq 95\%$</i>				



- A** Age at diagnosis (*per increase in age by one decade*)
B Age group (vs Age 60-69); dotted = 80+, dashed = 70-79, solid = 40-, dashed = 50-59, short-dash=40-49
C Anatomic Stage (vs Stage 0); *scale prevents interpretation of facet*
D Cardiac comorbidity (vs No cardiac comorbidity)
E Dementia (vs No dementia)
F Diabetes (vs No diabetes)
G Renal comorbidity (vs No renal comorbidity)
H Respiratory comorbidity (vs No respiratory comorbidity)
I Charlson comorbidity count (vs Zero additional comorbidity); solid = One additional, dotted = Two plus
J Support in Hospital (vs Monitoring); solid = Organ Support, dotted = Ward Level
K Hospital admission duration (vs < 1 week); solid = 2-3 weeks, dotted = 3-4 weeks, dashed = 4+ weeks
L Known Metastatic Disease (vs no known metastatic disease)
M Method of first detection (vs Clinical Presentation); dashed = Other, solid = Screening Examination, dotted = Incidental Finding
N Non-elective admission (vs Elective admission)
O Operations in admission (vs One); solid = Multiple, dotted = None
P No curative resection in admission (vs curative resection)
Q Female Sex (vs Male)
R Deprivation quintile (SIMD) (vs Q1); solid = Q2, dotted = Q3, long-dash = Q4, dashed = Q5
S Surgical Admission (vs medical admission)
T Therapy Objections (vs curative); dotted = Not Known, solid = Non Curative

Figure 7.5: Posterior probability distributions of the hazard ratio for five-year overall survival (total cohort), from univariable survival models fitted to each variable. Vertical line at HR 1 (no effect). Facet key provides title and comparator for each variable

7.3.3 Multivariable Analysis

Results from the multivariable model are shown in Figure 7.6 and Table 7.5. Estimates for the other variables included in the model are included in the Appendix in Table D.16

For elective admissions who have survived hospitalisation, it was extremely likely that Organ Support (when contrasted against Monitoring in Critical Care) is associated with increased hazard of mortality (median HR 1.19, 95% CrI 1.1-1.28). The probability of clinically meaningful increase in hazard of mortality was 98.76%, probability of no meaningful change combined with probability of decreased hazard was 1.23%.

For emergency admissions who have survived hospitalisation, it was virtually certain that emergency admission is associated with increased hazard of mortality (median HR 1.73, 95% CrI 1.63-1.83), and it was extremely unlikely that Emergency - Organ Support is associated with any further reduction in survival beyond emergency admission alone (median HR 1, 95% CrI 0.91-1.1).

The probability of clinically meaningful increase in hazard of mortality for emergency admissions was estimated at >99.5%, whereas the probability of clinically meaningful increase in hazard of mortality for Emergency - Organ Support was estimated at 3.2% (with estimated probability of no meaningful difference at 91.66%).

Investigating any association between Ward Level treatment and long term survival produced similar pattern of estimates. Elective - Ward Level contrasted against Elective - Monitoring was extremely likely to be associated with increased hazard of mortality (median HR 1.21 95% CrI 1.15-1.27), with an estimated probability of meaningful

increase in hazard of > 99.5%. Emergency - Ward Level was extremely unlikely to be associated with a further increase in hazard of mortality (median HR 0.95 95% CrI 0.9-1.01), with an estimated probability of no meaningful difference in hazard of 87.5% and probability of increased hazard of 0%.

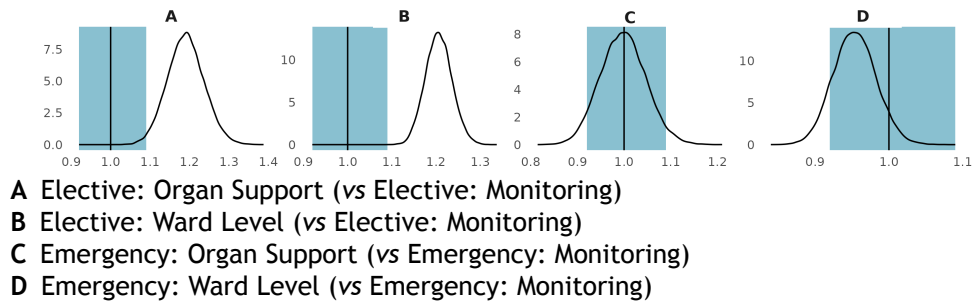


Figure 7.6: Multivariable Analysis Results - Posterior probability distribution of the hazard ratio for five-year overall survival (total cohort), from multivariable survival model using uninformative priors, for the key variables of interest
 Light blue shaded region indicates region of practical equivalence
 Vertical line indicates HR 1 (no effect)
 Facet key provided for variable names and comparators

Table 7.5: Multivariable Analysis Results - Summary of posterior probability distribution of the hazard ratio for five-year overall survival (total cohort), from multivariable survival model using uninformative priors, for the key variables of interest, with comparator provided beneath

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease	Percentage Of Largest Effect
Elective: Organ Support <i>vs Elective: Monitoring</i>	1.19	(1.1 - 1.28)	100.00	1.23	98.76	0.00	98.76% chance meaningful increase
Elective: Ward Level <i>vs Elective: Monitoring</i>	1.21	(1.15 - 1.27)	100.00	0.00	100.00	0.00	100% chance meaningful increase
Emergency: Organ Support <i>vs Emergency: Monitoring</i>	1.00	(0.91 - 1.1)	51.93	91.66	3.20	5.14	91.66% chance ROPE
Emergency: Ward Level <i>vs Emergency: Monitoring</i>	0.95	(0.9 - 1.01)	94.24	87.53	0.00	12.47	87.53% change ROPE

CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease

7.3.4 Sensitivity Analysis, Model Validation, and Posterior Predictive Check

For the question of impact of critical illness on long term survival, no model priors meaningfully changed the estimates of hazard ratio. Differences in posterior estimates of median hazard ratio ranged from 0.01 to 0.03 for elective patients, and from -0.01 to -0.04 for emergency patients.

Sensitivity analysis of model priors was performed, as shown in Figure 7.7 and Table 7.6

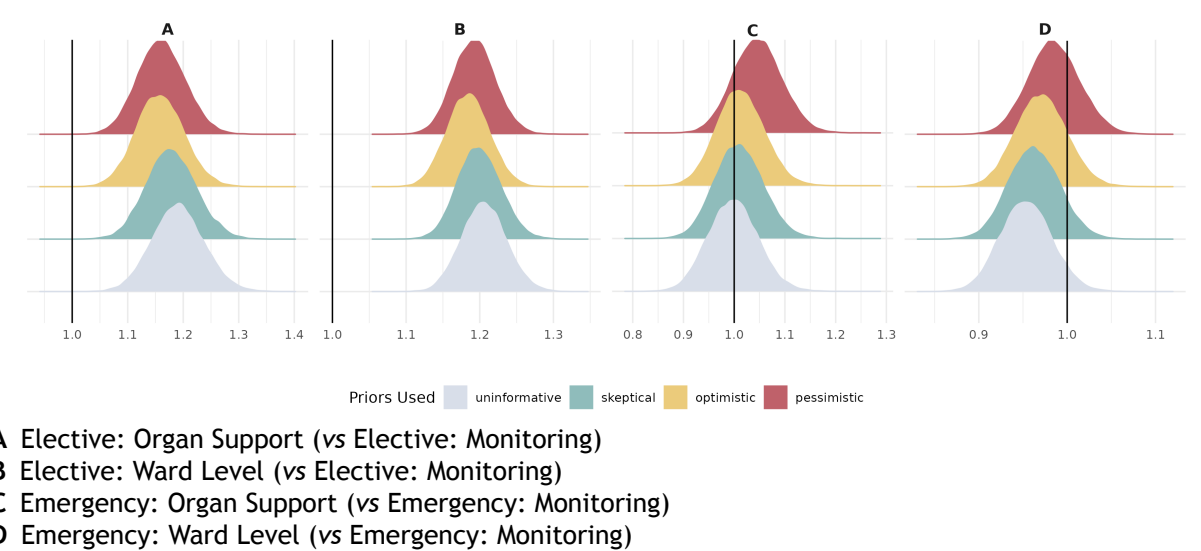


Figure 7.7: Sensitivity Analysis - Comparisons of posterior probability distribution of the hazard ratio for five-year overall survival (total cohort), from multivariable survival models using different prior probability distributions
Facet key provided for variable names and comparators

Variable	Uninf ¹	Skep ¹	Δ Skep ²	Opt ¹	Δ Opt ²	Pess ¹	Δ Pess ²
Elective:	1.19	1.18	0.01	1.16	0.03	1.16	0.03
Organ Sup-	(1.1 -	(1.09 -	(-0.11 -	(1.08 -	(-0.09 -	(1.08 -	(-0.09 -
port	1.28)	1.27)	0.14)	1.25)	0.16)	1.25)	0.15)
Elective:	1.21	1.2	0.01	1.18	0.02	1.19	0.01
Ward	(1.15 -	(1.14 -	(-0.08 -	(1.13 -	(-0.06 -	(1.14 -	(-0.07 -
	1.27)	1.26)	0.09)	1.24)	0.1)	1.25)	0.09)
Emergency:	1	1.01	-0.01	1.01	-0.01	1.05	-0.05
Organ Sup-	(0.91 -	(0.92 -	(-0.14 -	(0.92 -	(-0.15 -	(0.96 -	(-0.18 -
port	1.1)	1.11)	0.12)	1.11)	0.12)	1.14)	0.08)
Emergency:	0.95	0.96	-0.01	0.97	-0.02	0.98	-0.03
Ward	(0.9 -	(0.91 -	(-0.09 -	(0.92 -	(-0.1 -	(0.93 -	(-0.11 -
	1.01)	1.02)	0.07)	1.03)	0.06)	1.04)	0.05)
¹ Median Estimate of Hazard Ratio From Model							
² Median Estimate of Difference Between Uninformative Priors and Model							

Table 7.6: Sensitivity Analysis - Summary of comparisons of posterior probability distribution of the hazard ratio for five-year overall survival (total cohort), from multivariable survival models (PAMM) using different prior probability distributions
Facet key provided for variable names and comparators

Assessing convergence of the model in table D.17 there were good measures of model validity, with all values for $\hat{R}$ being less than 1.01, and all Effective Sample Size (ESS) being greater than 15000 (where Gelman and colleagues recommend a minimum of 400) (Vehtari et al. 2021). The posterior predictive check of the model, shown in the Appendix in Figure D.17, demonstrates predicted values overlap well with the actual observed values (to the point where on the figure predicted values (y_{rep}) are obscured by observed values (y)).

7.3.5 Multivariable Model Predicted Survival

As noted in Methods, use of PAMMs for survival analysis allows for sampling from the posterior distribution, and generation of predictions of long term survival. Predicted survival is shown in Figure 7.8, where a reference population was randomly sampled from the original dataset, adjusting for differences between subcohorts such as age, comorbidity, stage of disease, and treatment intent.

There is an observed mean difference of 4% in predicted survival at five years between Elective - Monitoring and Elective - Organ Support. The multivariable model predicted five year survival estimates for Elective - Monitoring (the reference group for elective patients) at 59% (95% CrI 58-60). Elective - Organ Support had predicted worse survival at 55% (95% CrI 54-55).

All emergency subcohorts had similarly poor survival to one another, with mean predicted five-year survival of 17-18%, with 95% credible intervals falling in the range of 16 to 18.

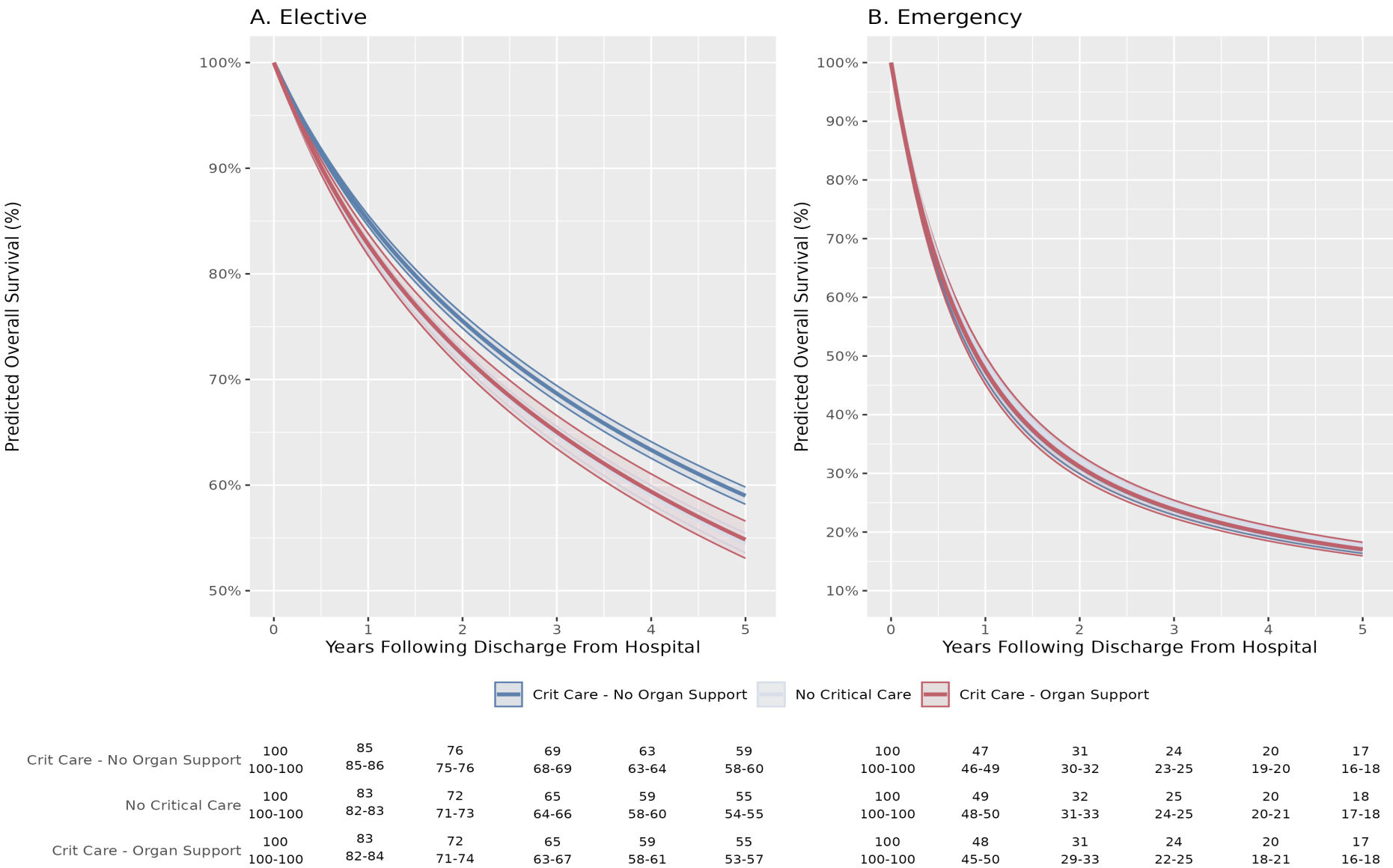


Figure 7.8: Predicted Five-Year Overall Survival For Subcohorts of Patients with CRC (All Stages) Following Discharge Alive From Hospital
Predictions demonstrating differences between levels of support during admission and long term overall survival

7.4 Results: Survival in Eligible Patients Treated with Adjuvant SACT

7.4.1 Kaplan Meier

Assessing the more homogenous population of the 1,582 patients with High Risk Stage II or Stage III disease, who received surgical resection of their CRC, and subsequently received adjuvant SACT, five-year survival following hospital discharge was 77% (95% CI 75-80), as shown in Figure 7.9 and Table 7.7. This absolute survival is 25% higher than the 52% (95% CI 52-53) seen among the total population of patients with CRC.

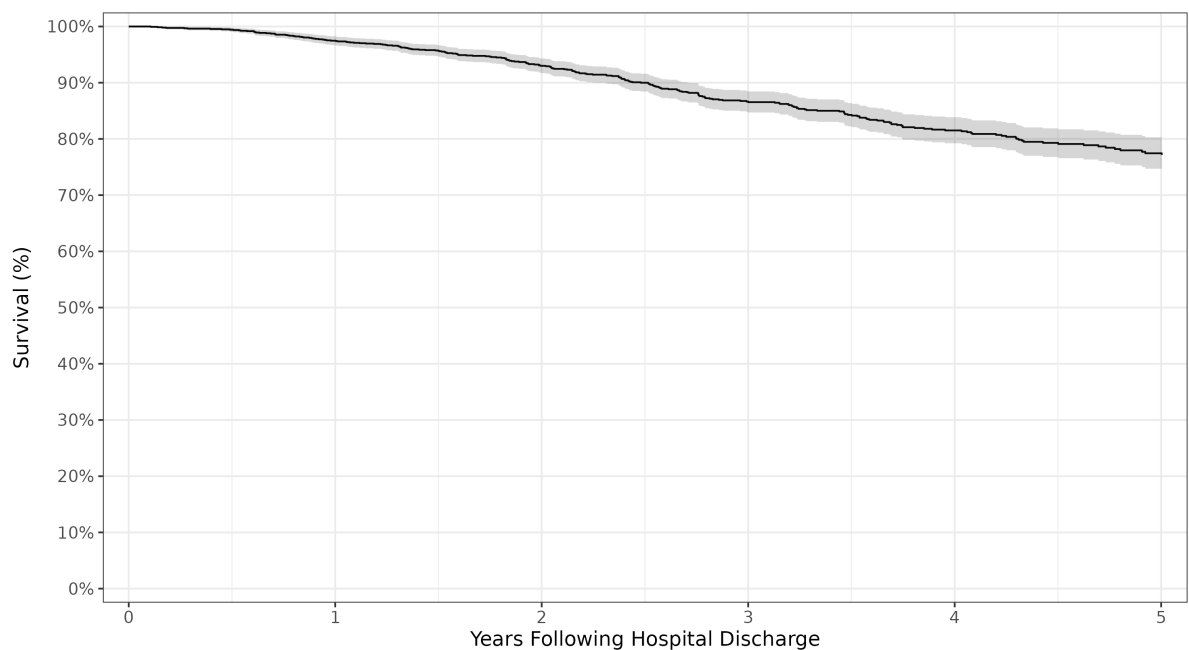


Figure 7.9: Kaplan Meier Overall Survival Curve for patients with High Risk II or Stage III CRC Who Received Adjuvant SACT Following Curative Resection
Time zero being discharge alive from hospital, survival being overall survival

Table 7.7: Summary of Kaplan Meier Overall Survival estimates for patients with High Risk II or Stage III CRC Who Received Adjuvant SACT Following Curative Resection
Time zero being discharge alive from hospital, survival being overall survival

Time	At Risk	Cumulative Events	Survival (95% CI)
0	1582	0	100% (100,100)
1	1542	40	97% (97,98)
2	1212	105	93% (92,94)
3	840	179	87% (85,88)
4	535	220	82% (79,84)
5	277	241	77% (75,80)

Assessing differences in survival by subcohort, as shown in Figure 7.10 this analysis suffers from the small number of patients remaining at risk throughout follow up. Similar trends in survival are seen to the subcohort analysis of the total population, where all elective subcohorts had greater mean estimates for five-year survival than all emergency subcohorts.

Elective - Monitoring, had five-year survival of 82% (95% CI 79-86). Elective - Organ Support, had lower five year survival of 77% (95% CI 67-88) In a similar pattern Emergency - Monitoring, had five-year survival of 65% (95% CI 57-75); Emergency - Organ Support, had lower five year survival of 47% (95% CI 30-75)

Whilst there were differences in mean estimates of survival between Organ Support and No Organ Support in critical care for both elective and emergency admissions. At each year of follow up, confidence intervals between Organ Support and Monitoring overlapped. This appears due to both the small size within each subcohorts, and the large amount of patient censoring. Censoring within this analysis was high, at five years ranging from 55-73% of each subcohort. This was a greater issue than in the analysis of the total cohort (where five year censoring ranged from 10-28% of each subcohort) as inclusion criteria relied on more recent data provided by QPI and chemocare, and as such was less likely to have full five-year follow up.

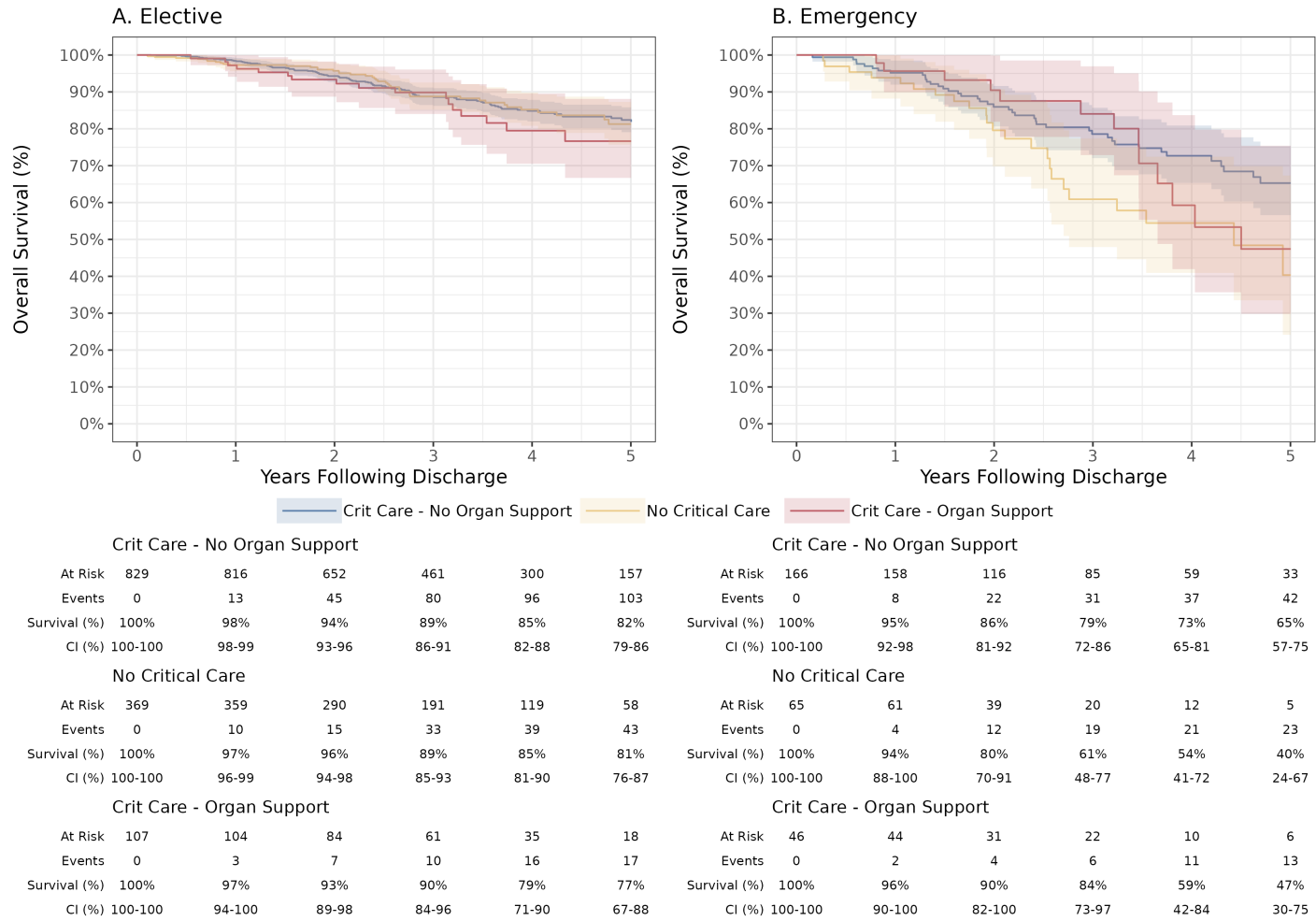


Figure 7.10: Kaplan Meier Plot and Risk Table - Five-Year Overall Survival For Patients With High Risk Stage II and Stage III CRC Treated With Adjuvant SACT - Stratified by nature of hospital admission and level of support during admission - Risk table provides counts of number at risk and events, as well as probability estimates and 95% confidence intervals for survival

7.4.2 Univariable Analysis

For this second analysis, a separate set of univariable survival models were constructed, where, as before a preset threshold of probability of direction was used to determine inclusion in multivariable analysis. Results of these models are shown in figure 7.11 and table 7.8.

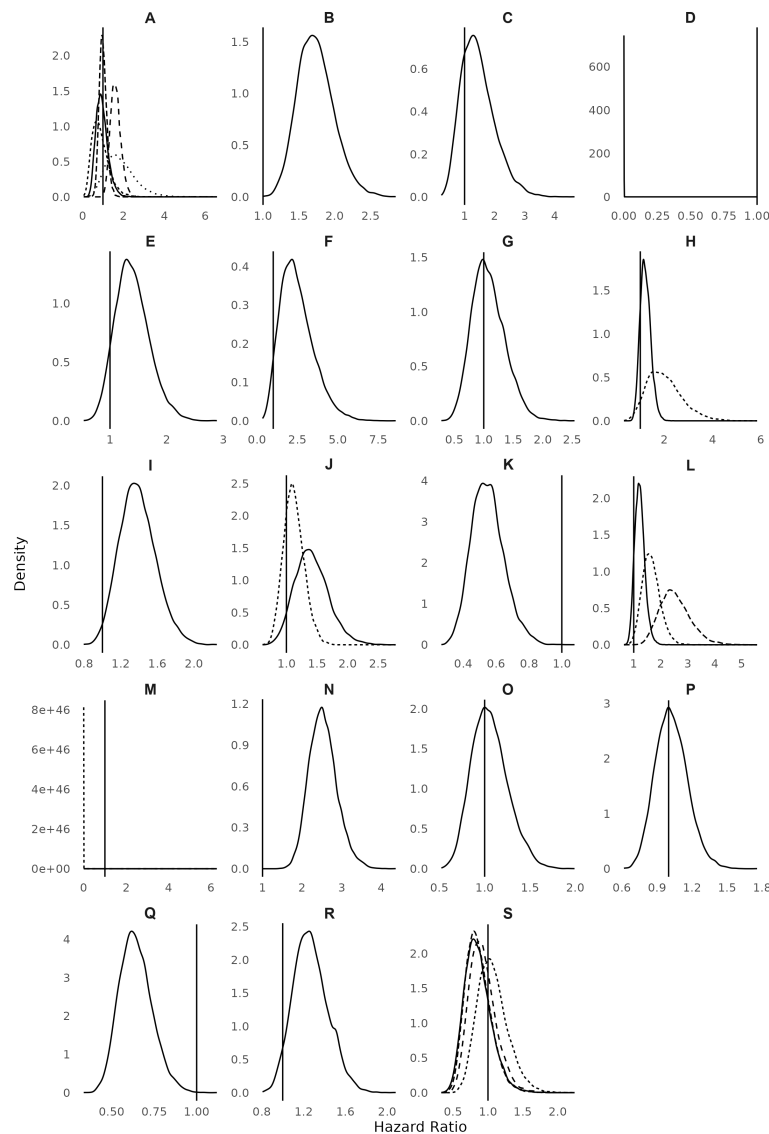
Table 7.8: Summary of posterior probability distributions of the hazard ratio for five-year overall survival among patients who received adjuvant SACT, from univariable survival models fitted to each variable.

Variable	Median	CrI	PD (%)	Threshold Reached
Age <40 vs age 60-69	0.92	(0.48 - 1.62)	60.80	FALSE
Age 40-49 vs age 60-69	0.81	(0.28 - 1.86)	67.14	FALSE
Age 50-59 vs age 60-69	0.99	(0.68 - 1.39)	53.28	FALSE
Age 70-79 vs age 60-69	1.60	(1.18 - 2.18)	99.92	TRUE
Age 80+ vs age 60-69	1.75	(0.73 - 3.51)	90.48	FALSE
Anatomic Stage High Risk II vs Anatomic Stage III	0.54	(0.37 - 0.77)	99.98	TRUE
Delay during chemotherapy vs no delay	1.72	(1.29 - 2.29)	99.99	TRUE
Cardiac vs no cardiac comorbidity	1.38	(0.58 - 2.74)	77.87	FALSE
Diabetes vs no diabetes	1.37	(0.88 - 2.06)	92.07	FALSE
Renal vs no renal comorbidity	2.33	(0.89 - 4.87)	96.05	TRUE
Respiratory vs no respiratory comorbidity	1.06	(0.61 - 1.68)	58.07	FALSE
One additional Charlson comorbidity vs zero additional comorbidity	1.20	(0.84 - 1.69)	83.87	FALSE
Two plus additional Charlson comorbidity vs zero additional comorbidity	1.92	(0.86 - 3.66)	94.84	FALSE
Delay commencing chemotherapy vs no delay commencing	1.37	(1.04 - 1.81)	98.59	TRUE
Organ Support vs Monitoring	1.40	(0.94 - 2.02)	95.06	TRUE
Ward Level vs Monitoring	1.11	(0.83 - 1.47)	76.22	FALSE
Admission duration 2-3 weeks vs <1 week	1.21	(0.9 - 1.63)	89.74	FALSE
Admission duration 3-4 weeks vs <1 week	1.62	(1.08 - 2.36)	99.06	TRUE
Admission duration 4+ weeks vs <1 week	2.48	(1.58 - 3.78)	99.99	TRUE
Non-elective admission vs elective admission	2.51	(1.91 - 3.3)	100.00	TRUE
Multiple operations vs single operation	1.04	(0.72 - 1.49)	58.58	FALSE
Single agent therapy vs dual agent therapy	1.02	(0.78 - 1.32)	55.38	FALSE
Screening diagnosis vs non-screening diagnosis	0.64	(0.47 - 0.85)	99.95	TRUE
Female sex vs male	1.26	(0.97 - 1.62)	95.92	TRUE
SIMD Quintile 2 vs 1	0.84	(0.54 - 1.28)	79.31	FALSE
SIMD Quintile 3 vs 1	1.04	(0.71 - 1.55)	58.83	FALSE
SIMD Quintile 4 vs 1	0.84	(0.56 - 1.27)	79.11	FALSE
SIMD Quintile 5 vs 1	0.90	(0.61 - 1.35)	69.06	FALSE

CrI - Credible Interval

PD - Probability of Direction

Threshold noted for potential inclusion in subsequent multivariable model $\geq 95\%$



- A** Age group (vs Age 60-69); dotted = 80+, dashed = 70-79, solid = 40-, dashed = 50-59, short-dash=40-49
- B** Delay during chemotherapy (vs no delay)
- C** Cardiac comorbidity (vs No cardiac comorbidity)
- D** Dementia (*inapplicable*)
- E** Diabetes (vs No diabetes)
- F** Renal comorbidity (vs No renal comorbidity)
- G** Respiratory comorbidity (vs No respiratory comorbidity)
- H** Charlson comorbidity count (vs Zero additional comorbidity); solid = One additional, dotted = Two plus
- I** Delay commencing chemotherapy (vs no delay commencing)
- J** Support in Hospital (vs Monitoring); solid = Organ Support, dotted = Ward Level
- K** Anatomic Stage High Risk II (vs Anatomic Stage III)
- L** Hospital admission duration (vs < 1 week); solid = 2-3 weeks, dotted = 3-4 weeks, dashed = 4+ weeks
- M** Method of first detection (*inapplicable*)
- N** Non-elective admission (vs Elective admission)
- O** Multiple operations (vs Single operation)
- P** Single Agent Therapy (vs dual agent therapy)
- Q** Screening Diagnosis vs non-screening diagnosis
- R** Female Sex (vs Male)
- S** Deprivation quintile (SIMD) (vs Q1); solid = Q2, dotted = Q3, long-dash = Q4, dashed = Q5

Figure 7.11: Posterior probability distributions of the hazard ratio for five-year overall survival among patients who received adjuvant SACT, from univariable survival models fitted to each variable. Vertical line at HR 1 (no effect). Facet key provides title and comparator for each variable

The following variables reached the preset threshold for probability of direction and were included in the multivariable model.

- Nature of Admission (Factor)
- Level of Support During Hospital Stay (Factor)
- Age Decade - Grouped (Factor)
- Duke Stage (High-Risk B or Stage C) (Factor)
- Delay During Receipt of Adjuvant SACT (Logical)
- Presence of Renal Disease - Charlson (Logical)
- Delay Commencing Adjuvant SACT (Logical)
- Duration of Hospital Stay Weeks - Grouped (Factor)
- Diagnosis Made Following Screening Examination (Logical)
- Sex

As variables “Presence of Dementia” and “Method of Diagnosis” contained levels with no events occurring, they were not included in the multivariable model. Method of Diagnosis was reshaped into the logical variable “Diagnosis Made Following Screening Examination”, which was included in the final model.

7.4.3 Multivariable Analysis

In multivariable analysis, Elective - Organ Support was unlikely to be associated with either increased or decreased hazard of mortality, with a central estimate of hazard that centred on no effect (median HR 1.02, 95% CrI 0.67-1.53). The probability of clinically meaningful increase in hazard was 28.4%, the probability of decrease was 19.3%, the probability of ROPE was 52.3%.

It was virtually certain that emergency admission remained associated with increased hazard of mortality (median HR 1.8, 95% CrI 1.3-2.5) The probability of clinically meaningful increase in hazard of mortality was 99.5%. It was unlikely that Emergency - Organ Support was associated with increase or decreased hazard of mortality, with a central estimate of hazard that centred on no effect (median HR 1, 95% CrI 0.57-2.72).

The only subcohort of nature of admission and support during admission that appeared likely to be associated with hazard of long term mortality, was Emergency - Ward (contrasted against Emergency - Monitoring). This subcohort had a 94.5% probability of clinically meaningful increase in hazard (median HR 1.71 (1.05 - 2.72)).

Results from the multivariable model using uninformative priors are shown in figure 7.12 and table 7.9.

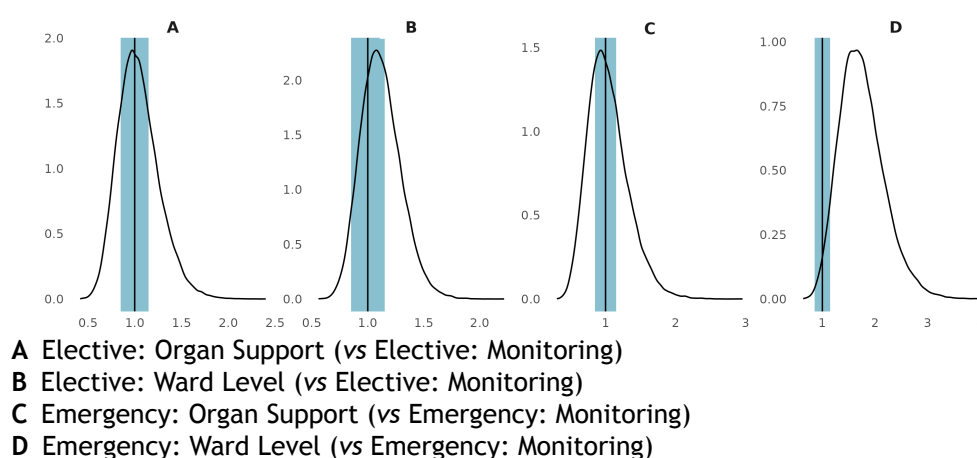


Figure 7.12: Multivariable Analysis Results - Posterior probability distribution of the hazard ratio for five-year overall survival among patients who received adjuvant SACT, from multivariable survival model using uninformative priors, for the key variables of interest

Light blue shaded region indicates region of practical equivalence

Vertical line indicates HR 1 (no effect)

Facet key provided for variable names and comparators

Table 7.9: Multivariable Analysis Results - Summary of posterior probability distribution of the hazard ratio for five-year overall survival among patients who received adjuvant SACT, from multivariable survival model using uninformative priors, for the key variables of interest, with comparator provided beneath

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease	Percentage Of Largest Effect
Elective: Organ Support <i>vs Elective: Monitoring</i>	1.02	(0.67 - 1.53)	53.98	52.30	28.39	19.31	28.39% chance meaningful increase
Elective: Ward Level <i>vs Elective: Monitoring</i>	1.10	(0.81 - 1.5)	73.03	54.82	39.97	5.22	39.97% chance meaningful increase
Emergency: Organ Support <i>vs Emergency: Monitoring</i>	1.00	(0.57 - 1.69)	50.60	41.47	31.08	27.45	31% chance meaningful increase
Emergency: Ward Level <i>vs Emergency: Monitoring</i>	1.71	(1.05 - 2.72)	98.44	5.27	94.50	0.23	94.5% chance meaningful increase
<i>CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease</i>							

7.4.4 Sensitivity Analysis, Model Validation, and Posterior Predictive Check

Through sensitivity analysis, this multivariable model based on groups with small sample sizes, was demonstrated to be particularly susceptible to changes in model priors. For both Elective and Emergency Organ Support, optimistic priors resulted in central estimates of hazard ratio associated with increased survival, pessimistic priors resulted in central estimates of hazard ratio estimates associated with increased mortality. Sensitivity analysis using different model priors is shown in Figure 7.13 and Table 7.10.

Emergency - Ward was the level most resilient to choice of priors, where all four prior choices still resulted in posterior median estimates for hazard ratio of increased mortality (> 1.17 , the threshold chosen for exceeding ROPE).

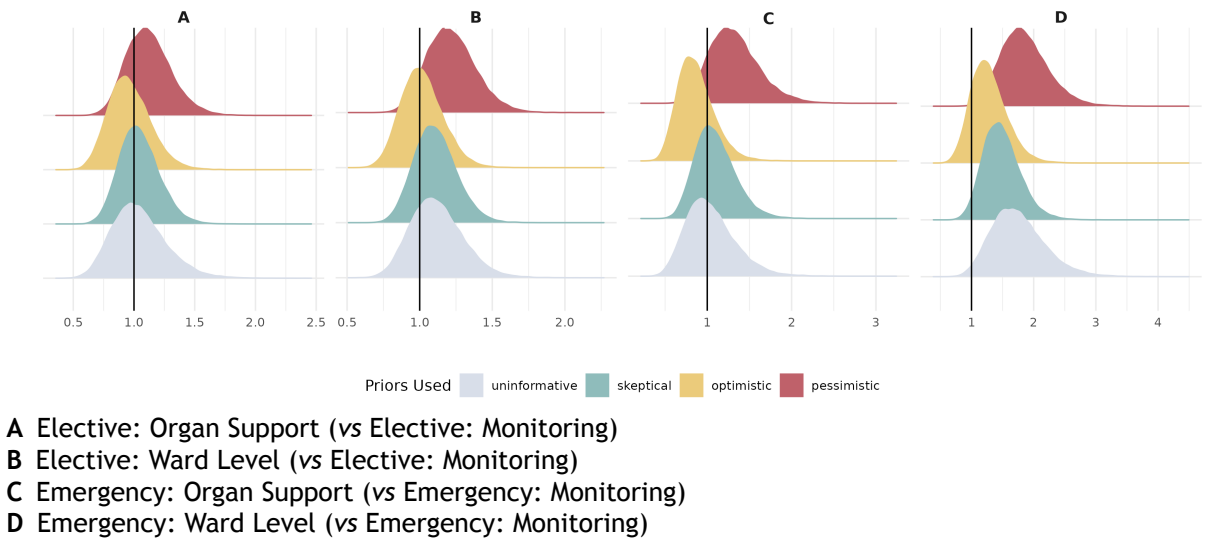


Figure 7.13: Sensitivity Analysis - Comparisons of posterior probability distribution of the hazard ratio for five-year overall survival among patients who received adjuvant SACT, from multivariable survival models using different prior probability distributions
Facet key provided for variable names and comparators

Variable	Uninf ¹	Skep ¹	ΔSkep ²	Opt ¹	ΔOpt ²	Pess ¹	ΔPess ²
Elective:Organ Support	1.02 (0.67 - 1.53)	1.03 (0.76 - 1.39)	-0.01 (-0.52 - 0.57)	0.95 (0.67 - 1.34)	0.07 (-0.45 - 0.66)	1.11 (0.81 - 1.52)	-0.09 (-0.63 - 0.5)
Elective:Ward	1.1 (0.81 - 1.5)	1.1 (0.85 - 1.41)	0.01 (-0.43 - 0.47)	1.01 (0.76 - 1.32)	0.1 (-0.33 - 0.56)	1.21 (0.92 - 1.57)	-0.1 (-0.57 - 0.39)
Emergency:Organ Support	1 (0.57 - 1.69)	1.07 (0.7 - 1.62)	-0.07 (-0.76 - 0.72)	0.84 (0.52 - 1.34)	0.16 (-0.49 - 0.92)	1.29 (0.84 - 1.98)	-0.29 (-1.09 - 0.54)
Emergency:Ward	1.71 (1.05 - 2.72)	1.46 (0.98 - 2.14)	0.24 (-0.69 - 1.34)	1.25 (0.8 - 1.91)	0.45 (-0.48 - 1.56)	1.82 (1.22 - 2.69)	-0.12 (-1.21 - 1.05)
¹ Median Estimate of Hazard Ratio From Model							
² Median Estimate of Difference Between Uninformative Priors and Model							

Table 7.10: Sensitivity Analysis - Summary of comparisons of posterior probability distribution of the hazard ratio for five-year overall survival among patients who received adjuvant SACT, from multivariable survival models using different prior probability distributions
Facet key provided for variable names and comparators

Model convergence was assessed, as shown in Appendix Table D.19. This demonstrated good measures of convergence with all values for $\hat{R}$ being less than 1.01, and all values for effective sample size (ESS) being greater than 20,000.

Assessing the posterior predictive check of the model, shown in Appendix Figure D.18, we see predicted values overlap well with actual observed values.

7.4.5 Multivariable Model Predicted Survival

Using the same methods as predictive models for the total cohort, the multivariable model using uninformative priors was used to make predictions for survival, stratified by nature of admission and level of support during hospital stay, for patients who received adjuvant SACT. The results of these predictions are shown in figure 7.14.

As already indicated by the small proportion of posterior estimates exceeding the region of practical equivalence, in the multivariable model of figure 7.12, there is no difference between the predicted survival of patients receiving organ support in critical care, when compared to those receiving monitoring in critical care.

Emergency: Ward Level patients have a mean estimate (44%, 95% CrI 51-59) for five-year survival substantially lower than the comparator of Emergency: Monitoring (61%, 95% CrI 52-69). However with the small number of patients that such a prediction is based on, credible intervals are large and overlapping.

For all elective subcohorts, the predicted overall survival at five years is centred between 76-78%. Whilst Elective: Ward Level patients have the lowest mean predicted survival of elective patients at 76% (95% CrI 70-82), the absolute difference is only 2% from the estimate for Elective: Monitoring patients at 78% (95% CrI 74-82). Among emergency subcohorts, the difference between Ward Level and Monitoring, was an absolute difference of 15% lower survival in Ward Level Patients.

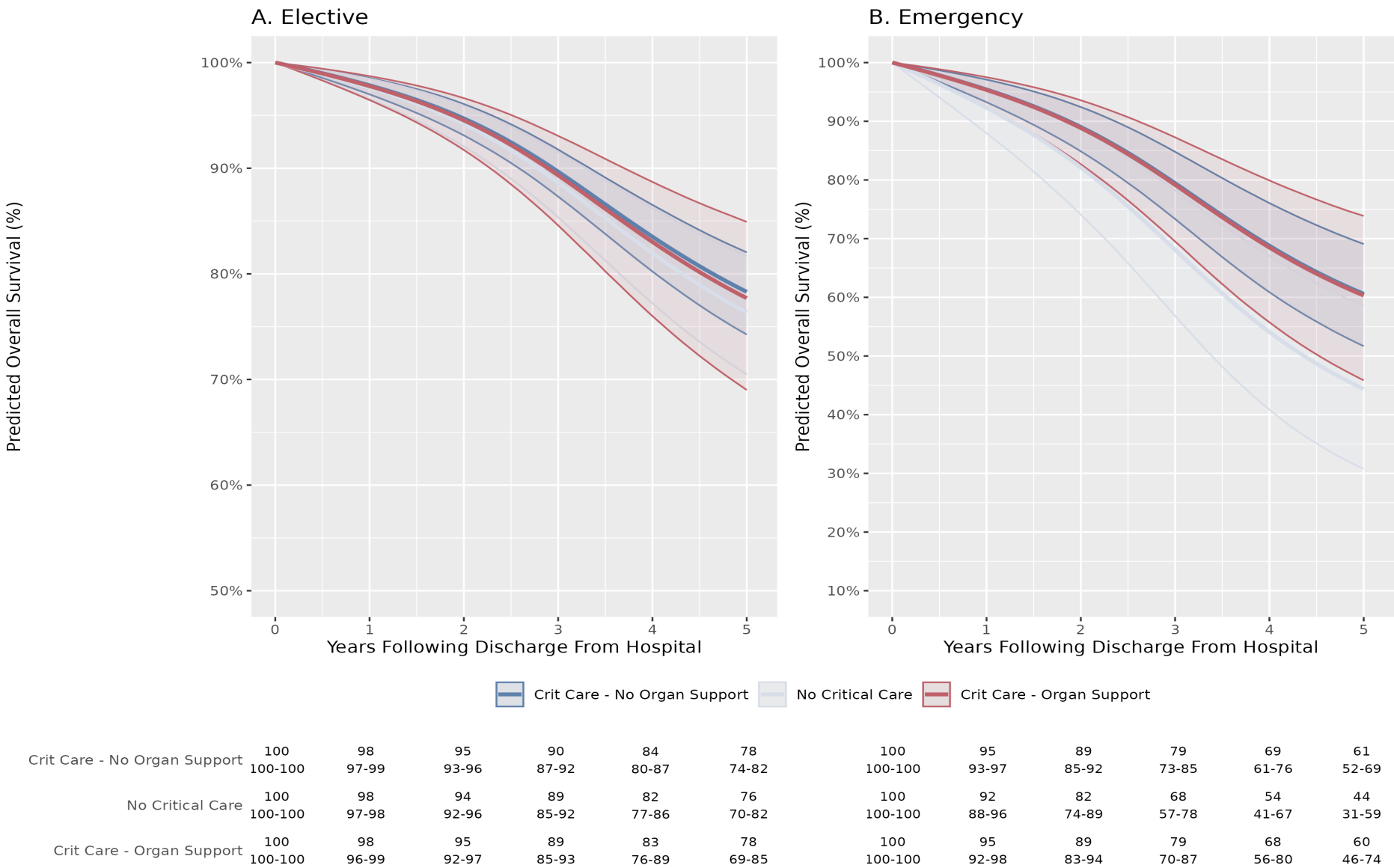


Figure 7.14: Predicted Survival Amongst Subcohorts In Population Who Received SACT

7.5 Discussion

In this cohort of hospital survivors with colorectal cancer, I observed 52% five-year survival for the total population. This chapter demonstrates again that the population of patients with CRC studied in this thesis are comparable to previously described Scottish cohorts, with similar overall survival rates to those previously reported. Taking in-hospital mortality into consideration, my observed value of 52% would reduce to 46% overall survival at five years following cancer diagnosis. Published Scottish outcomes for patients with CRC is a five year survival of 46.9% (Public Health Scotland 2022b).

Patients admitted electively had greater five-year survival than those admitted as an emergency. In addition, those who received organ support in critical care had worse 5 year survival than those who were admitted to critical care for monitoring alone. Whilst an unsurprising statement, such a result had not been previously reported for patients with CRC.

Both Elective - Organ Support (five-year survival 61%), and Emergency - Organ Support (five-year survival 34%) had worse five year overall survival than observed in previous descriptions of a general (all diagnoses, not limited to cancer) intensive care population (where five-year survival was 68%) (Lone et al. 2016). My work is not directly comparable to the population reported by Lone et al. 2016, considering my use of 'critical-care' including high dependency in addition to intensive care, and stratifying patients to a greater degree by level of support and admission. However these results are consistent with previous findings that long-term survival following critical care is poorer for patients with solid cancers than those without cancer (Puxty et al. 2018).

I observed an extremely likely (posterior probability of meaningful HR 98.76%) association between Organ Support and reduced five-year overall survival, for patients admitted to hospital electively, with a predicted absolute reduction in survival of 4%, when compared to Monitoring - Critical Care. Such a magnitude in reduction of survival would be considered clinically meaningful by ESMO-MCBS, where a 4% improvement would be sufficient to prompt recommendation of a form of additional SACT (Cherny et al. 2025). I observed an almost certain (posterior probability of meaningful HR > 99.5%) association between Emergency Admission and reduced five-year overall survival. This association, with median estimate of 70% increase in hazard, appeared to overwhelm any additional difference in hazard for Emergency - Organ Support, as Emergency - Organ Support was not predicted to have meaningful difference in five year survival when compared against Emergency - Monitoring.

Within the smaller subgroup of patients with High Risk II and Stage III disease who received surgical resection and adjuvant SACT, selected for homogeneity within the subcohorts. I did not observe any association between Organ Support and differences in five year survival. However the association between emergency admission and hazard of mortality, HR 1.73 (95% CrI 1.63-1.83) amongst the total cohort, remained within this subgroup, with median HR 1.81 (95% CrI 1.28-2.54).

Among the total population, in a series of unadjusted survival analyses (univariable models), I observed the following factors to have association with worse five-year survival: increasing age, increasing deprivation, increasing stage of disease, increasing number of comorbidities, and diagnosis through a mechanism different to screening. Additionally treatment that did not involve surgical intervention, and treatment with non-curative intent were also associated with worse five-year survival. These findings were all in keeping with expectations from previous literature. Among the unadjusted total population, with the caveat that the relationship between Age and Survival was not the primary focus of this chapter, this chapter does appear to provide additional detail to what has been reported in previous work. (Li et al. 2014) reported from their

large analysis (69,835 patients) of patients with non-metastatic CRC, that young patients (≤ 40 years) had greater five-year cancer specific survival (78.6%) than patients >40 years (75.3%). My findings are in keeping with the concept that survival is worse for older patients, patients aged 40-49 had a median HR 0.54 (95% CrI 0.37-0.77) when compared against those aged 60-69. However, patients aged < 40 had a median HR 1.04 (0.87-1.22) when compared against aged 60-69, suggesting their hazard of mortality was similar to those approximately 20-30 years older. Considering that this unadjusted analysis of younger patients does not take into account form of colorectal cancer, stage, or mechanism of diagnosis (among a cohort too young for current screening programmes), it would seem likely that differences in these other factors would explain differences in hazard of mortality.

Observing that Elective - Ward patients have similar predictions in hazard of mortality, to Elective - Organ Support, as reported in previous chapters, this could potentially be explained by selection biases in who gets admitted to critical care. Patient factors such as performance status and frailty were not recorded in this dataset, and other relevant factors had a high level of missing data, such as cancer stage (and to a lesser extent comorbidity). A similar relationship may explain the increase in hazard amongst patients who received no operations during their index admission (unadjusted HR 3.56 95% CrI 3.35-3.79), where rather than being too well for surgery, it rather reflects no surgical option being available to the patient.

7.5.1 Limitations

Unfortunately the work of this chapter has several limitations, both inherent limitations resulting from the available registry data, but also potentially avoidable limitations resulting from choices I made early during this thesis process.

Beginning with limitations of registry data. As noted in Chapter 4, SMR06 (the Scottish Cancer Registry) dataset suffers from substantial missing data (> 50%) on anatomic stage of disease, likely not missing at random. Anatomic stage is clearly relevant to long term survival, and it is likely that the six subcohorts investigated differ in proportion of patients with each anatomic stage (BF > 100, Table 4.3). Other variables were used in analysis to partially take account of this, such as Treatment Intent, which had much smaller proportions of missing data. However whilst Treatment Intent will be correlated with Stage and have some relevance, it will likely also be influenced by other factors.

This analysis relies on the accuracy of total population registry information. Whilst my methods took steps for data validation, requiring confirmation of key variables in multiple datasets where possible, this limitation remains. Certain measures used in this analysis, such as comorbidity, are extracted from coding of hospital records, and as such are only as accurate as the records themselves.

Whilst attempting to describe survival between each subcohort, the first analysis of this chapter is limited by the heterogeneity of the total cohort, where not all relevant factors can be accounted for. The second analysis used recorded information from the QPI programme on staging information to provide a more homogenous study population. Details on anatomic stage were much more complete than that seen in SMR06. However this stratification using QPI creates new limitations. Whilst the total cohort contained information for the interval of 2006-2018, the QPI programme is much more limited, with patients only from 2012 onwards. Additionally, with QPI dataset being available for only the final years of data access, a much greater proportion of patient censoring was observed. In reality only those patients diagnosed in 2012 and 2013 would have a full five years of potential follow up before censoring, those diagnosed in 2018 would have at most 12 months of follow up. Each successive year of follow up was subject to greater censoring than the last. As such it could be thought that a three-year analysis or shorter may provide more useful estimates. However, PAMMs

(and Cox PH) allow for variation in baseline hazard estimates over time. As a result, estimates of three year survival in this highly censored five year model would closely approximate estimates of three year survival in a model limited to three years of follow up (using this dataset). In this five year model, predicted survival for patients with No Organ Support and Organ Support was essentially identical at each year of follow up, with wide overlapping credible intervals. As such models with shorter durations of follow up would not have provided any additional meaningful information. Ultimately though this degree of censoring at each year of follow up substantially limits our ability to accurately report association in this second analysis. An additional alternative approach would be to investigate any association between organ support and cancer-related deaths. Such an analysis may allow for identification of differences in cancer-related outcomes following critical illness. Unfortunately, as noted above, such an analysis would rely on the accuracy of registry data; for death reporting, there is no second source to allow validation of whether a death was cancer-related or not. As such I would have been unable to verify the accuracy of any death being 'cancer-related'. Additionally, from the perspective of ESMO-MCBS, overall survival is the more relevant measure; switching to cancer-related deaths would result in the loss of a strength of this chapter, that ESMO-MCBS provides established values for what should be considered clinically meaningful for this outcome. In the next chapter, Chapter 8, I attempt to address these limitations by undertaking further survival analyses with more robust methods to investigate overall survival. These analyses result in more informative estimates about any causal relationship between critical illness and mortality.

Restricting the study duration to half of the total duration, and restricting stage of disease to those with High Risk II and Stage III, who all received the same treatments (surgical resection and adjuvant SACT) resulted in a study population approximately 5% of the size of the total cohort (total cohort 38,385, SACT cohort 1,582). This small size results in analysis suffering in two ways. Firstly as a smaller group, any modelling will inherently have wider credible intervals. As a separate second issue, patients

with this stage of disease had greater baseline five year survival. To identify the same absolute difference in overall survival, of 3% or greater a larger hazard ratio would be required to achieve this, and as such the range of hazard ratios considered as ROPE expands. So this analysis needed to observe a greater effect, but also had less scope to identify any effect.

This limitations from a small sample size are observed in the sensitivity analysis for this second analysis. In sensitivity analysis I observed choosing different prior probability distributions meaningfully impacted the posterior estimates from each model. This demonstrates that there is insufficient data for the posterior distribution to become resilient to different choices of relatively weak priors. In presenting the model with uninformative priors, I present estimates following the most “neutral” starting assumptions; however, the limitation of small data size remains.

The decisions made when restricting the study size in the selection also highlight the other more self-inflicted limitation in this analysis. I selected patients with High Risk II and Stage III disease, who received surgical resection, and subsequent adjuvant SACT. This choice was made in attempt to provide subcohorts more closely matched to one another. However, this choice has also resulted in my stratifying by a post treatment variable, the receipt of SACT following critical care. If the aim of this analysis was to understand the full relationship between Organ Support and subsequent mortality, then stratifying by receipt of adjuvant SACT, is to remove a potential causal influence of Organ Support on mortality. Hypothetically, Organ Support may reduce long term survival through reducing likelihood of receiving subsequent SACT. By only studying those who received adjuvant SACT, I am unable to comment on that causal path. Similarly, I used variable screening for inclusion in the multivariable model for the SACT population, and included delays commencing SACT, and delays during SACT in the model. In doing so, I have removed some causal paths of Organ Support on subsequent mortality, as it could be that Organ Support causes increased mortality through reducing timeliness or intensity of adjuvant SACT. I comment on causal paths here,

however as noted early in this thesis, this thesis was not designed to interpret causal relationships between variables. These wider methodological limitations are common among medical literature, and in the final results chapter, Chapter 8, I attempt to address these limitations using analysis more focussed on causal inference.

To summarise some of the key limitations described above, in my first analysis and set of modelling, I described the relationship between Organ Support and long term mortality amongst a heterogenous cohort where it is likely that significant differences in anatomic stage and frailty remain. In my second analysis, through attempting to account for the differences between the six subcohorts, I am left with much smaller patient groups where it becomes more difficult to identify any association. Additionally through choices made in cohort and model definitions, I closed potential causal paths between Organ Support and long term mortality.

As a final limitation, in restricting the investigation to hospital survivors, I was able to more accurately describe factors impacting long term rather than immediate survival. However, as highlighted in the introduction, a substantial proportion of patients die during their admission with critical illness. Excluding these deaths will make percentage predicted survival appear higher than is truly the case at the point of hospitalisation.

7.5.2 Clinical Implications

The above limitations are notable, but should not be considered to prevent any interpretation of the work of this chapter.

Describing overall survival amongst the total cohort may be less specific than more accurate description of survival at each individual stage, however it still provides a starting point for understanding long term survival for patients with colorectal cancer who experience organ support in critical care. Using five year follow up when available has provided a greater duration of follow up than used in the majority of literature for critical illness amongst patients with cancer. Stratification for a single cancer type provides additional detail than the majority of work that has focussed on solid organ cancers more generally. Last the stratification by receipt of organ support versus monitoring in critical care is truly novel for an analysis of long term survival for patients with colorectal cancer.

This chapter is able to state that in an elective cohort of patients with colorectal cancer, long term survival is estimated to reduce for those who survivors who experienced organ support. The estimated association in this chapter is a 4% absolute reduction in five-year survival, when contrasted those elective patients who experienced organ support against those who were admitted to critical care for monitoring alone.

An effect of this size is unlikely to result in an individual patient or clinician making different decisions about cancer care. However on a population scale, such a difference in hazard is one that the European Society of Medical Oncology MCBS would score as meaningful. A 4% impact on overall survival is comparable to the provision of adjuvant SACT for High-Risk Stage II disease (3-4%), or the addition of a second adjuvant agent for Stage III disease (4-5%), as noted in the introduction to Chapter 6 (Argilés et al. 2020).

Managing to avoid the harm associated with critical illness, may be of the same protective magnitude to an adjuvant treatment that ESMO would recommend for patients with CRC. It is unclear why such disparity exists. Potential explanations include the impact of critical illness on inflammation, the impact of critical illness on frailty, or the impact of critical illness on psychological outcomes and willingness to undergo futures treatment (Lone et al. 2016; Docherty et al. 2023; McPeake and Mikkelsen 2018) Future work will need to focus on interpreting causal relationships of such a disparity, to then allow for focused interventions to minimise such a difference.

Clinicians caring for critically unwell patients with colorectal cancer, can interpret these findings to understand that whilst long term survival may be reduced for such patients that survive their hospital stay, it is not reduced as much as some would fear, and that potential benefit from critical care interventions can still be achieved.

7.6 Conclusion

This analysis of a national dataset of Scottish patients with Colorectal Cancer, predicted a 4% reduction in five-year survival among patients who had undergone organ support in critical care. This association of critical illness was dependent on nature of hospital admission, as this difference in survival was observed solely in patients who had been admitted electively. Emergency admission to hospital itself had a more overwhelming impact on long term survival regardless of level of support (HR 1.73).

In the more focused subgroup analysis, of patients with CRC of a similar stage treated with curative intent, critical illness was not demonstrated to be associated with long-term survival. This may be due to the lack of such an impact, insufficient sample size to detect such an influence, or due to choices made in the methodology of this analysis. In the next chapter, Chapter 8, I undertake additional analysis with more robust methodology, to investigate further the relationships between critical illness and long-term overall survival.

Chapter 8

Critical Illness

8.1 Introduction

8.1.1 Critical Illness in Colorectal Cancer

Throughout this thesis so far the patient population has been defined as: adult patients with colorectal cancer (CRC) who have survived their index hospital admission following CRC diagnosis. The cohort of interest has been patients who received any organ support in critical care.

These definitions do provide useful information on long term outcomes for patients, are in keeping with prior work, and enhance the previously used definitions, by requiring receipt of organ support. There are still limitations with these definitions, and this chapter aims to address these.

In describing a population of hospital survivors, I am able to investigate any association between critical illness and patient outcomes, that persists after accounting for differences in short term mortality. Use of a cohort of hospital survivors, without also describing in hospital mortality, could risk giving a misleadingly positive impression of long term outcomes. As an example, in Chapter 7 I noted 52% five-year overall survival in the total cohort, however taking in-hospital mortality into account this percentage falls to 46%. For clinicians discussing possible outcomes with patients and families during hospital admission, outcomes that allow for in-hospital mortality may be more relevant, rather than values that assume hospital survival.

In this thesis I have stratified patients by both admission to critical care, and receipt of organ support in critical care. Puxty et al. 2015 provides one of the most comparable patient populations to those studied in this thesis. In their population-based (Scotland) observational study of critical illness for patients with solid cancers, Puxty et al. 2015 defined critical illness as admission to intensive care. Where patients were admitted to a shared intensive and high dependency unit, receipt of organ support (which they defined as invasive ventilation, inotropic or vasopressor therapy, or renal replacement therapy) was used to differentiate patients. Among most other published work, this further stratification by receipt of organ support is not undertaken.

In the limited published work investigating outcomes for patients with solid organ cancers after critical illness, the most common classification of 'critical illness' is by admission to intensive care. There is no population-level work that links severity of critical illness (beyond ICU admission) to long term outcomes for patients with solid organ cancers generally, or CRC specifically. Gheerbrant et al. 2021 included all patients admitted to intensive care ($n = 253$), when describing short and long term survival after critical illness, with no stratification of outcomes by receipt of organ support. When Borcoman et al. 2020 investigated subsequent anti-cancer therapy and mortality for patients with solid organ cancers, they included all patients who survived an unplanned admission to intensive care ($n = 622$), without further in-

investigation on the association of receipt of organ support. Similarly Kim et al. 2015 investigated factors associated with likelihood of subsequent chemotherapy receipt for patients with Stage II and III CRC (n = 750). Within this they identified admission to intensive care as associated with reduced odds of subsequent chemotherapy receipt, but did not stratify further by severity of illness or receipt of organ support.

In this thesis so far I have provided evidence that for patients with colorectal cancer in Scotland, admission to critical care for monitoring should be considered the 'well' baseline. Among elective patients admission to critical care for monitoring is the most common occurrence, accounting for 55% (n = 14,524) of elective admissions. These patients attain the greatest proportion of Quality Performance Indicators (76%, contrasted against 67% in Ward and 33% in Organ Support), and have the greatest five-year overall survival estimates (70%, contrasted against 52% in the overall cohort). As such I have demonstrated that critical care requires stratification to distinguish the subcohort of patients that are critically unwell.

Whilst the papers above described a range of solid organ cancers rather than solely colorectal cancer, the other key difference is they aimed to investigate 'Intensive Care' admissions rather than both high dependency and intensive care in 'Critical Care'. As such an argument could be made that their work did not require stratification by organ support receipt, as by definition intensive care includes only the more unwell patients. However it appears likely that Gheerbrant et al. 2021 and Borcoman et al. 2020 included patients in their intensive care cohorts that did not receive any organ support. For Gheerbrant et al. 2021 the most commonly received form of organ support was invasive ventilation, accounting for 41% of their intensive care cohort. 35% of their patients received vasoactive support. Considering the nature of critical illness it is likely that there was significant overlap between these groups, although

they do not provide details of this. Allowing for overlap, this allows for a range of 24 - 59% of their intensive care cohort not receiving organ support. For Borcoman et al. 2020, 21-67 % of their Intensive Care cohort may not have received organ support, depending on overlap of receipt of different forms.

Stratifying by receipt of organ support in critical care would seem to provide greater discrimination of the patients experiencing critical illness than is seen in previous published work. As a proxy definition of critical illness, it can be improved further. Without a minimum duration of organ support, patients who return to critical care for enhanced recovery after theatre may inadvertently fall into our grouping of those 'critically ill'. As examples, those more 'well' patients who are admitted with a plan to extubate within a few hours post theatre, or on small amounts of cardiovascular support, would currently fall into the Organ Support subcohort. If there was a significant proportion of such patients, this may dilute any observed association between receipt of organ support (for those more sick patients experiencing prolonged multi-organ support) and long term patient outcomes.

Stratifying those who receive organ support further, by greater or lesser durations of organ support, may improve discrimination between those who have or have not experienced critical illness. A patient who requires cardiovascular, respiratory, or renal support for greater than one day may be more likely to be critically ill, than someone who manages to come off support after less than one day of admission to critical care.

Considering the above, in this chapter I make the following changes to population and subcohort definitions. Having identified that those admitted to critical care for monitoring should be considered the well comparator of patients, I choose to restrict the population of patients to those admitted to critical care (excluding those treated at a ward level). Recognising that the cohort of patients who receive greater than one day of organ support are more likely to contain the population of interest (those critically unwell), I choose to stratify patients admitted to critical care into:

- Critical Care - Monitoring Alone (0 Days Organ Support)
- Critical Care - Single Day Organ Support Recorded
- Critical Care - Multiple Days (2+) of Organ Support Recorded

Recognising that describing all admissions (rather than just those who survive hospital) provides a more representative description of short and long term survival, in this chapter I first describe the characteristics and short term outcomes of all admissions to critical care. Later in this chapter, when appropriate, I restrict the population to hospital survivors. With these changes to population and subcohort definitions, the aim is to allow for descriptors and outcomes more relevant to those working in critical care, aiming to understand the possible outcomes for their patients, and hoping to have more informed conversations with all relevant parties.

8.1.2 A Causal Approach

As noted throughout this thesis, each analysis in the preceding chapters used the commonly undertaken technique of single variable screening prior to inclusion in a final multivariable model. Such a technique can result in models with adequate fit to observed data. This thesis demonstrates this, with the posterior predictive checks

provided for each model. However the aim of this thesis is to better understand the relationship between critical illness and long term outcomes for patients with CRC. To achieve that goal, approaches that use causal inference may be more appropriate (McElreath 2020).

To describe the causal effect on an outcome of interest, we are describing the expected outcome under a series of counterfactuals (Smit et al. 2023; Stovitz and Shrier 2019). In this thesis the exposure of interest is critical illness, defined in this chapter as the receipt of organ support for multiple days in critical care. The outcomes of interest are subsequent anti-cancer therapy, and long term overall survival. As a result the comparison in counterfactuals for a patient may be: what do we predict long-term survival to be if this patient does experience critical illness, and what do we predict long-term survival to be if they do not experience critical illness.

The causal effect of an exposure can have multiple definitions. We may talk about the ‘total effect’, this is when all pathways (or mechanisms) between exposure and outcome of interest are combined into one effect (Westreich and Greenland 2013; Stovitz and Shrier 2019; Krishnamoorthy et al. 2020a). As illustration, when talking about the causal effect of critical illness on timely adjuvant chemotherapy, one path may be that those with critical illness remain in hospital for longer, delaying subsequent chemotherapy. Another pathway may be that patients with critical illness are more frail on discharge, and less likely to be fit to receive chemotherapy at all. We can also assume there are multiple other pathways, and the combination of all pathways is the ‘total causal effect’ (Westreich and Greenland 2013). Each individual pathway’s contribution is known as the ‘direct effect’ of that factor (Westreich and Greenland 2013).

In the above example, if we adjusted for length of hospital stay, we would be ‘blocking’ length of stay’s direct effect, and inadvertently reducing the estimate for the total effect of critical illness on timely chemotherapy receipt. I use this example in part as an admission of error, highlighting that I made this exact adjustment in Chapter 5. Whilst a mis-step, an analysis with blocked pathways can still provide useful information; observing that the odds of timely chemotherapy receipt are reduced despite adjusting for length of stay, allows inference that any mechanism that reduces chemotherapy receipt among those surviving critical illness, is not limited to the pathway of length of stay in hospital (McElreath 2020; Krishnamoorthy et al. 2020b). Any proposed intervention that aimed to shorten length of hospital stay for patients with critical illness, would likely be insufficient to fully improve receipt of chemotherapy for this population.

Describing causal pathways between factors, is to describe the assumed scientific model. A commonly used method is to represent the model graphically, plotting all relevant factors (nodes) and the relationships between them (edges), in a directed acyclic graph (DAG) (Krishnamoorthy et al. 2020a; Swarbrick et al. 2025a; McElreath 2020). DAGs are so-called as they demonstrate the direction of how variables affect each other, and do not allow for loops (e.g $A \rightarrow B$ would be valid in a DAG, but $A \leftrightarrow B$ is not) (Krishnamoorthy et al. 2020a). A DAG describes a process as it moves forward through time: so whilst we might assume a loop of performance status (PS) impacting likelihood of critical illness, and critical illness impacting future performance status, in a DAG this would need to be described as something like Pre-morbid PS $\rightarrow$ Critical Illness $\rightarrow$ Post-morbid PS, to clarify the temporal relationship (Krishnamoorthy et al. 2020b).

Figure 8.1 shows a simplified example, where the exposure of interest is experiencing critical illness, followed by multiple causal pathways, that lead to the outcome of interest of timely chemotherapy receipt. These pathways that sit between exposure and outcome of interest may be referred to as ‘mediators’ or as ‘pipes’ (Krishnamoorthy et al. 2020b; McElreath 2020).

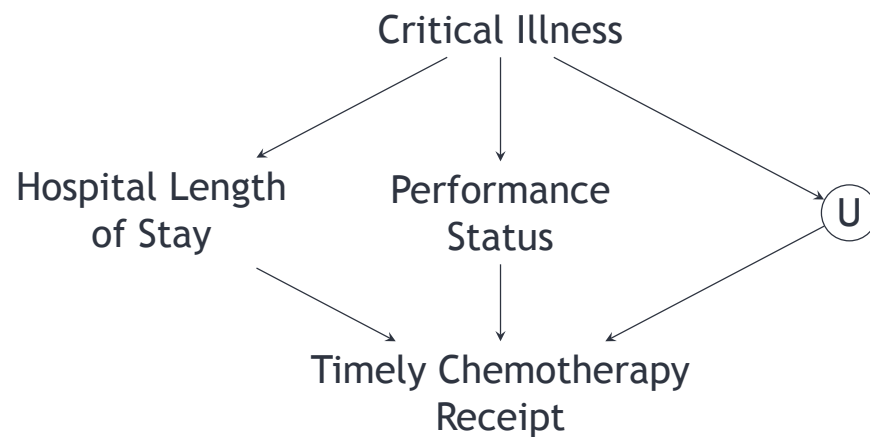


Figure 8.1: Example directed acyclic graph for the effect of critical illness on timely chemotherapy receipt; U is an unobserved variable.

When attempting to understand the total causal effect, we would not want to adjust for mediators. There are other factors we do need to adjust for, those that impact both the exposure of interest, and the outcome of interest. These factors that impact our exposure of interest, and our outcome of interest are known as confounders, and are also an example of ‘forks’ (where one variable impacts the likelihood of more than one other variable) (McElreath 2020). The causal pathways coming from these ‘secondary’ exposures can be referred to as ‘secondary effects’ (Westreich and Greenland 2013). In Figure 8.2 age has been added to the scientific model, and assumed to impact likelihood of critical illness, length of hospital stay, and performance status. To understand the causal effect of critical illness on timely chemotherapy receipt, age must be adjusted for.

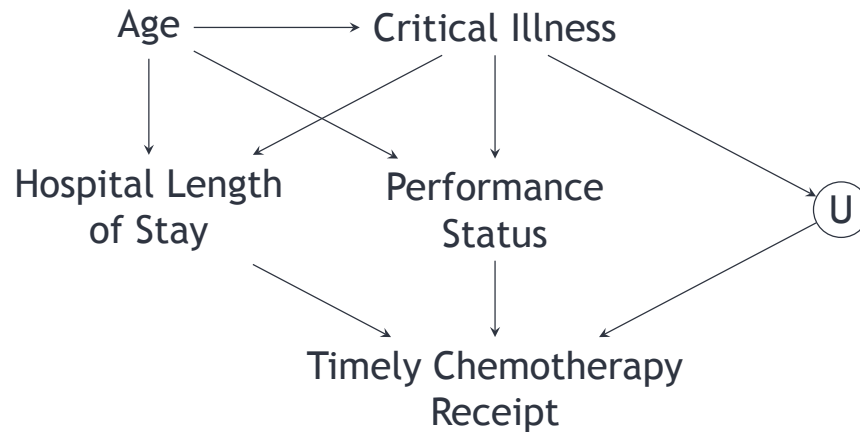


Figure 8.2: Example directed acyclic graph for the effect of critical illness on timely chemotherapy receipt; Age is a confounder that impacts likelihood of critical illness, performance status, and length of stay

When attempting to describe the total causal effect of an exposure, we want to adjust for confounders, and not adjust for pipes/mediators. It is also important to note that inappropriate inclusion of variables may not only result in underestimation of causal effects, inappropriate adjustment may also result in the creation of spurious relationships between variables (Krishnamoorthy et al. 2020b; McElreath 2020). This is revisited in Methods in Section 8.2.5, for a specific example of considerations for this chapter.

Last, as well as statistical model generation requiring thought, statistical model interpretation also requires care. In the paradigm of causal inference, interpretation of each coefficient needs to consider if the variable was the exposure of interest or included to account for confounding. A regression that aimed to understand the causal relationship between critical illness and SACT receipt from the model described in Figure 8.2 would look as below, with coefficients produced for each variable:

$$\text{Timely Chemotherapy Receipt} \sim \text{Critical Illness} + \text{Age}$$

In the regression estimates produced, the estimate for critical illness would be the total causal effect on timely chemotherapy receipt. More specifically, it is the conditional total effect, the total effect conditional on confounders being held constant (Westreich and Greenland 2013). However the estimate produced for age would be the direct effect of age on timely chemotherapy receipt, with the pathways for Age's impact on critical illness, length of stay, and performance status being blocked. This first model will likely underestimate the total causal effect of age; If we wanted to provide an estimate for the total causal effect of age, this would require its own separate model.

Use of causal inference, with DAGs to describe one aspect of the scientific model, is becoming increasingly common in observational medical research. One particularly useful example published in 2025, was the use of causal inference in the Third Snap Anaesthesia Project (SNAP-3), investigating the impact of frailty, multimorbidity, and delirium on outcomes for undergoing surgery in the UK (Swarbrick et al. 2025a; Swarbrick et al. 2025b). Like in Chapter 2, when the importance of justification of choices of prior probabilities was introduced, any relationship between variables in a scientific model also requires justification, through methods such as previous published work, or consensus expert opinion (Swarbrick et al. 2025a).

In Section 8.2 I provide specific detail on this chapter's question of interest (estimand), scientific model interrogated (building on evidence provided by Swarbrick et al. 2025a), statistical techniques used to investigate the questions of interest.

8.2 Methods

This chapter uses routinely collected registry information from SMR01, SICSAG, Chemo-care, NRS Deaths as described in more detail in Chapter 3. With the aim to first describe the cohort of patients with CRC admitted to critical care, their reasons for admission, and their short term outcomes, the first cohort is of those unique adult patients with CRC (of any stage), admitted to critical care (including those who died during admission). This cohort is used to describe initial demographics, reason for admission, and short term mortality. As noted in Chapters 4 and 7, and later within this chapter, such a cohort is heterogenous in its baseline characteristics. To compensate for this, in further description and regression models of long term outcomes, patients are stratified further. The second half of the chapter that uses this stricter cohort definition, investigates hospital survivors (defined as surviving both to hospital discharge and the following 30 days) with High Risk II or III stage disease, who underwent curative resection during their index admission.

Unlike previous chapters, this chapter excludes patients treated at a ward level, considering those who received monitoring in critical care as the well comparator. As noted in Section 8.1.1, patients treated in critical care were classified into those who received:

- Critical Care - Monitoring Alone (0 Days Organ Support)
- Critical Care - Single Day Organ Support Recorded
- Critical Care - Multiple Days (2+) of Organ Support Recorded

This stratification was undertaken using the daily records of care provided by SICSAG. As before, organ support was defined as receipt of one or more of: inotropic/vasopressor support, high-flow nasal oxygen, non-invasive ventilation, invasive ventilation, or renal replacement therapy. Considering the interaction between nature of admission and level of support in hospital, patients were again stratified by nature of admission into Elective versus Emergency hospital admissions.

A CONSORT diagram detailing patient inclusion and exclusion is provided in Figure 8.3. The first descriptive half of this chapter describes those identified as ‘Critical Care Admissions’, the second half of this chapter, with regression modelling uses the final step from the CONSORT diagram, ‘Hospital Survivors with CRC Stage HRII / III’.

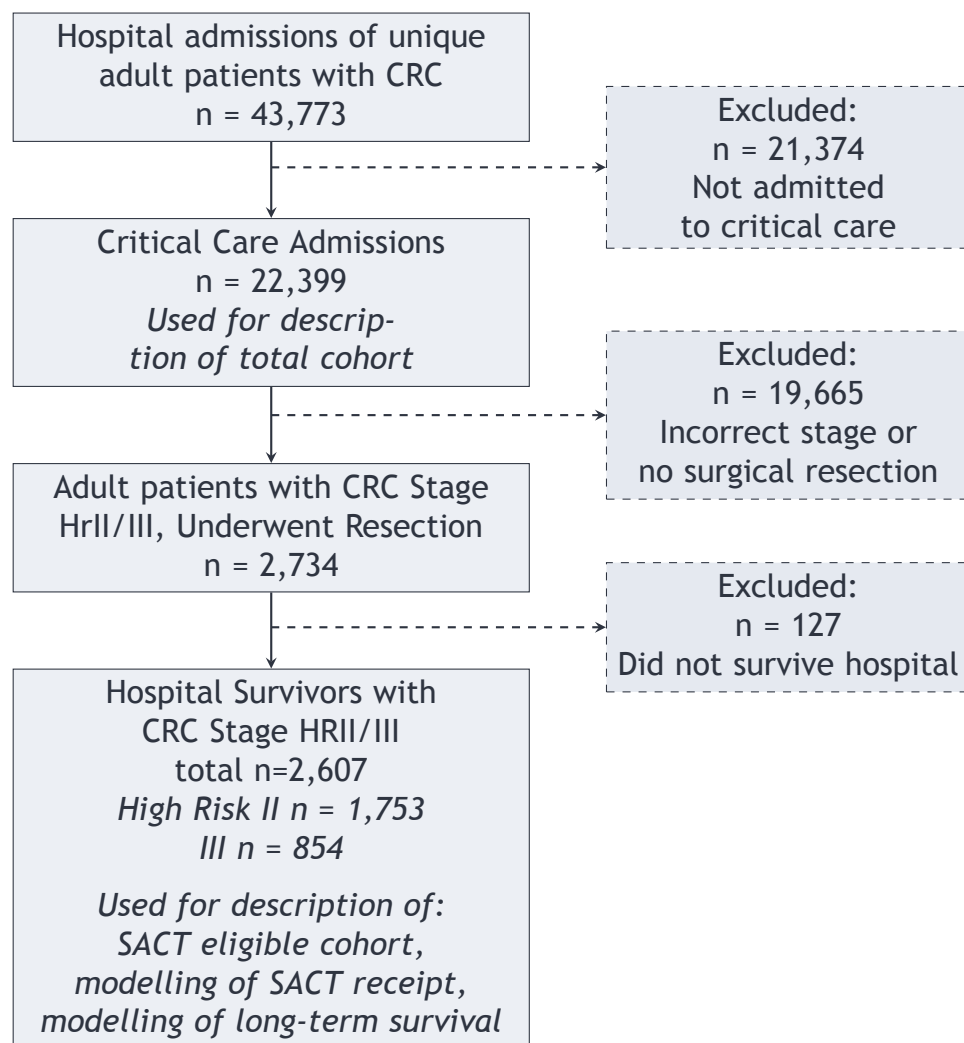


Figure 8.3: CONSORT diagram showing patient selection. Dashed branches show exclusions at each step.

8.2.1 Estimand

Modelling within this chapter aims to address the following questions of interest:

1. What is the causal effect of critical illness on subsequent receipt of adjuvant systemic anti-cancer therapy (SACT), in patients with High Risk Stage II and Stage III disease who have undergone curative surgical resection, conditional on hospital survival.
2. What is the causal effect of critical illness on long term overall survival, in the same cohort of patients as the above estimand, again conditional on hospital survival.

Whilst stating causal effect, in this context our questions are conditional on hospital survival, but include all other pathways. Considering the well established causal effect of critical illness on hospital mortality, the more relevant question of interest to many intensivists would be, considering the established burdens of invasive treatment in critical care, what would be the odds of longer term benefit to the patient being referred, if they were to survive this hospital stay. Conditioning on hospital survival will reduce the estimate of total effect of critical illness on SACT receipt and long term mortality, and also introduce other risks discussed in Section 8.2.5, but ultimately will provide a more meaningful estimate to the above question.

The models used, that provide causal estimates of the impact of critical illness, can also be used to provide estimates of effect of nature of admission on patient outcomes.

8.2.2 Unadjusted Analyses

The questions of interest are considered the most relevant for causal inference in this chapter, however unadjusted descriptors of demographics, SACT receipt, and short and long term mortality are also likely of benefit.

This chapter provides description of the demographics of each subcohort using frequency tables with counts and medians (with interquartile ranges), as well as comparison of differences using Bayes Factors. Counts of reasons for critical care admission are also provided in frequency tables.

Long term survival is provided for the overall population of patients with CRC admitted to critical care, and stratified into the above six subcohorts. Unadjusted kaplan-meier estimates for five year survival are provided for all patients. Kaplan-meier estimates are provided twice, first estimates (from hospital admission) that include in-hospital mortality, second (from 30 days post discharge) providing estimates that are conditional on surviving hospital admission.

Unadjusted analyses continue for the ‘SACT-eligible’ population, those who have High Risk Stage II and III disease, who underwent curative resection in their index admission, and survived the first 30 days following hospital discharge. Frequency tables are provided for patient demographics, reason for critical care admission. Unadjusted estimates for overall cumulative incidence of adjuvant SACT are provided (with death following discharge treated as competing risk), followed by cumulative incidence of adjuvant SACT stratified by subcohorts. Kaplan meier estimates for overall survival in the subcohorts of this SACT-eligible population is also provided.

8.2.3 Regression Modelling

Within the SACT eligible population, regression modelling is undertaken to address the questions of interest noted in Section 8.2.1. As described in Chapter 7, regression modelling utilises Bayesian PAMMs. This allows estimates of the causal effect of critical illness on the outcomes of interest, and sampling from posterior distribution to generate predictions of SACT receipt and overall survival. Prior selection, sensitivity analysis, validity checks, posterior predictive checks, and software were as described in Chapter 3, and in more detail in Chapter 7. For survival, ROPE was specified to categorise an absolute difference in overall survival of less than 3% as being practically equivalent (as seen in Chapter 7). For SACT receipt, ROPE was specified to categorise an absolute difference in SACT receipt of less than 5% as being practically equivalent.

8.2.4 Adjustment Set and Causal Framework

Within SNAP-3, Swarbrick et al. 2025b provide a proposed scientific model for the causal effects of exposures of interest on surgical outcomes for comorbid, more frail patients. No similar proposed scientific model (in the form of DAGs) has been published on the impact of critical illness on solid organ cancer outcomes.

Considering their inclusion of relevant patient characteristics, similarity in question of interest, and methodological rigour when describing their proposed scientific model, I chose to use their DAG as a starting point (Swarbrick et al. 2025a). To clarify the point of similarity in question of interest, they aimed to understand the causal relationship between frailty and multimorbidity, with post operative mortality, amongst a cohort

of older patients undergoing surgical intervention. As my question of interest also involves the relationship between a disease state and outcomes (including mortality), amongst a cohort of older patients undergoing surgical intervention, this appeared similar enough as a beginning.

Amongst the DAG proposed by Swarbrick et al. 2025a, relationships between Age, Sex, Socioeconomic Status, Frailty, Comorbidity, Nature of Surgery (Elective vs Unplanned) and Mortality are all described. Additionally they note the additional specific relationships of Dementia on Frailty, and post-operative outcomes that extend beyond the impact of comorbidity alone (Swarbrick et al. 2025a; White et al. 2019; Möllers et al. 2018). In their methodology, they propose the inclusion of an interaction term as a node in itself in their DAG, as utilised by Attia et al. 2022. For the purposes of this chapter however, a DAG proposes which factors influence each other, without providing additional detail on the nature of that influence (DAGs can be described as non-parametric for this reason), or how such an influence should be modelled. To provide that additional detail on interaction, other parametric methods such as structural equation modelling or fully generative Bayesian models could be used. Within this chapter as I include interaction within the statistical model itself, and inclusion of an interaction node would not change which additional variables are considered confounders, use of an interaction node in the DAG is unnecessary (McElreath 2020).

As noted throughout this thesis and by Swarbrick et al. 2025a, patient frailty is noted to be likely of great importance to the questions of interest, whilst remaining a significant limitation as an unmeasured confounder, that registry information has not historically recorded. I chose to partially account for this using the following mechanisms: first limiting regression models to the cohort of patients who were admitted to critical care having undergone curative surgical resection for colorectal cancer. Acknowledging that frailty impacts decision making both for admission to critical care, and who undergoes surgical resection, it is likely (although not-provable) that this restricted cohort is more homogenous in frailty incidence (Bryden et al. 2024; Lourenço

et al. 2025) Secondly comorbidity, dementia, socioeconomic deprivation, sex and age all partially influence the incidence of frailty (although they do not fully predict it), in accounting and adjusting for these factors, I can partially adjust for the confounding nature of frailty (Walsh et al. 2023; Espinoza et al. 2018).

8.2.5 Conditioning on Hospital Survival: Selection Bias

It is well established that those who experience critical illness have greater hospital mortality than those who do not. In Chapter 4, Table 4.2 I note that among patients admitted electively, hospital mortality was 1.6% ($n = 232$) among those who were admitted to critical care for monitoring, and 13% ($n = 349$) among those who received any organ support in critical care. This chapter uses a more strict definition of critical illness, and will likely demonstrate a greater hospital mortality in the critical illness group. It would be unsurprising for any involved in the care of critically ill patients to state that chemotherapy receipt and long term survival are reduced due to the increased likelihood of dying in hospital. To provide new meaningful information for intensivists, oncologists, and patients, in this chapter I wish to understand any ongoing impact of critical illness that persists after hospital survival.

Two important points have been raised in the Introduction and Methods that create some difficulty for this question. First is that adjusting for certain nodes in a DAG can introduce spurious associations; in particular adjustment on what are known as ‘colliders’. The second is that within our dataset an important variable (frailty) is unmeasured. In Figure 8.4 below I aim to represent this problem. We see that frailty is assumed to influence the probability of critical illness. Then both through the mechanism of critical illness, and independent to it, frailty influences the probability of hospital survival and chemotherapy receipt. Critical illness is assumed to influence probability of hospital survival, and also independently chemotherapy receipt.

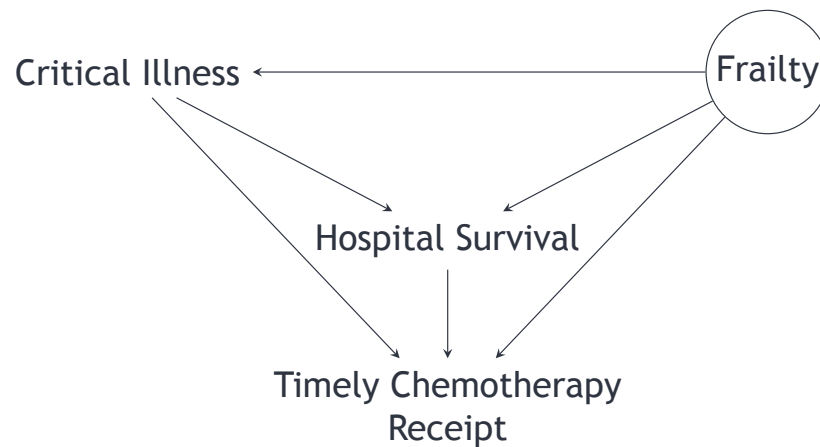


Figure 8.4: Example directed acyclic graph, demonstrating the collider inherent in conditioning on hospital survival, with the unmeasured confounder of Frailty

As both the nodes of critical illness and frailty have edges to hospital survival, hospital survival is considered a collider between these variables (McElreath 2020).

$$\text{Critical Illness} \rightarrow \text{Hospital Survival} \leftarrow \text{Frailty}$$

Conditioning by hospital survival not only reduces the estimated causal effect of critical illness, something we allowed for and desired, but also risks additional spurious associations. Assuming that both critical illness and frailty increase risk of hospital mortality, then conditioning on hospital survival results in a cohort of critical illness survivors that are less likely to be frail (if you experience critical illness and frailty you have two insults to overcome to survive admission, whereas a frail patient without critical illness only has to overcome one). Following the cohort of critical illness survivors (who are less likely to have premonitory frailty), and comparing them against the cohort of survivors who didn't experience critical illness (who are more likely to have premonitory frailty), and investigating subsequent outcomes such as chemotherapy receipt and long term survival, this selection bias we have induced will result in estimates of effect that will be biased towards 'no effect' of critical illness (McElreath 2020). Adjustment for frailty, similar to how I adjust for other variables which have

independent impacts on outcome, such as comorbidity and age, would effectively counter this limitation. Unfortunately as frailty is unobserved, the methodological limitation remains and must be noted. To partially account for frailty, I used the mechanisms as described in Section 8.2.4.

8.2.6 Directed Acyclic Graph

Figure 8.5 provides the proposed underlying scientific model to be investigated within this chapter. In this model age, socio-economic status (SIMD), comorbidities, dementia, cancer stage (high risk stage II, and stage III disease), and sex are considered confounders that require adjustment. Frailty is considered an unobserved confounder, with limitations and adjustment for as noted in Section 8.2.5. Nature of admission to hospital and receipt of organ support are the exposures of interest. Whilst method of diagnosis is assumed to have causal influence on long term outcomes, its causal pathway operates through nature of admission and cancer stage at the time of diagnosis. In this model I adjust for both nature of admission and cancer stage, as such adjusting for method of diagnosis becomes redundant (McElreath 2020). Duration of hospital admission (length of stay) is considered a mediator and is not adjusted for. In models of SACT receipt, SACT receipt is the outcome of interest, in models of long term survival, overall-survival is the outcome of interest and SACT receipt is considered another mediator. Noted in Chapter 1, Post Intensive Care Syndrome (PICS) is a clinically relevant outcome following critical illness. Whilst it may seem reasonable to a clinician that incidence of PICS would likely impact long term cancer outcomes, such work investigating the relationship between PICS and cancer outcomes has not been published. For the purpose of this thesis, PICS would be considered a mediator for any total causal effect of critical illness on cancer outcomes; as such it being unobserved does not negatively impact our modelling, as if we had detail on incidence of PICS (or equally, frailty post critical illness) it would not be adjusted for.

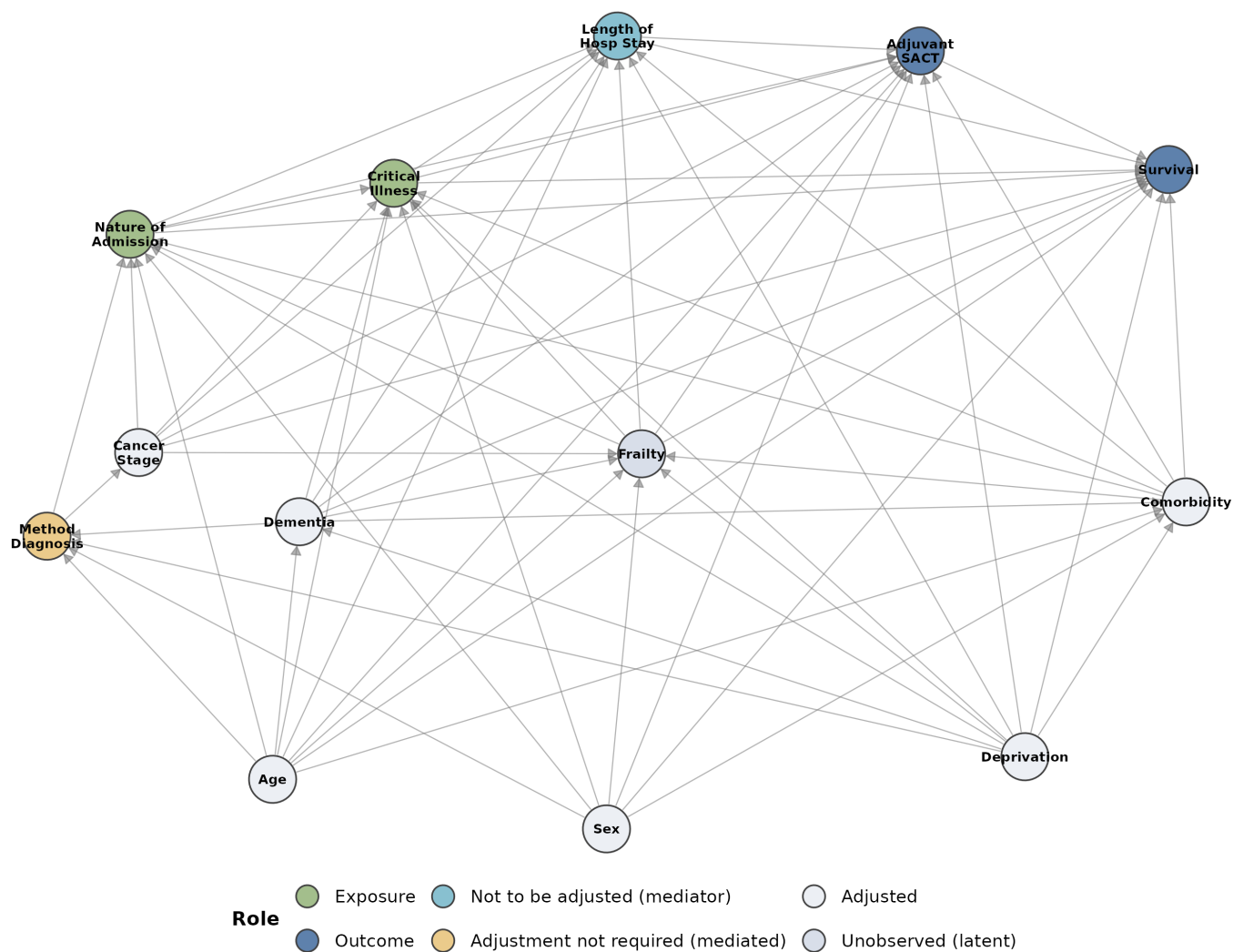


Figure 8.5: DAG representing the assumed causal structure for the analyses in this chapter. Critical Illness and Nature of Admission are the exposures; receipt of adjuvant SACT and overall survival are the outcomes. Both analyses target the total causal effect of critical illness.

8.3 Results: Total Critical Care Cohort

43,773 unique adult patients with colorectal cancer were admitted to hospital, 22,399 patients were admitted to critical care during their index hospital admission. 78% of admissions were elective (n=17,443), 22% of admissions were as an emergency (n = 4,956). Within elective and emergency admissions, receiving monitoring only in critical care were the largest cohorts, accounting for 85% of elective admissions (n = 14,756) and 72% of emergency admissions (n = 3,589). 1,776 elective patients received multiple days of organ support, this chapters' definition of critical illness (10% of elective admissions), 953 emergency patients received multiple days of organ support (19% of emergency admissions).

8.3.1 Demographics

Full demographics of the overall population and subcohorts are provided in Table 8.1.

Median age of the overall population of CRC patients admitted to critical care was 70 (IQR 62-78), Elective - Multiple had median age 71 (IQR 65-78), Emergency - Multiple had median age 74 (IQR 65-81). Overall proportion of male patients was 56% (n = 12,490), with Elective - Multiple having 62% (n = 1,099), and Emergency - Multiple having 57% (n = 547).

The overall proportion of patients with no additional comorbidities to cancer was 75% (n = 16,845), and multiple additional comorbidities was 5.8% (n = 1,299). Patients with critical illness had a greater proportion with multiple additional comorbidities (BF > 100, strong evidence for difference). Elective - Multiple had 9.9% (n = 176), Emergency - Multiple had 9% (n = 86). For the comorbidities of Cardiac, Respiratory, Renal, and

Diabetes, critical illness subcohorts each had a greater proportion of patients with each comorbidity ($BF > 100$). The only comorbidity that did not follow this pattern was Dementia, where the overall proportion was 0.7% ($n = 161$), Elective - Multiple had 0.6% ($n = 11$), and Emergency Multiple had 1.3% ($n = 12$), with $BF < 0.001$ (strong evidence of no difference between cohorts).

In the overall population, diagnosis through screening was 16% ($n = 3,661$) and through clinical presentation was 81% ($n = 18,049$). There was clear difference between Elective and Emergency subcohorts, rather than difference observed between levels of support. Elective - Multiple had 79% ($n = 1,408$) diagnosed following clinical presentation, whilst Emergency - Multiple had 94% ($n = 897$) ($BF > 100$).

As described in Chapter 4, SMR06 is limited by the significant amount of missing data on anatomic stage. 67% of the overall population ($n = 14,932$) did not have TNM score recorded in SMR06. With this limitation noted, differences between subcohorts here appear between Elective and Emergency admissions ($BF > 100$). The overall proportion recorded with Stage IV disease was 12% of all patients (percentage of the total with recorded information, $n = 859$). Elective - Multiple had 9.4% ($n = 68$) patients recorded with Stage IV disease, Emergency - Multiple had 17% ($n = 61$). These differences persisted after the addition of SMR01 disease codes to SMR06, overall identification of Metastatic Disease was 25% in the overall population ($n = 5,689$), 23% ($n = 403$) in Elective - Multiple, and 28% ($n = 263$) in Emergency - Multiple. Of note, emergency admissions treated with Monitoring alone had a greater observed proportion of metastatic disease, with 36% ($n = 1,286$, $BF > 100$).

Treatment Intent did not appear markedly different between levels of support, but did differ dependent on nature of admission ($BF > 100$). 77% ($n = 17,203$) of the overall population were treated with curative intent, 80% ($n = 1,429$) of Elective - Multiple patients, and 58% ($n = 556$) of Emergency - Multiple patients. Treatment intent did have missing data (missing data for overall population 7.2%, $n = 1602$), although not at the magnitude seen for disease stage.

All subcohorts had greater than 90% of patients admitted under the care of surgical specialties, with 99% of the overall population treated by surgeons in their index admission ($n = 22,120$). Emergency admissions had slight but notable increase in medical admissions as coded by SMR01. Elective - Multiple had close to 100% surgical admissions ($n = 1,770$), Emergency - Multiple had 96% surgical admissions ($n = 915$, $BF > 100$). The overall population saw 76% ($n = 17,008$) of patients undergo one operation during their index admission, and 16% received multiple operations ($n = 3,536$). The critical illness subcohorts had a greater proportion of patients with multiple operations ($BF > 100$), where Elective - Multiple had 29% ($n = 507$), and Emergency - Multiple had 23% ($n = 217$). All emergency subcohorts had a greater proportion of patients receiving no operation during index admission ($BF > 100$), 18% of Emergency - Multiple admissions ($n = 168$) did not receive an operation, contrasted against the population average of 8.3% ($n = 1,855$).

Patients with critical illness had longer critical care and hospital stays ($BF > 100$). The overall population median duration of admission in critical care and hospital were 3 (IQR 2-5) days and 11 (IQR 7-17) days respectively. For Elective - Multiple, these durations were 6 (IQR 3-10) and 17 (IQR 10-32) days. For Emergency - Multiple, these durations were 6 (IQR 3-10) and 23 (IQR 13-42) days.

APACHE II scoring had high proportions of missing data, known to be missing not at random, with a high risk of bias, discussed in more detail in Section 8.7.3. Amongst the overall population 75% of admissions did not have APACHE II recorded (n = 16,710), patients with critical illness had greater completion of APACHE II, where Elective - Multiple had 40% missing data (n = 706), and Emergency - Multiple had 29% missing data (n = 275).

In regards to organ support: 82% (n = 1,450) of Elective - Multiple and 75% (n = 719) of Emergency - Multiple received cardiovascular support. 51% (n = 898) of Elective - Multiple and 68% (n = 646) of Emergency - Multiple received respiratory support. 9.6% (n = 170) of Elective - Multiple and 12% (n = 111) of Emergency - Multiple received renal support.

Table 8.1: Characteristics of all adult colorectal cancer patients admitted to critical care, stratified by days of organ support (0 / 1 / 2+).

Characteristic	Overall	Elective	Elective	Elective	Emergency	Emergency	Emergency	Bayes
		Monitoring	Single	Multiple	Monitoring	Single	Multiple	Factor
	N = 22,399	N = 14,756	N = 911	N = 1,776	N = 3,589	N = 414	N = 953	
Age At	70 (62, 78)	70 (61, 76)	72 (64, 78)	71 (65, 78)	72 (62, 80)	75 (66, 82)	74 (65, 81)	>100
Diagnosis								
Sex								>100
Male	12,490 (56%)	8,265 (56%)	555 (61%)	1,099 (62%)	1,804 (50%)	220 (53%)	547 (57%)	
Female	9,909 (44%)	6,491 (44%)	356 (39%)	677 (38%)	1,785 (50%)	194 (47%)	406 (43%)	
SIMD (quintile)								<0.001
1	4,103 (18%)	2,629 (18%)	163 (18%)	321 (18%)	687 (19%)	90 (22%)	213 (22%)	
2	4,542 (20%)	2,940 (20%)	199 (22%)	374 (21%)	722 (20%)	83 (20%)	224 (24%)	
3	4,609 (21%)	3,009 (20%)	214 (23%)	370 (21%)	744 (21%)	91 (22%)	181 (19%)	
4	4,632 (21%)	3,068 (21%)	188 (21%)	411 (23%)	701 (20%)	85 (21%)	179 (19%)	
5	4,493 (20%)	3,096 (21%)	147 (16%)	299 (17%)	731 (20%)	64 (15%)	156 (16%)	
Unknown	20	14	0	1	4	1	0	
Additional								>100
Charlson								
Comorbidities								
0	16,845 (75%)	11,527 (78%)	596 (65%)	1,146 (65%)	2,695 (75%)	260 (63%)	621 (65%)	
1	4,255 (19%)	2,567 (17%)	228 (25%)	454 (26%)	650 (18%)	110 (27%)	246 (26%)	
2+	1,299 (5.8%)	662 (4.5%)	87 (9.5%)	176 (9.9%)	244 (6.8%)	44 (11%)	86 (9.0%)	
Cardiac Disease	1,629 (7.3%)	884 (6.0%)	101 (11%)	210 (12%)	271 (7.6%)	55 (13%)	108 (11%)	>100
(Charlson)								
Unknown	17	12	0	2	3	0	0	
Respiratory	2,152 (9.6%)	1,214 (8.2%)	132 (14%)	246 (14%)	363 (10%)	65 (16%)	132 (14%)	>100
Disease								
(Charlson)								
Unknown	17	12	0	2	3	0	0	

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Characteristic	Overall	Elective	Elective	Elective	Emergency	Emergency	Emergency	Bayes
		Monitoring	Single	Multiple	Monitoring	Single	Multiple	Factor
	N = 22,399	N = 14,756	N = 911	N = 1,776	N = 3,589	N = 414	N = 953	
Renal Disease (Charlson)	933 (4.2%)	467 (3.2%)	57 (6.3%)	117 (6.6%)	184 (5.1%)	33 (8.0%)	75 (7.9%)	>100
Unknown	17	12	0	2	3	0	0	
Diabetes (Charlson)	2,231 (10.0%)	1,363 (9.2%)	123 (14%)	262 (15%)	320 (8.9%)	51 (12%)	112 (12%)	>100
Unknown	17	12	0	2	3	0	0	
Dementia (Charlson)	161 (0.7%)	78 (0.5%)	5 (0.5%)	11 (0.6%)	47 (1.3%)	8 (1.9%)	12 (1.3%)	<0.001
Unknown	17	12	0	2	3	0	0	
Method of First Detection								>100
Screening examination	3,661 (16%)	3,053 (21%)	164 (18%)	300 (17%)	108 (3.0%)	11 (2.7%)	25 (2.6%)	
Incidental finding	470 (2.1%)	293 (2.0%)	26 (2.9%)	53 (3.0%)	65 (1.8%)	11 (2.7%)	22 (2.3%)	
Clinical presentation	18,049 (81%)	11,262 (76%)	719 (79%)	1,408 (79%)	3,377 (94%)	386 (93%)	897 (94%)	
Other / Not Known	219 (1.0%)	148 (1.0%)	2 (0.2%)	15 (0.8%)	39 (1.1%)	6 (1.4%)	9 (0.9%)	
Anatomic Stage								>100
0	43 (0.6%)	21 (0.4%)	2 (0.6%)	5 (0.7%)	8 (0.7%)	1 (0.7%)	6 (1.7%)	
I	1,114 (15%)	861 (18%)	61 (18%)	120 (17%)	45 (4.2%)	7 (4.9%)	20 (5.6%)	
IIA	1,865 (25%)	1,354 (28%)	84 (25%)	183 (25%)	178 (16%)	19 (13%)	47 (13%)	
IIB	490 (6.6%)	254 (5.3%)	16 (4.7%)	37 (5.1%)	115 (11%)	20 (14%)	48 (14%)	
III	3,096 (41%)	1,969 (41%)	127 (37%)	308 (43%)	453 (42%)	66 (46%)	173 (49%)	
IV	859 (12%)	368 (7.6%)	50 (15%)	68 (9.4%)	282 (26%)	30 (21%)	61 (17%)	
Unknown	14,932	9,929	571	1,055	2,508	271	598	
Metastatic Disease Found	5,689 (25%)	3,420 (23%)	195 (21%)	403 (23%)	1,286 (36%)	122 (29%)	263 (28%)	>100
Objectives of Treatment								>100
Curative Intent	17,203 (77%)	12,157 (82%)	732 (80%)	1,429 (80%)	2,098 (58%)	231 (56%)	556 (58%)	
Non-curative Intent (palliative)	3,594 (16%)	1,561 (11%)	120 (13%)	239 (13%)	1,198 (33%)	151 (36%)	325 (34%)	

Continued on next page

8.3. Results: Total Critical Care Cohort

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Characteristic	Overall	Elective	Elective	Elective	Emergency	Emergency	Emergency	Bayes
		Monitoring	Single	Multiple	Monitoring	Single	Multiple	Factor
	N = 22,399	N = 14,756	N = 911	N = 1,776	N = 3,589	N = 414	N = 953	
Not Known	1,602 (7.2%)	1,038 (7.0%)	59 (6.5%)	108 (6.1%)	293 (8.2%)	32 (7.7%)	72 (7.6%)	
Surgical Admission								>100
False	279 (1.2%)	41 (0.3%)	5 (0.5%)	6 (0.3%)	155 (4.3%)	34 (8.2%)	38 (4.0%)	
True	22,120 (99%)	14,715 (100%)	906 (99%)	1,770 (100%)	3,434 (96%)	380 (92%)	915 (96%)	
Operation During Admission								>100
None	1,855 (8.3%)	832 (5.6%)	80 (8.8%)	127 (7.2%)	559 (16%)	89 (21%)	168 (18%)	
One	17,008 (76%)	11,794 (80%)	636 (70%)	1,142 (64%)	2,619 (73%)	249 (60%)	568 (60%)	
Multiple	3,536 (16%)	2,130 (14%)	195 (21%)	507 (29%)	411 (11%)	76 (18%)	217 (23%)	
Diagnosis To Admission (days)	44 (18, 88)	51 (31, 98)	58 (34, 114)	57 (34, 112)	0 (0, 24)	0 (0, 29)	0 (0, 16)	>100
Duration Hospital Stay (days)	11 (7, 17)	9 (7, 14)	13 (8, 20)	17 (10, 32)	15 (10, 25)	18 (10, 32)	23 (13, 42)	>100
Duration Critical Care Stay (days)	3.00 (2.00, 5.00)	3.00 (1.00, 4.00)	4.00 (2.00, 6.00)	6.00 (3.00, 10.00)	3.00 (2.00, 4.00)	3.00 (2.00, 5.00)	6.00 (3.00, 10.00)	>100
APACHE II Score	16.0 (12.0, 20.0)	15.0 (11.0, 20.0)	13.0 (11.0, 17.0)	17.0 (13.0, 21.0)	17.0 (11.0, 20.0)	17.0 (13.0, 21.0)	18.5 (15.0, 24.0)	>100
Unknown	16,710	12,085	537	706	2,888	219	275	
Vasoactive Support	3,048 (14%)	0 (0%)	636 (70%)	1,450 (82%)	0 (0%)	243 (59%)	719 (75%)	>100
Ventilated	2,070 (9.2%)	0 (0%)	325 (36%)	898 (51%)	0 (0%)	201 (49%)	646 (68%)	>100
Renal Replacement Therapy	309 (1.4%)	0 (0%)	13 (1.4%)	170 (9.6%)	0 (0%)	15 (3.6%)	111 (12%)	>100
Hospital Mortality	1,456 (6.5%)	232 (1.6%)	66 (7.2%)	283 (16%)	433 (12%)	107 (26%)	335 (35%)	>100

8.3.2 Days of Organ Support

As noted in Section 8.1.1, patients were included in the ‘Multiple’ days of organ support subcohorts, when they had two or more daily records noting organ support during their critical care admission. For both Elective - Multiple and Emergency admissions, the median number of days of organ support was 3; 3 (IQR 2-4) and 3 (IQR 2-5) respectively as shown in Table 8.3.

Table 8.3: Summary of days of organ support among CRC patients admitted to critical care, stratified by nature of admission.

Characteristic	Median (IQR): Maximum	
	Elective N = 1,776	Emergency N = 953
Number Days of Organ Support	3 (2, 4): 67	3 (2, 5): 47

8.3.3 Reason for Admission

Similar to other characteristics noted above, reason for admission appeared more dependent on nature of admission rather than level of support during critical care. These are shown in Table 8.4. For all Elective subcohorts ‘GI Surgery For Neoplasm’ was the most common reason for admission (55-58% of admissions). For all Elective subcohorts ‘GI Perforation / Obstruction’ was the third most common cause (15-17%). Inverting what was seen in Elective admissions, for all Emergency subcohorts ‘GI Perforation / Obstruction’ was the most common cause (38-42% of admissions), with ‘GI Surgery for Neoplasm’ the second or third reason most commonly cited (16-29%).

Table 8.4: Top three reasons for critical care admission among CRC patients, stratified by nature of admission and level of support.

Rank	Elective: Monitoring	Elective: Single	Elective: Multiple	Emergency: Monitoring	Emergency: Single	Emergency: Multiple
1	GI surgery for neoplasm, n=8448(57.3%)	GI surgery for neoplasm, n=529(58.1%)	GI surgery for neoplasm, n=980(55.2%)	GI perforation / obstruction, n=1355(37.8%)	GI perforation / obstruction, n=165(39.9%)	GI perforation / obstruction, n=402(42.2%)
2	Other gastrointestinal disorder, n=3064(20.8%)	Other gastrointestinal disorder, n=147(16.1%)	Other gastrointestinal disorder, n=348(19.6%)	GI surgery for neoplasm, n=1047(29.2%)	GI surgery for neoplasm, n=82(19.8%)	Other gastrointestinal disorder, n=165(17.3%)
3	GI perforation / obstruction, n=2498(16.9%)	GI perforation / obstruction, n=136(14.9%)	GI perforation / obstruction, n=261(14.7%)	Other gastrointestinal disorder, n=760(21.2%)	Other gastrointestinal disorder, n=80(19.3%)	GI surgery for neoplasm, n=160(16.8%)

8.3.4 Overall Survival - Short and Long Term

Among the total population, admission mortality was 6.5% ($n = 1,456$). Admission mortality was 16% ($n = 283$) among Elective - Multiple and 35% ($n = 335$) among Emergency - Multiple. Figure 8.6 demonstrates Kaplan-Meier (KM) estimates of overall survival for the total population of patients with CRC admitted to critical care, where time zero is day of admission to index hospital admission following CRC diagnosis, faceted by short-term (2 months) and long term (5 year) estimates of survival probability. Within this, 2 month estimate of overall survival (OS) was 94% (95% CI 94-94%), one-year OS was 85% (95% CI 84-85%), and five-year OS was 59% (95% CI 59-60%).

Figures 8.6 and 8.7 provide greater stratification of this overall population estimate. Figure 8.6 provides estimates of overall survival that include in-hospital mortality and long-term outcomes, faceted by nature of admission, and split by level of support in hospital, resulting in 6 KM estimates in total. Figure 8.7 provides 6 KM estimates, however for this figure only those who survived hospital admission are included, and time zero is 30 days following hospital discharge. In the following description, each estimate provided will first be from Figure 8.6 (all patients), then from Figure 8.7 (hospital survivors). For ease of reading, confidence intervals will not be in the text, but are on the figures themselves.

In these stratified KM estimates, emergency admissions consistently had worse overall survival than elective, and for both admission types 'Multiple' organ support days had worse survival than those who received monitoring alone. This difference remained present, but was less pronounced, in the Emergency subcohorts once difference in hospital mortality had been accounted for. Within estimates that included and excluded hospital mortality, those who were admitted as an Emergency who did not receive organ support in critical care, had worse overall survival estimates than those admitted Electively who did experience 'critical illness' (receipt of multiple days of

organ support). Elective - Monitoring patients had one-year overall-survival estimates of 93% (also 93% among hospital survivors), contrasted against Elective - Multiple OS estimates of 77% (90% among hospital survivors). These were greater than seen for Emergency - Monitoring one-year OS estimates of 68% (74%), and Emergency - Multiple of 51% (73%). The differences persisted at estimates of five-year overall survival. For Elective - Monitoring five-year OS estimates were 69% (70%), where Elective - Multiple was lower at 51% (59%). Emergency - Monitoring five-year OS estimates were 36% (40%), and Emergency - Multiple was 22% (33%).

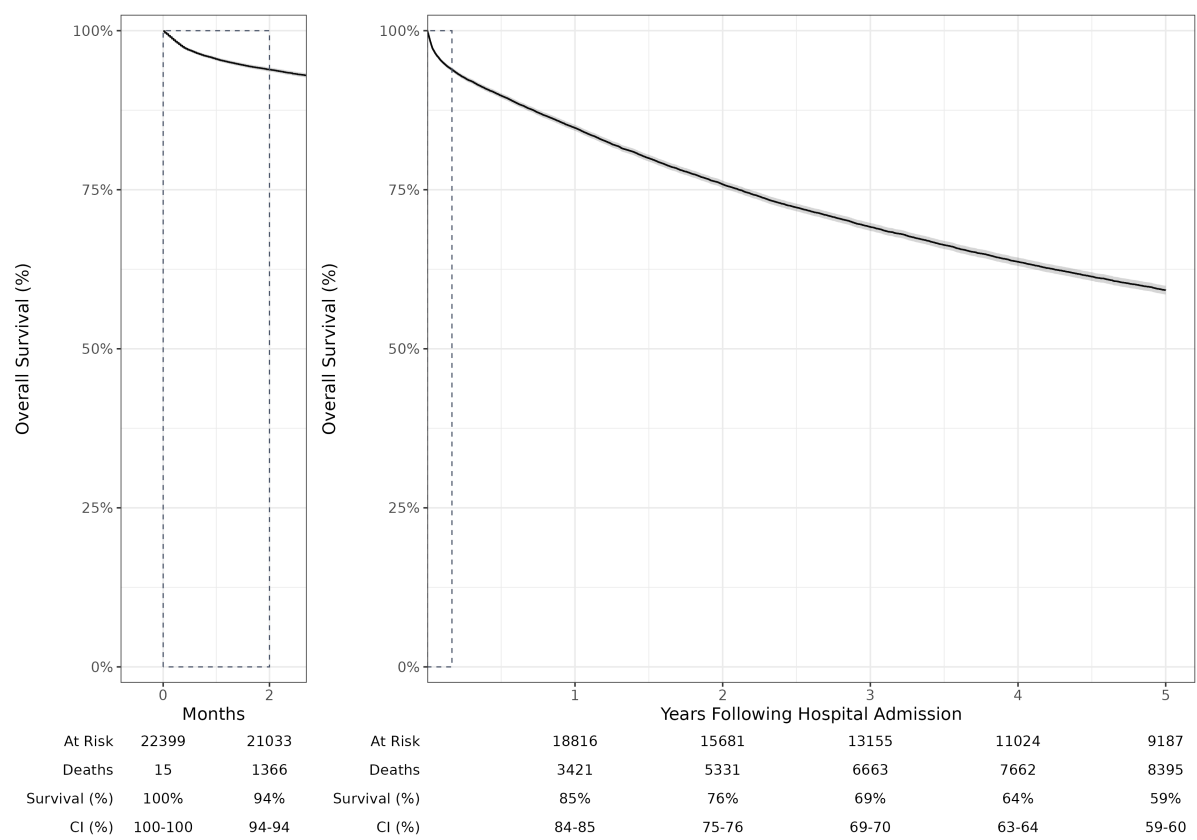


Figure 8.6: Kaplan-Meier estimates of overall survival for the total population of patients with CRC admitted to critical care, faceted by short-term (two months) and long term (five-year) estimates of survival probability.

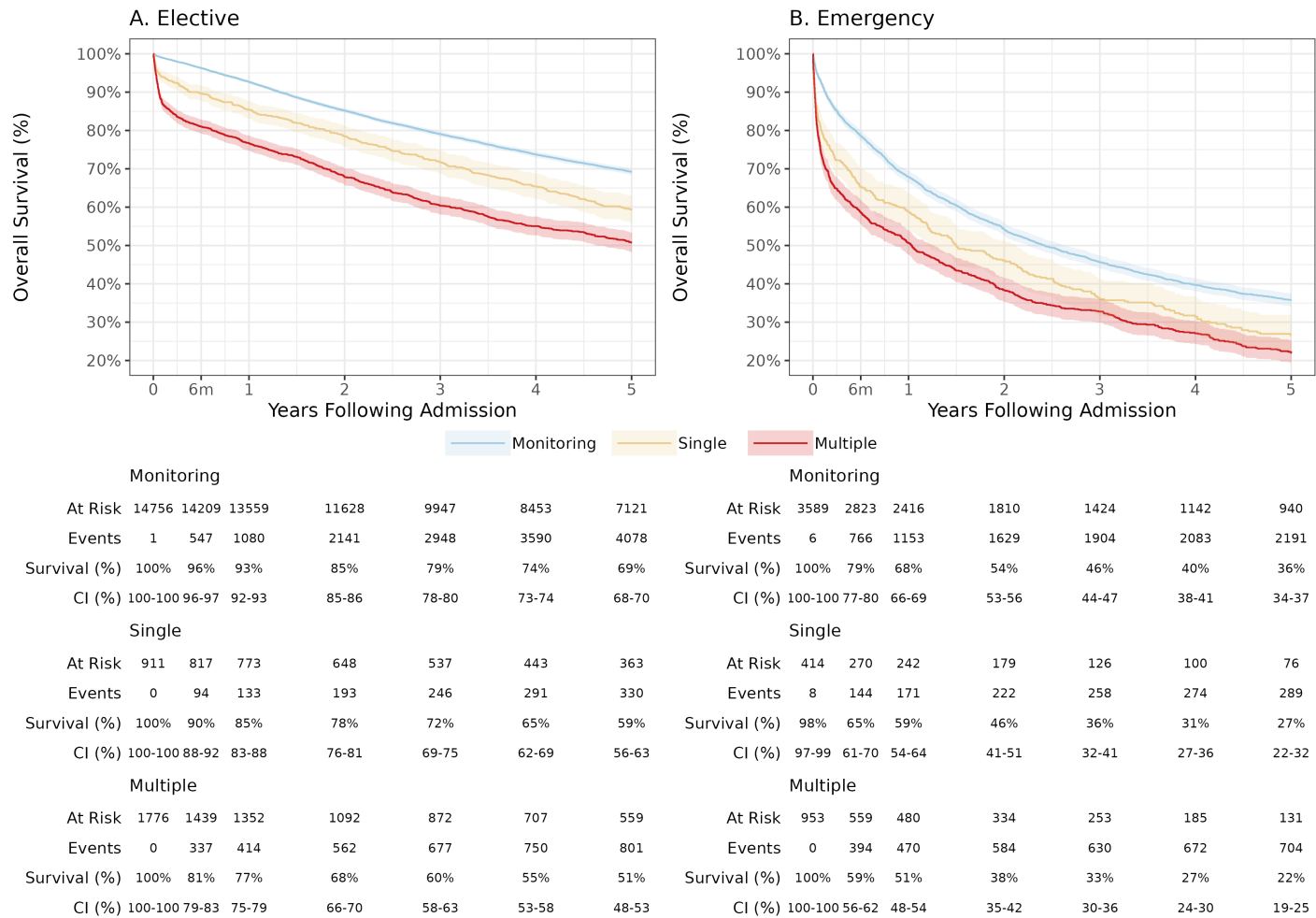


Figure 8.7: Kaplan-Meier long-term survival, stratified by days of organ support (0 / 1 / 2+). Facetted by nature of admission. Includes in-hospital mortality. Day 0 is admission to hospital.

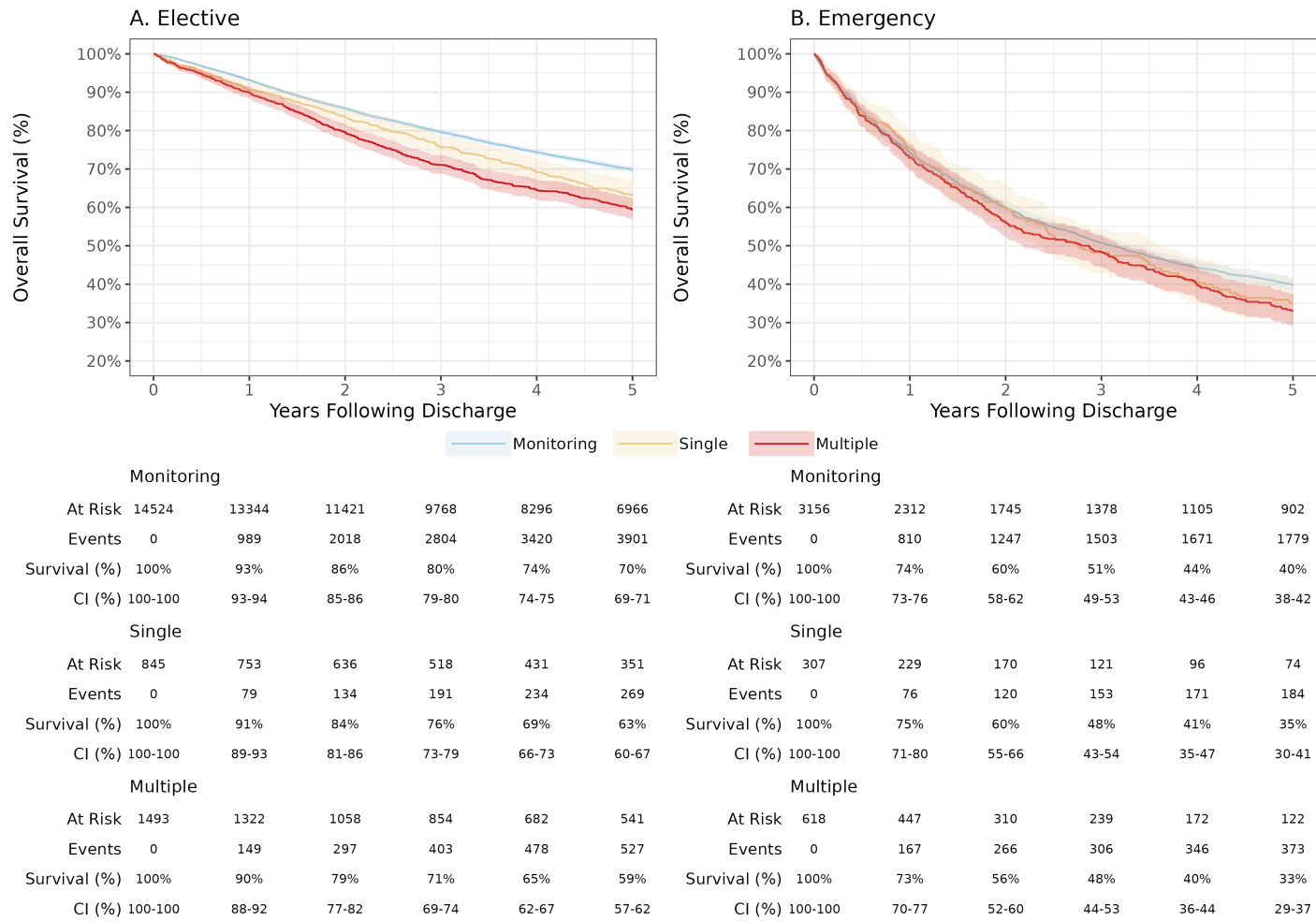


Figure 8.8: Kaplan-Meier long-term survival for CRC patients admitted to critical care who survived to hospital discharge, stratified by days of organ support. Facetted by nature of admission. Excludes in-hospital mortality. Day 0 is 30 days following discharge from hospital.

8.4 Results: SACT-eligible Analytic Cohort

As noted in the previous chapters of this thesis, and in Section 8.3.1, when all patients with CRC are included, each subcohort has significant differences in patient characteristics. In relation to CRC specific measures, patients differ by cancer stage, admitting specialty, and treatment undertaken. To extract estimates on the impact of critical illness itself, the remainder of this chapter focuses on a population of patients more similar in baseline characteristics, with theoretically identical treatment paths proposed. Details of patients included are shown in the CONSORT diagram in Figure 8.3. Following the same stratification seen in Chapters 6 and 7, the remainder of this chapter focuses on adult patients with no maximum age, who had CRC High Risk II or Stage III disease at point of diagnosis, who received curative resection of their cancer during their index-admission, and survived their hospital admission. These patients should all be eligible for adjuvant SACT following their surgery. This stratification was undertaken using additional details available in the QPI dataset, which has fewer missing data on cancer stage than SMR06, although covers fewer patients and a smaller time-period. These patients are similar to those considered for QPI 11 in Chapter 5, although QPI 11 uses an upper age limit that excludes those aged 75 and above.

8.4.1 Demographics

Full details of patient characteristics are provided in Table 8.5. The aim was to identify a more homogenous group of patients suitable for comparison of cancer-related outcomes. Within this population of SACT-eligible patients, Elective - Monitoring remained the single largest subcohort accounting for 65% of all patients (n=1695). Emergency - Monitoring was the second largest subcohort with 16% of all patients (n=416). There were 216 Elective - Multiple patients (10.5% of elective admissions), and 119 Emergency - Multiple patients (20% of emergency admissions).

Table 8.5: Characteristics of SACT-eligible adult colorectal cancer patients admitted to critical care, stratified by days of organ support (0 / 1 / 2+).

Characteristic	Overall N = 2,607	Elective Monitoring N = 1,695	Elective Single N = 110	Elective Multiple N = 216	Emergency Monitoring N = 416	Emergency Single N = 51	Emergency Multiple N = 119	Bayes Factor
Age At Diagnosis	71 (62, 79)	70 (62, 78)	71 (63, 78)	73 (65, 80)	72 (63, 80)	74 (62, 82)	73 (64, 80)	0.143
Sex								0.068
Male	1,440 (55%)	942 (56%)	71 (65%)	128 (59%)	198 (48%)	28 (55%)	73 (61%)	
Female	1,167 (45%)	753 (44%)	39 (35%)	88 (41%)	218 (52%)	23 (45%)	46 (39%)	
SIMD (quintile)								<0.001
1	475 (18%)	285 (17%)	22 (20%)	45 (21%)	72 (17%)	14 (27%)	37 (31%)	
2	493 (19%)	321 (19%)	20 (18%)	41 (19%)	85 (21%)	6 (12%)	20 (17%)	
3	541 (21%)	343 (20%)	21 (19%)	52 (24%)	88 (21%)	10 (20%)	27 (23%)	
4	532 (20%)	351 (21%)	24 (22%)	49 (23%)	81 (20%)	10 (20%)	17 (14%)	
5	562 (22%)	393 (23%)	23 (21%)	29 (13%)	88 (21%)	11 (22%)	18 (15%)	
Unknown	4	2	0	0	2	0	0	
Additional Charlson Comorbidities								<0.001
0	1,939 (74%)	1,300 (77%)	66 (60%)	145 (67%)	303 (73%)	38 (75%)	87 (73%)	
1	494 (19%)	303 (18%)	30 (27%)	47 (22%)	82 (20%)	10 (20%)	22 (18%)	
2+	174 (6.7%)	92 (5.4%)	14 (13%)	24 (11%)	31 (7.5%)	3 (5.9%)	10 (8.4%)	
Dementia (Charlson)	18 (0.7%)	9 (0.5%)	1 (0.9%)	1 (0.5%)	7 (1.7%)	0 (0%)	0 (0%)	<0.001
Unknown	4	3	0	0	1	0	0	
Clinical Diagnosis	2,027 (78%)	1,222 (73%)	77 (70%)	164 (76%)	404 (97%)	46 (90%)	114 (96%)	>100
Unknown	11	11	0	0	0	0	0	
Anatomic Stage								0.002
C	1,753 (67%)	1,161 (68%)	76 (69%)	145 (67%)	252 (61%)	37 (73%)	82 (69%)	
HRB	854 (33%)	534 (32%)	34 (31%)	71 (33%)	164 (39%)	14 (27%)	37 (31%)	
Operation During Admission								>100

Continued on next page

Characteristic	Overall	Elective	Elective	Elective	Emergency	Emergency	Emergency	Bayes
		Monitoring	Single	Multiple	Monitoring	Single	Multiple	Factor
	N = 2,607	N = 1,695	N = 110	N = 216	N = 416	N = 51	N = 119	
One	2,216 (85%)	1,483 (87%)	88 (80%)	154 (71%)	367 (88%)	39 (76%)	85 (71%)	
Multiple	391 (15%)	212 (13%)	22 (20%)	62 (29%)	49 (12%)	12 (24%)	34 (29%)	
Diagnosis To Admission (days)	42 (16, 68)	50 (34, 75)	55 (37, 78)	50 (34, 76)	0 (0, 10)	0 (0, 30)	0 (0, 5)	>100
Duration Hospital Stay (days)	10 (7, 16)	8 (6, 12)	11 (8, 18)	16 (10, 32)	14 (10, 22)	17 (13, 25)	27 (17, 46)	>100
Duration Critical Care Stay (days)	3.00 (1.00, 5.00)	2.00 (1.00, 4.00)	4.00 (2.00, 6.00)	5.00 (3.00, 9.00)	3.00 (2.00, 4.00)	4.00 (2.00, 7.00)	6.00 (4.00, 12.00)	>100
APACHE II Score	13.0 (10.0, 16.0)	11.0 (9.0, 13.0)	12.0 (10.0, 14.0)	16.0 (12.0, 19.0)	11.0 (9.0, 13.5)	10.0 (8.0, 18.0)	16.0 (13.0, 19.0)	>100
Unknown	2,122	1,492	75	118	372	36	29	
Vasoactive Support	444 (17%)	0 (0%)	90 (82%)	204 (94%)	0 (0%)	41 (80%)	109 (92%)	>100
Ventilated	183 (7.0%)	0 (0%)	24 (22%)	73 (34%)	0 (0%)	13 (25%)	73 (61%)	>100
Renal Replacement Therapy	22 (0.8%)	0 (0%)	3 (2.7%)	11 (5.1%)	0 (0%)	0 (0%)	8 (6.7%)	>100

In the original total population (Table 8.1) there was strong evidence of difference between subcohorts in regards to Age, Sex, Additional Comorbidities, and Cancer Stage, with Bayes Factor > 100. Within this SACT-eligible cohort, there was strong evidence of no difference between subcohorts for all of these measures, with Bayes Factors < 1. Median age for the SACT-eligible population was 71 (IQR 62-79), with 55% male patients (n=1,440). 74% (n=1,939) of the overall population had no additional comorbidities to cancer, 6.7% (n=174) had two or more additional comorbidities. All patients in this SACT-eligible population had cancer stage recorded (being ineligible for inclusion without stage recorded), with 67% (n=1,753) had Stage III disease, and 33% (n=854) had High Risk Stage II disease.

Following admission differences did persist between subcohorts, 15% (n=391) of the overall population underwent multiple operations during admission. This was greater in the critical illness subcohorts, with 29% (n=62) of Elective - Multiple patients undergoing multiple operations, and 29% (n=34) of Emergency - Multiple patients. By nature of definition of being SACT-eligible, there were no patients who did not receive an operation during their admission. Within the SACT-eligible population there remained significant amount of missing data on APACHE II (81%, n = 2,122).

Among patients receiving multiple days of organ support, the median duration was the same for both elective and emergency admissions, with 3 (IQR 2-4) days of organ support.

8.4.2 Reason for Admission

Similar to reasons for admission observed for the total population in Table 8.4, in Table 8.7 we see the reasons for admission to critical care in the SACT-eligible population. Again, ‘GI surgery for neoplasm’ was the most common reason for elective admissions (56-61%), and ‘GI Perforation / Obstruction’ was the most common emergency diagnosis (44-50%).

Table 8.7: Top three reasons for critical care admission among the SACT-eligible analytic cohort, stratified by nature of admission and level of support.

Rank	Elective: Monitoring	Elective: Single	Elective: Multiple	Emergency: Monitoring	Emergency: Single	Emergency: Multiple
1	GI surgery for neoplasm, n=1029(60.1%)	GI surgery for neoplasm, n=64(56.1%)	GI surgery for neoplasm, n=151(59.9%)	GI perforation / obstruction, n=192(44.4%)	GI perforation / obstruction, n=33(58.9%)	GI perforation / obstruction, n=84(50%)
2	Other gastrointestinal disorder, n=310(18.1%)	GI perforation / obstruction, n=29(25.4%)	GI perforation / obstruction, n=48(19%)	GI surgery for neoplasm, n=137(31.7%)	Other gastrointestinal disorder, n=9(16.1%)	GI surgery for neoplasm, n=31(18.5%)
3	GI perforation / obstruction, n=306(17.9%)	Other gastrointestinal disorder, n=15(13.2%)	Other gastrointestinal disorder, n=42(16.7%)	Other gastrointestinal disorder, n=75(17.4%)	GI surgery for neoplasm, n=8(14.3%)	Other gastrointestinal disorder, n=26(15.5%)

8.4.3 Long-Term Survival, Conditional on Hospital Discharge

For the population of SACT-eligible patients, single and stratified estimates of overall survival (including in-hospital mortality) are provided in Appendix E, Figures E.19 and E.20.

Figure 8.9 demonstrates Kaplan-Meier estimates for overall survival (OS) for SACT eligible patients who survived hospital admission, where time zero is 30 days following hospital admission. This figure is faceted by nature of admission and stratified by level of support during admission. As seen in the total population, each emergency subcohort has worse OS than its elective counterpart. Whilst the central estimates

for OS follow the same pattern as the total population, with multiple days of organ support having worse survival than monitoring alone, and no critical illness amongst emergency admission having worse survival than critical illness during elective admission, there is overlap of 95% CIs.

For Elective - Monitoring one-year OS estimate is 94% (95% CI 93-95%) for this SACT-eligible population, contrasted against 88% (95% CI 84-92%) for Elective - Multiple. Emergency - Monitoring one-year OS estimate is 84% (95% CI 80-88%), contrasted against 81% (95% CI 74-88%) for Emergency - Multiple.

At five-year OS estimates, Elective - Monitoring patients are estimated to have 70% (95% CI 68-73%), and Elective - Multiple patients are estimated to have 59% (95% CI 51-67%). Emergency - Monitoring patients are estimated to have 45% (95% CI 40-52%) five-year OS, with Emergency - Multiple patients estimated to have 36% (95% CI 26-52%).

These estimates of survival for SACT-eligible patients are similar to those seen for the overall population. This is despite excluding patients with advanced disease and those not receiving treatment with curative intent. Chapter 7, Figure 7.3 demonstrated a marked difference in five-year OS when stratifying by treatment intent (Non-Curative five-year OS 9%, Curative five-year OS 71%). It seems likely that the patients with advanced stages of disease make up a small proportion of this critical care population, even if significant amounts of missing data prevents accurate estimates of this. Looking at either extreme of survival estimate and group size (Elective - Monitoring, and Emergency - Multiple). Among the total population, conditional on hospital survival, five-year OS was estimated at 70% (95% CI 69-71%) for Elective - Monitoring. Among SACT-eligible Elective - Monitoring five-year OS was estimated at 70% (95% CI

68-73%). Among the total population, conditional on hospital survival, five-year OS was estimated at 33% (95% CI 29-37%) for Emergency - Multiple. When looking just at SACT-eligible patients Emergency - Multiple five year OS was estimated at 36% (95% 26-52).

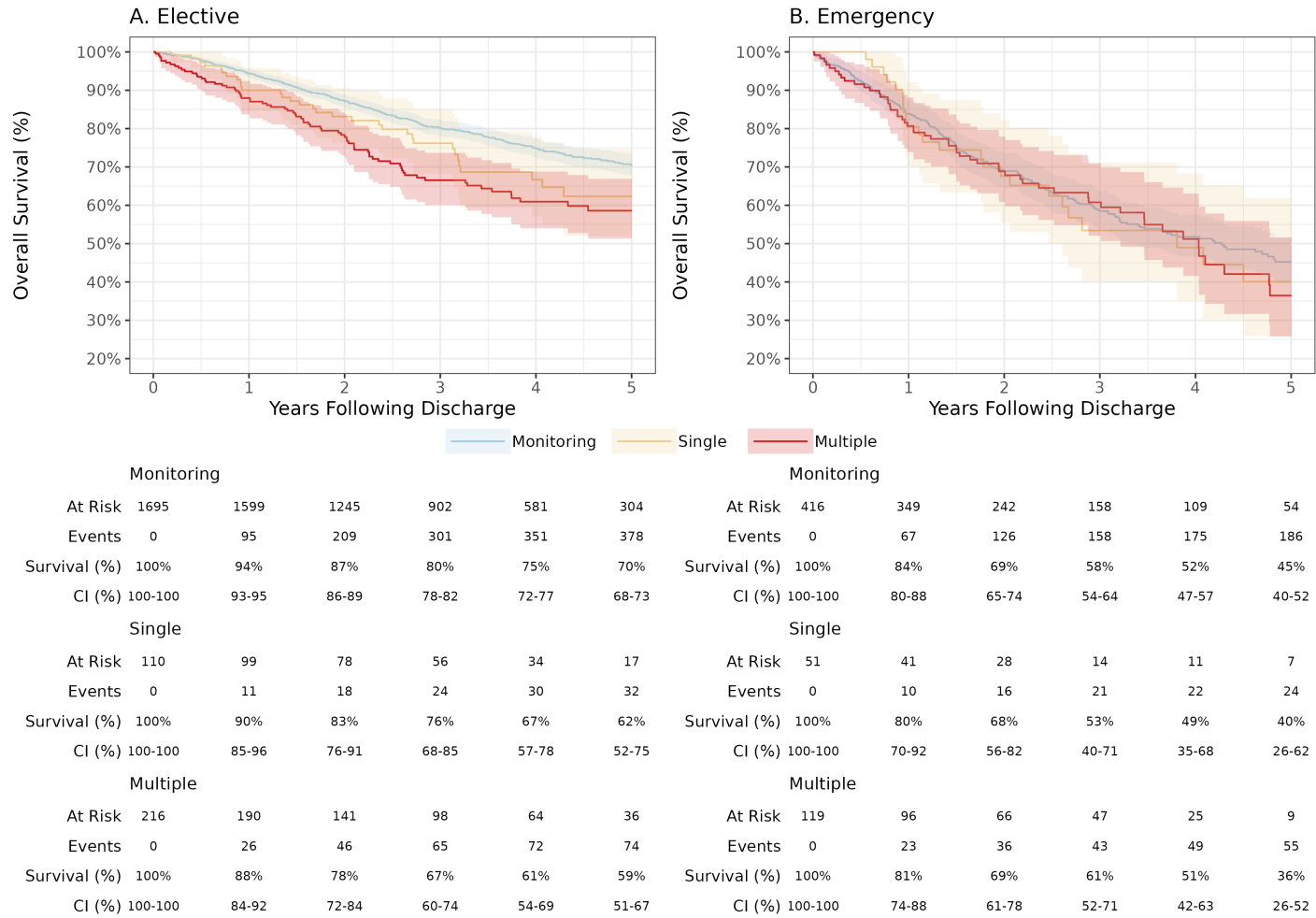


Figure 8.9: Kaplan-Meier long-term survival for the SACT-eligible analytic cohort, stratified by days of organ support. Conditional on surviving the index hospital admission. This provides the unadjusted comparator for the survival model in Section 8.6.

8.4.4 Cumulative Incidence of Adjuvant SACT

Figure 8.10 provides a single cumulative incidence (CI) estimate of adjuvant SACT receipt for the SACT-eligible critical care population. Patients with in-hospital mortality have been excluded, subsequent post-hospital mortality is treated as a competing risk. Time zero in this figure is date of curative surgical resection. Estimates of CI are provided at every four weeks following surgical resection, with 8 weeks (ESMO recommended maximum duration from surgery to SACT), and 12 weeks (Scottish QPI target at time of data collection) highlighted. Amongst the overall population, estimates for probability of SACT CI at 8 weeks was 40% (95% CI 38-42%), and at 12 weeks this rose to 53% (95% 51-55%).

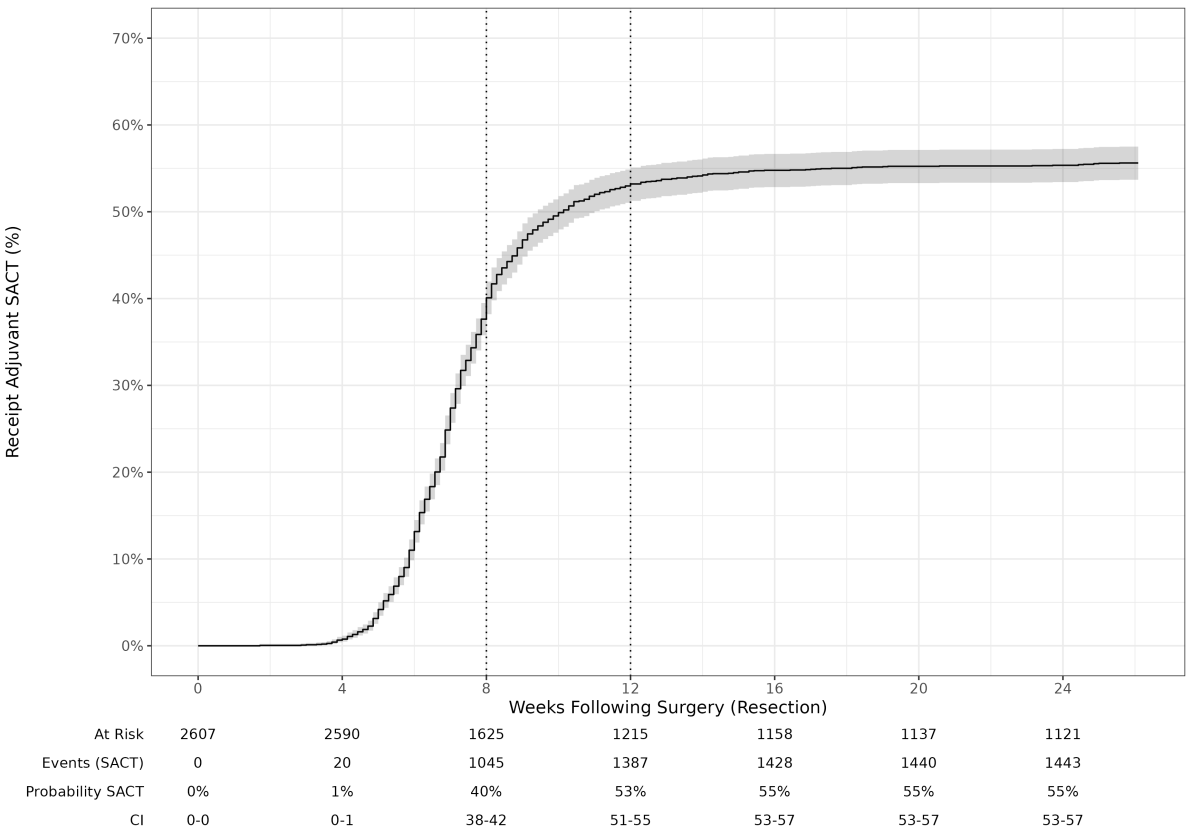


Figure 8.10: Cumulative incidence of receipt of adjuvant SACT among SACT-eligible hospital survivors (single curve; death without SACT treated as a competing event).

Using the same split as seen in KM plots above, Figure 8.11 demonstrated estimates of SACT receipt for the six subcohorts, where the figure is faceted by nature of admission, and each facet is stratified by level of support during critical care admission. 95% confidence intervals are provided in the figure. The largest subcohort, Elective - Monitoring, had estimates of 46% probability of SACT receipt at 8 weeks, rising to 59% at 12 weeks. Among Elective - Multiple, 8 week probability of SACT receipt was 25%, rising to 38% at 12 weeks. For emergency admissions, Emergency - Monitoring had 8 week probability of SACT receipt of 36%, becoming 49% at 12 weeks. For Emergency - Multiple, 8 week probability of SACT receipt was only 14%, rising to the lowest 12 week estimate of SACT receipt at 27%.

Similar to the pattern seen for overall survival, those patients who received less than 2 days of organ support had CI estimates that fell between those who received no organ support, and those who received multiple days. Elective - Single had 12 week probability of SACT estimated at 50%, Emergency - Single had 12 week probability of SACT estimated at 45%. Considering this and the initial estimates provided in Chapter 6, Figure 6.2, where 12 week SACT receipt estimates for patients who received any organ support, was 41% for Elective - Organ Support, and 31% for Emergency - Organ Support, does suggest some dilution of the initial findings by patients who received organ support but were ‘more well’.

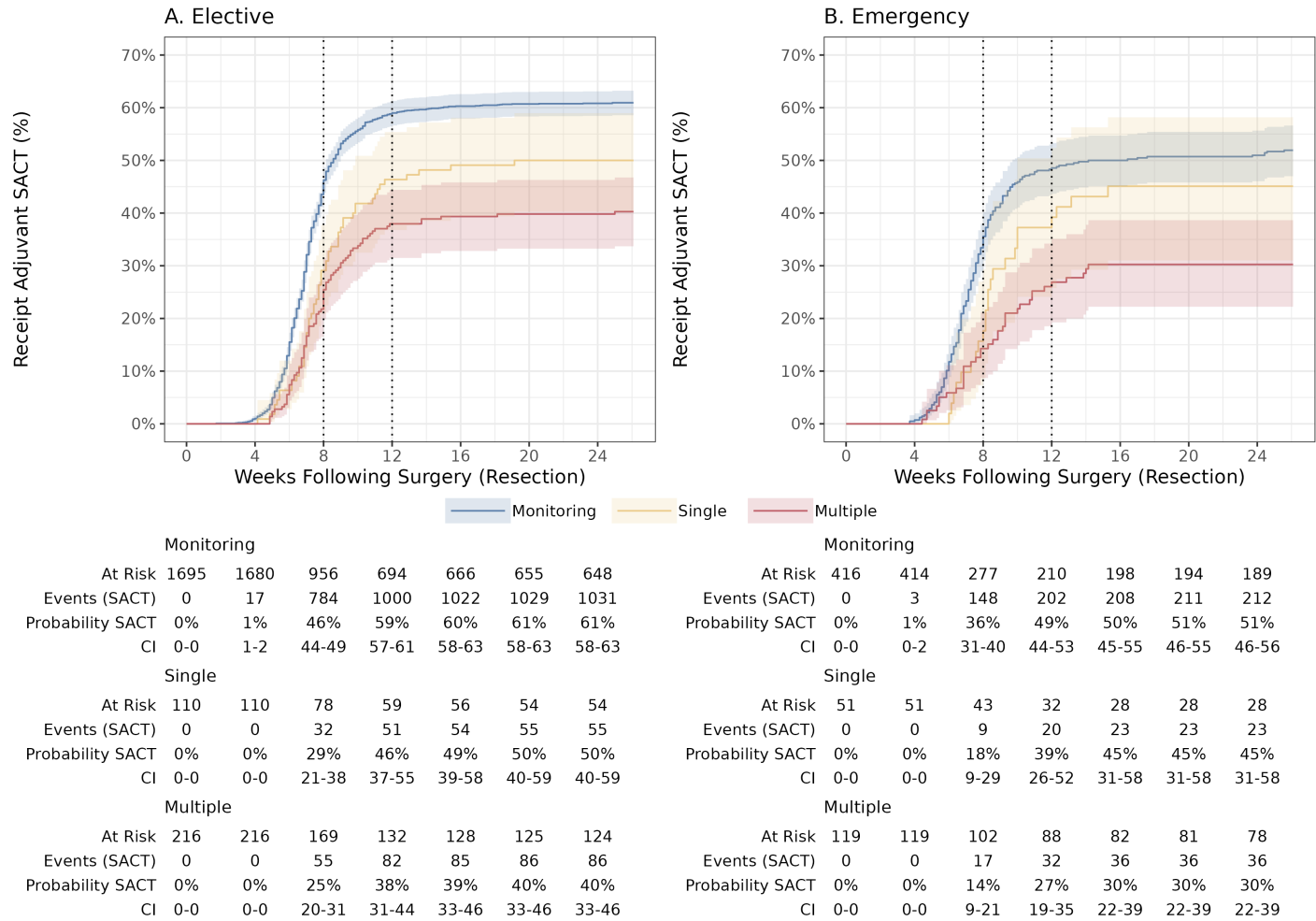


Figure 8.11: Cumulative incidence of receipt of adjuvant SACT, stratified by days of organ support.

8.5 Results: Receipt of Adjuvant SACT

Following adjustment for confounders, estimated total causal effect of critical illness (receipt of multiple days of organ support, conditional on hospital survival), indicated that critical illness decreases hazard of subsequent timely SACT receipt. Elective - Multiple contrasted against Elective - Monitoring, had estimated median HR 0.59 (95% CrI 0.48-0.71). Emergency - Multiple contrasted against Emergency - Monitoring, had estimated median HR 0.43 (95% CrI 0.31-0.59). Each of these estimates were associated with close to 100% posterior probability of being a clinically meaningful difference. These results are provided in Table 8.8 and shown in Figure 8.12.

Accounting for confounders with the multivariable model, median predicted probability of adjuvant SACT receipt at 12 weeks, was 41% (95% CrI 36-47%) for Elective - Multiple, and 56% (95% CrI 54-58%) for Elective - Monitoring. The central estimates for these two subcohorts differ by approximately 14 percentage points at this time point. For emergency admissions, predicted SACT receipt at 12 weeks was 28% (22-34%) for Emergency - Multiple, and 48% (95% CrI 45-52%) for Emergency - Monitoring. The central estimates for these two subcohorts differ by approximately 20 percentage points at this time point. Predicted cumulative incidence of adjuvant SACT following surgical resection is shown in Figure 8.13, with estimates and credible intervals for each of the six subcohorts, at each four-week interval from surgery to twenty-four weeks.

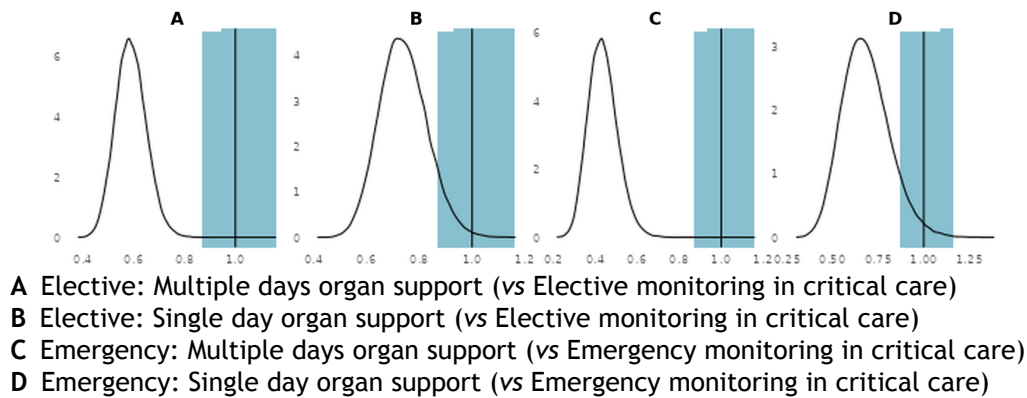
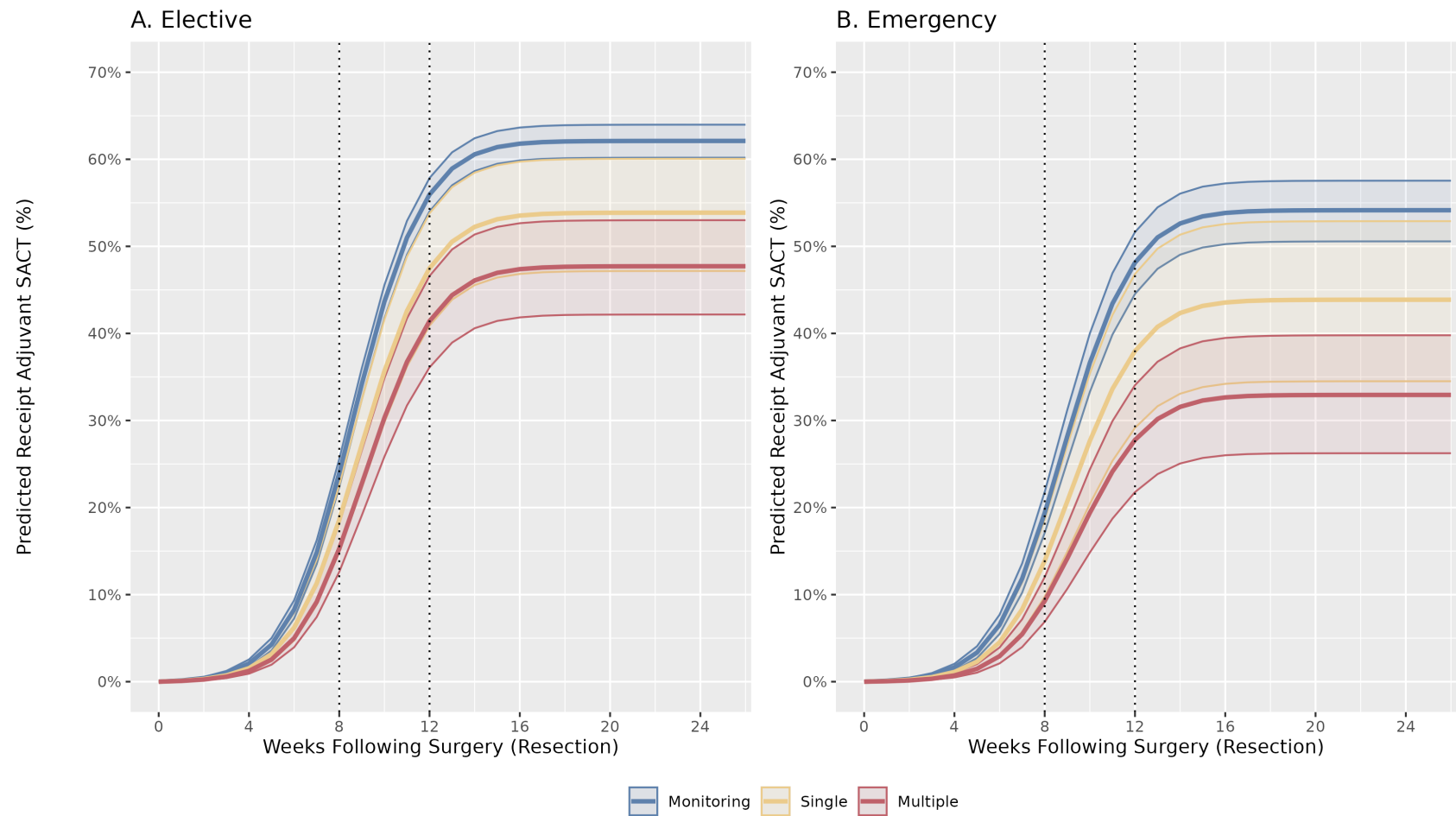


Figure 8.12: Multivariable Analysis Results - Posterior probability distribution of the hazard ratio for receipt of adjuvant SACT, from multivariable time-to-event model using uninformative priors, for the key variables of interest
 Light blue shaded region indicates region of practical equivalence
 Vertical line indicates HR 1 (no effect)
 Facet key provided for variable names and comparators

Table 8.8: Multivariable Analysis Results - Summary of posterior probability distribution of the hazard ratio for receipt of adjuvant SACT, from multivariable time-to-event model using uninformative priors, for the key variables of interest, with comparator provided beneath

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease	Percentage Largest Effect	Of Explained
Elective: Multiple Days vs <i>Elective: Monitoring</i>	0.59	(0.48 - 0.71)	100.00	0.00	0.00	100.00	100% chance	mean- ingful reduction
Elective: Single Day vs <i>Elective: Monitoring</i>	0.74	(0.57 - 0.93)	99.56	7.96	0.00	92.04	92.04% chance	mean- ingful reduction
Emergency: Multiple Days vs <i>Emergency: Monitoring</i>	0.43	(0.31 - 0.59)	100.00	0.00	0.00	100.00	100% chance	mean- ingful reduction
Emergency: Single Day vs <i>Emergency: Monitoring</i>	0.67	(0.46 - 0.96)	98.56	8.12	0.09	91.79	91.79% chance	mean- ingful reduction

CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease



Monitoring	0(0-0)	2(3-2)	24(26-22)	56(58-54)	62(64-60)	62(64-60)	62(64-60)	Monitoring	0(0-0)	2(2-1)	19(22-17)	48(52-45)	54(57-50)	54(58-51)	54(58-51)
Single	0(0-0)	2(2-1)	19(23-15)	47(54-41)	54(60-47)	54(60-47)	54(60-47)	Single	0(0-0)	1(2-1)	14(19-10)	38(47-29)	44(53-34)	44(53-34)	44(53-35)
Multiple	0(0-0)	1(2-1)	15(18-13)	41(47-36)	47(53-42)	48(53-42)	48(53-42)	Multiple	0(0-0)	1(1-0)	9(12-7)	28(34-22)	33(39-26)	33(40-26)	33(40-26)

Figure 8.13: Predicted cumulative incidence of adjuvant SACT receipt stratified by days of organ support, facettted by nature of admission.

8.5.1 Sensitivity Analysis, Validity, Posterior Predictive Checks

As sensitivity analyses, models were repeated using pessimistic, optimistic, and sceptical priors. No model prior choice meaningfully changed central estimates for the effect of critical illness. Results of these analyses are provided in Appendix E.2 in Figure E.21 and Table E.21.

Measures of chain convergence and estimated sample size are provided in Table E.22. All chains converged well with $\hat{R}$ close to 1 and ESS > 20,000. Similarly posterior predictive check demonstrated good fit between observed data and that drawn from the posterior distribution.

8.6 Results: Five-Year Survival

Following adjustment for confounders, estimated five-year overall mortality among hospital survivors, is increased among those who experienced critical illness during their index admission. This estimate persists despite the population comprising solely of those who survived hospital admission. Elective - Multiple, contrasted against Elective - Monitoring, had estimated median HR of 1.43 (95% CrI 1.14-1.79). For patients admitted emergently, the impact of emergency admission appears greater than any effect of level of support during admission. The statistical model that resulted from the proposed DAG, allows for comment on the causal impact of nature of admission, as well as critical illness. Estimated direct effect of emergency admission (excluding the pathway between nature of admission and critical illness) is associated with HR of overall mortality of 2.21 (95% CrI 1.87-2.61), with close to 100% posterior probability of meaningful increased hazard. Emergency - Multiple, contrasted against Emergency - Monitoring, has estimated median HR of 1.07 (95% CrI 0.81-1.4). However, whilst

the posterior probability of any hazard from critical illness is estimated at 68%, the majority of this (65%) is considered to be in the region of practical equivalence. These posterior probability estimates of HR are provided in Table 8.9 and shown in Figure 8.14.

Median predicted overall survival, with credible intervals, is provided for each of the subcohorts in Figure 8.15. Median predicted probability of five-year overall survival, was 68% (95% CrI 66-71%) for Elective - Monitoring, and 59% (95% CrI 52-65%) for Elective - Multiple. For patients admitted electively who had undergone curative resection of CRC (High Risk II and Stage III) at reference covariate values, the central estimates for these two subcohorts differ by approximately 9 percentage points at five years. For patients admitted as an emergency, predicted overall survival is lower than all elective subcohorts, although the central estimates for Emergency - Monitoring and Emergency - Multiple differ by less than the 3 percentage point absolute-scale threshold for a clinically meaningful effect adopted in this chapter. Median predicted probability of five-year overall survival, was 44% (95% CrI 39-49%) for Emergency - Monitoring, and 42% (95% CrI 34-50%) for Emergency - Multiple. For patients admitted emergently who had undergone curative resection of CRC (High Risk II and Stage III) at reference covariate values, the central estimates for these two subcohorts differ by approximately 2 percentage points at five years.

With the caveat that it excludes the causal pathway where those admitted as an emergency are more likely to experience critical illness, and so underestimates the total causal effect; the central estimates for Elective - Monitoring and Emergency - Monitoring at five years, for patients who underwent curative resection of CRC (High Risk II and Stage III) during admission at reference covariate values, differ by approximately 24 percentage points.

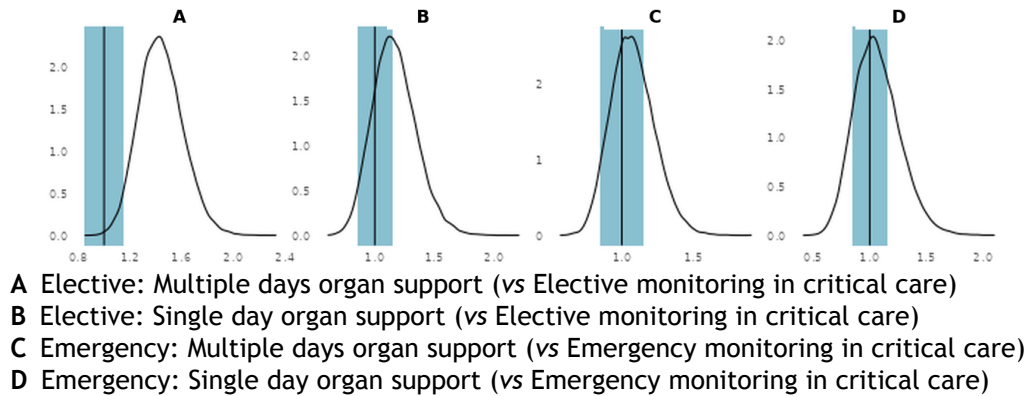


Figure 8.14: Multivariable Analysis Results - Posterior probability distribution of the hazard ratio for five-year overall survival, from multivariable survival model using uninformative priors, for the key variables of interest

Light blue shaded region indicates region of practical equivalence

Vertical line indicates HR 1 (no effect)

Facet key provided for variable names and comparators

Table 8.9: Multivariable Analysis Results - Summary of posterior probability distribution of the hazard ratio for five-year overall survival, from multivariable survival model using uninformative priors, for the key variables of interest, with comparator provided beneath

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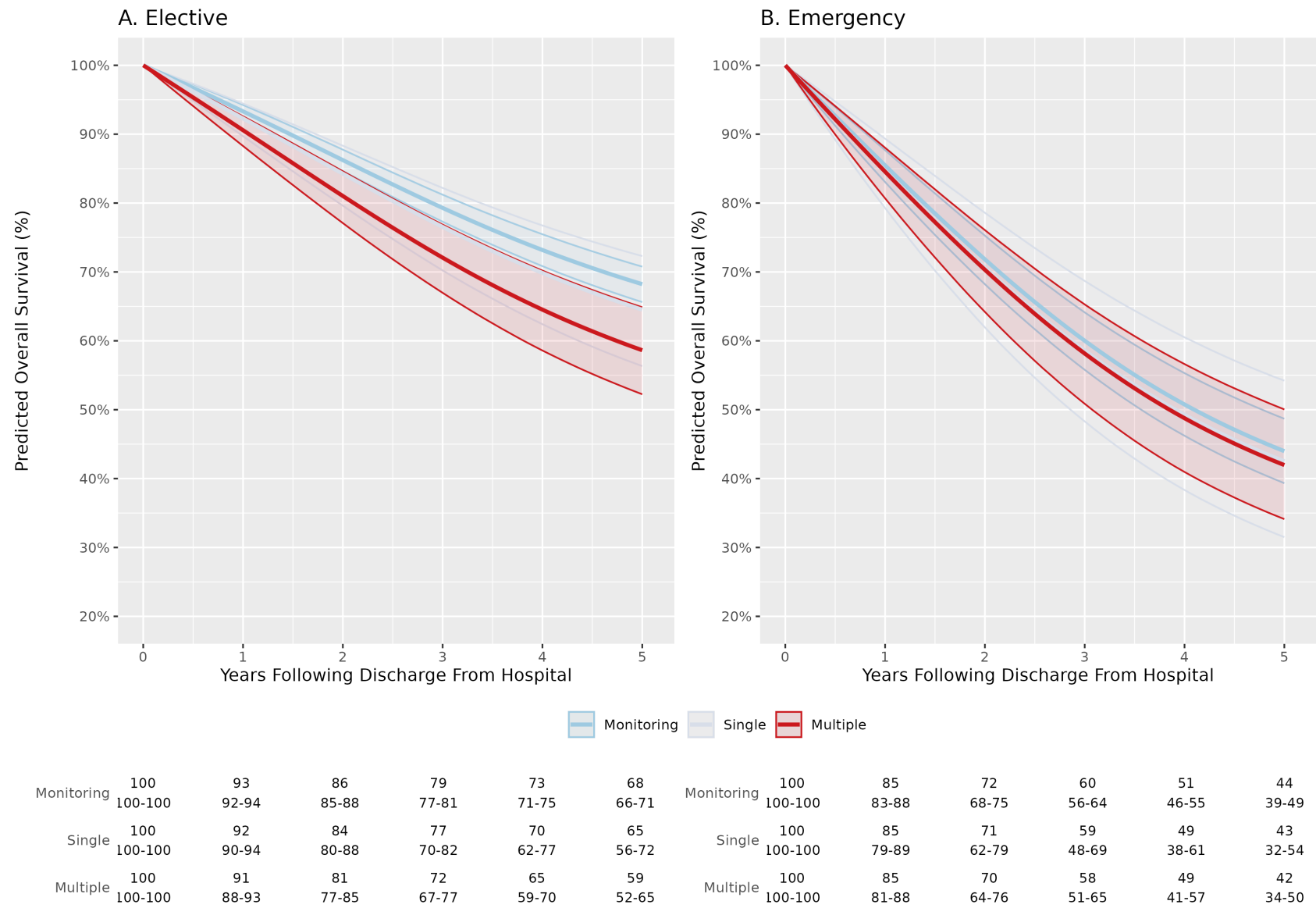


Figure 8.15: Predicted overall survival, stratified by days of organ support, facettted by nature of admission

8.6.1 Sensitivity Analysis

Models were repeated using pessimistic, optimistic, and sceptical priors. No model prior choice meaningfully changed central estimates for the effect of critical illness, or nature of admission. Results of these analyses are provided in Appendix E.4 in Figure E.23 and Table E.24.

Measures of chain convergence and estimated sample size are provided in Table E.25. All chains converged well with $\hat{R}$ close to 1 and ESS > 20,000. Similarly posterior predictive check demonstrated good fit between observed data and that drawn from the posterior distribution.

8.7 Discussion

8.7.1 Principal Findings and Comparison with Literature

This chapter identified 22,399 patients admitted to critical care during their index admission following CRC diagnosis, 51% of the total population (43,773) diagnosed with CRC over the time period. 2,729 patients experienced critical illness, defined as multiple days of organ support, accounting for 12% of all patients admitted to critical care and 6% of all patients diagnosed with CRC. Where previous work by Puxty et al. 2015 noted that CRC accounts for a high proportion of solid cancer admissions to ICU (44%), this work clarifies that only a small proportion of these patients are likely to

be critically ill. Chapter 4 noted that the majority of patients following CRC surgery are admitted to critical care, the finding of this chapter that 12% of critical care admissions received multiple days of organ support is similar to the 10% noted by Dale et al. 2016.

Hospital mortality for all patients with critical illness was 22% among all patients with critical illness (16% among Elective, 35% among Emergency). Hospital mortality for CRC patients with critical illness is seen to be notably lower than the 38% hospital mortality seen among all solid-cancer ICU admissions seen by Puxty et al. 2014, and closer to the 16.6% for all ICU admissions reported by ICNARC (ICNARC 2024).

The proportion of patients with advanced disease is likely to differ dependent on the health care system studied, Camus et al. 2014 noted 70% of their ICU CRC admissions had metastatic disease. In this chapter approximately 12% of patients admitted to critical care had Stage IV disease recorded, close to the 9% observed previously by Puxty et al. 2015. However as noted, information on stage of disease in this study is significantly limited due to missing data. Stratification by stage of disease and intervention received, as this chapter does when investigating patients with High Risk Stage II and Stage III CRC, who receive curative surgical resection, successfully allows for a more homogenous population for study.

In this population of patients with CRC admitted to critical care, considered adjuvant SACT-eligible, key differences are observed during hospital admission, and in both short and long-term patient outcomes. Patients admitted as an emergency appear on a different disease and treatment trajectory at the point of admission to critical care. The most common reason for emergency admission is following GI perforation or obstruction, in contrast to those admitted electively following surgery for their CRC.

Differences in hospital mortality are noted as above, and once conditioning for only those who survive hospital admission, emergency patients had a smaller proportion who receive adjuvant SACT, and survive at each year of follow up, when contrasted against those admitted electively.

This chapter aimed to investigate two key questions of interest:

1. What is the causal effect of critical illness on subsequent receipt of adjuvant systemic adjuvant anti-cancer therapy (SACT), in patients with High Risk Stage II and Stage III disease who have undergone surgical resection, conditional on hospital survival.
2. What is the causal effect of critical illness on long term overall survival, in the same cohort of patients as the above estimand, again conditional on hospital survival.

To address question one, among the total cohort of patients admitted to critical care, eligible for SACT, there was a 53% probability of receiving adjuvant SACT in the 12 weeks following surgical resection. For elective patients with critical illness, estimated HR of SACT receipt was reduced to 0.59 (95% CrI 0.48-0.71). This resulted in a predicted probability of 41% of adjuvant SACT receipt for elective patients with critical illness. For emergency patients with critical illness, estimated HR of SACT receipt was reduced to 0.43 (95% CrI 0.31-0.59). This resulted in a predicted probability of 28% of adjuvant SACT receipt for emergency patients with critical illness.

When we consider the median length of stay in hospital was greater for patients with critical illness, it appears likely that length of stay is a meaningful mediator on this causal path. However noting the observed cumulative incidence of SACT prior to any modelling, SACT receipt is not only delayed, but also occurs less overall among the critical illness subcohorts.

In contrast to the limited wider literature on SACT receipt following critical illness, Kim et al. 2015 noted an association between ICU admission and adjuvant SACT *omission* (HR 2.4), but did not stratify further by severity of illness, and did not identify an association with timing of SACT receipt. This work involves a cohort approximately three times greater in size (2,607 unique patients in contrast to 750), with some key differences in population and outcomes, Kim observed a ratio of patients with Stage II to Stage III disease of 0.73:1, this chapter's cohort has a ratio of 2.05:1. Additionally Kim et al. 2015 investigated SACT receipt for all patients with resection, including those treated outwith intensive care. Last they studied a different health care system (Korea), with likely different patterns of care and SACT receipt than Scotland. Considering the stronger recommendation for adjuvant SACT in Stage III disease, the relationship between critical care admission and reduced SACT, and the different health care settings, these may have contributed to the differences in proportions of overall SACT receipt observed (40% at 8 weeks in this chapter, compared to their 75% at 8 weeks).

Kim's methods were closer to what was performed in earlier chapters in this thesis (univariable screening, followed by multivariable regression). Their multivariable model also did not include nature of admission (likely resulting in emergency admissions being more represented in the intensive care group), potentially increasing any estimated effect of ICU admission. With those methodological differences noted, their observed association of ICU admission with SACT omission was OR 2.4 (95% CI 1.6-3.7), so an inverted description would be an association with SACT receipt of OR 0.42 (95% CI 0.27-0.63). I estimated relationship of critical illness with timely SACT receipt as HR 0.59 (95% CrI 0.48-0.71) for elective patients, and HR 0.43 (95% CrI 0.31-0.59) for emergency patients, both estimates with a posterior probability of close to 100% of a clinically meaningful effect. These results are consistent with one another, and differences can be likely explained by the factors noted above.

The estimates provided by this chapter have the advantages of: being causal estimates of relationship of critical illness, with a greater clarity of accounting for severity of illness, demonstrating an effect on both receipt and timing of SACT, and greater relevance to an NHS Critical Care environment, being based on population data from a Scottish cohort admitted to critical care with a larger sample than previous work.

In this chapter I suggest that reduced timely receipt of SACT could be due to multiple pathways, that include greater length of hospital stay, and greater post-operative complications. However without a greater level of mediation analysis, it is not possible to investigate further relative contribution of any such pathways. Merkow et al. 2013 noted in an North American cohort of patients with Stage III CRC, that of those who did not receive adjuvant SACT, there was a greater proportion of patients who experienced what they described as ‘post operative complications’, including: prolonged ventilation (definition of prolonged not provided in their paper), renal failure, pneumonia, and reintubation, as well as anastomotic leak, and abscess. The level of detail available through SICSAG, and SMRO1 would allow for further investigation of most of these pathways, and the associations/potential pathways suggested by Merkow et al. 2013 could be investigated in future work in this Scottish cohort.

In regards to the clinical relevance of the findings of reduced timely SACT receipt, as noted before, ESMO guidance suggest that adjuvant SACT receipt improves long-term overall survival for patients with CRC, with a 3-4% reduction in mortality for patients with High Risk Stage II disease, and a 15-20% reduction in mortality for patients with Stage III disease (assuming receipt of two agents) (Argilés et al. 2020). Time of SACT receipt is also important, with well established relationships between delayed SACT receipt and reduced overall survival (Knapen et al. 2020; Des Guetz et al. 2010; Hanna et al. 2020). The work in this chapter demonstrates that critical illness is associated with both reduced and delayed receipt of adjuvant SACT, with those experiencing critical illness having a 14-20 (depending on nature of admission) percentage point absolute reduction in SACT receipt at 12 weeks post resection (the historic Scottish

target of timely receipt). Whilst 12 weeks is a historic target, now accepted to be too lax, and current Scottish targets follow ESMO recommendations of 8 weeks, a similar reduction in timely SACT receipt is also observed in this cohort at the 8 week time point (Healthcare Improvement Scotland 2025; Argilés et al. 2020). This reduction is a potential partial explanation for the reduction in overall survival among survivors of critical illness observed below.

To address question two, using the same cohort as above, where differences in Stage, Comorbidity, (and whilst unmeasured, other factors such as Frailty are likely partially) accounted for. Unadjusted Kaplan-Meier estimates of five-year overall survival among the total cohort was 70%. For elective patients with critical illness, estimated HR of mortality was increased to 1.43 (95% CrI 1.14-1.79). This resulted in a predicted probability of 59% of five-year survival for elective patients with critical illness. For emergency admissions (regardless of critical illness), estimated HR of mortality was 2.21 (95% CrI 1.87-2.61), resulting in predicted five year survival, for patients admitted as an emergency without critical illness, of 44%. There was not a meaningful decrease further in survival, when investigating patients with both emergency admission and critical illness. Estimated HR of mortality for these patients, contrasted against emergency without critical illness was 1.07 (95% CrI 0.81-1.4), with a posterior probability of 65% of no clinically meaningful difference, and a predicted five-year survival of 42%.

As noted, the potential pathways that could explain the observed causal effect may include: reduction in timely SACT receipt as observed above, reduction in overall health quality and physical function (as would be seen with PICS, or post hospital frailty). The no meaningful difference seen contrasting Emergency - Monitoring against Emergency - Multiple, may be due to there truly being no additional burden of critical illness to those who have already experienced emergency hospital admission (as emergency admission is associated with an HR > 2), or residual confounding

that this analysis was unable to account for, or related to the fact that Emergency - Multiple was the smallest subcohort ($n = 119$), with 23% of the subcohort lost to censoring at three years, and 46% lost by five years, resulting in wide credible intervals (95% CrI 0.81-1.4).

8.7.2 Strengths

The work of this chapter builds on the estimates provided by the preceding chapters in this thesis. Results of previous chapters were partially limited in two ways. First they considered all receipt of organ support as ‘critical illness’, likely including more well patients and diluting any association between critical illness and patient outcomes. This chapter supports that assumption of dilution. In both measures of SACT receipt and survival, observed values and estimates for patients who received less than two days of organ support sit between the values of ‘Monitoring’ and ‘Multiple’. These patients who received some, but not extensive amounts of organ support, do appear more sick than those who received no support, but less sick than those who received multiple days. The second related limitation was the design of each statistical model. Whilst undertaken using well established techniques, the methods of univariable screening again risked providing underestimates of any association between critical illness and patient outcomes. In this chapter, addressing both limitations, associations which were previously obscured are now identified.

Where Chapter 6 investigated SACT receipt, and delay to commencing SACT into two separate binomial models, this chapter uses the more appropriate choice of cumulative incidence modelling, building on the experience gained during Chapter 7. The predicted curve of CI provides information both on delays in commencing SACT, and also on SACT omission, within the single model. Chapter 6 could state a 66.5% probability of association between Elective - Organ Support and reduced SACT receipt,

and an 84% probability for Emergency - Organ Support. Following the above improvements in cohort definition, causal inference, and model selection, this chapter can state a close to 100% probability of decreased hazard of timely SACT receipt, for both Elective and Emergency patients who experience critical illness.

Similarly where Chapter 7 investigated long term survival, the same dilution effect when defining critical illness was present. Within this chapter, cohort definitions are more strong. From a causal inference perspective, the second set of modelling in Chapter 7, which aimed to account for differences in baseline characteristics, inadvertently adjusted for a 'post-treatment' variable (including only those who had received adjuvant SACT). In doing so that model blocked any causal path between critical illness and survival that was mediated by differences in SACT receipt. With the stronger cohort definition, and reframing of the model question using a causal framework, this chapter is able to positively identify the increased long term hazard of mortality for elective patients who experienced critical illness (HR 1.43 95% CrI 1.14-1.79), with a posterior probability of a meaningful increased hazard of 97%, that Chapter 7 did not identify. It may be tempting to point at the difference in results between this chapter, and the results of the SACT-received cohort in Chapter 7, treat that as a mediation analysis, and pin the causal pathway of reduced survival on SACT-receipt. However there are multiple other differences in variable and cohort selection between these two models, that prevent a clean interpretation in that manner.

8.7.3 Limitations

The work of this chapter builds on the prior chapters, and gains methodological rigour with its clarity of estimand and causal framework. In prioritising the total causal effect however (or rather, the total causal effect conditional on hospital survival), more precise assessment of the impact of each causal pathway is lacking. In the paragraphs

above I mention that causal pathways between critical illness and long term survival could include the mediator of subsequent SACT receipt. Similarly for timely SACT receipt itself duration of hospital stay could likely act as a mediator. Formal mediation analysis could provide quantification of the estimate of each mediators direct effect on the outcome of interest. Due to time and data availability constraints, this chapter was not able to undertake these analyses and provide such estimates. As a result this chapter can only comment on the observed impact due to critical illness, and not on which mechanisms this impact emerges from. Any future work that aimed to derive interventions to improve SACT receipt or long-term survival, would first need to clarify these mechanisms further. This chapter is only able to say critical illness has an impact on SACT receipt and long-term survival, it cannot say ‘why’ critical illness has that impact, or how to fix it.

Future work using this dataset could investigate some but not all mediators, multiple operations, re-intubation, or later reintroduction of organ support as proxies for post-operative complications. A cohort collected of patients from 2020 onwards would provide SICSAG records of clinical frailty, and records already in this dataset such as later hospital diagnoses, and prescribing information could allow for crude approximates of post-hospital frailty and performance status.

This chapter uses an imprecise definition of critical illness, which could arguably be improved upon using more formalised metrics of disease severity such as APACHE II. As noted, APACHE II information is not recorded for all patients admitted to critical care, and is not missing at random, with a high proportion of stand-alone high dependency units not recording severity of illness scoring (SICSAG 2014). As a result, a more precise definition of critical illness, or comparison of APACHE II scores between subcohorts was not possible for this chapter. Within this chapter critical illness was defined as those who received multiple days of organ support, to exclude those patients admitted to critical care still recovering from the surgical intervention they had undergone, who received less than 24 hours of organ support. Whilst this defini-

tion does exclude those more ‘well’ patients, it will also exclude those who were so critically unwell that they died in the first 24 hours of their admission to critical care, and risk inflating any estimated impact for the ‘Single’ day cohort of organ support (in regards to hospital mortality and long term outcomes) I aim to partially account for this, by limiting most analyses to those who survived admission, and restricting any comparisons to between the ‘Monitoring’ and ‘Multiple’ days of organ support groups.

Linking the definition of ‘critical illness’ to the place that care was provided (high dependency and intensive care) is standard practice among the literature published so far on cancer and critical illness. This chapter has aimed to build on such a definition. Another noteworthy limitation is the unstated assumption in this thesis that access to critical care, and decision-making about admission to critical care, is uniform across Scotland. Many working in intensive care (myself included) would argue that decision-making about admission to critical care is not uniform within a single intensive care unit, let alone across a nation. Further work that investigates admission practices across multiple units, could use hierarchical modelling to take such differences into account.

The choice to restrict analyses to those who survived admission has its own limitations, as described above in Section 8.2.5. As noted in that section, I attempt to partially account for the selection bias that arises due to the unmeasured confounder of frailty, through restriction to a population that is similar in disease stage, and decision to undergo surgical intervention. Of note, estimates of impact of critical illness on long term survival in this chapter are the estimates conditional on hospital survival. Subtracting the impact of critical illness on hospital mortality may provide more meaningful information on hospital survivors, but it does also bias any estimates of causal effect towards the null.

As noted in the limitations of Chapter 7, Section 7.5.1 the analyses of long-term survival in this chapter were limited by relatively small groups and large amounts of censoring. In that chapter, I was unable to identify any relationship between critical illness and long term survival for a homogenous group of hospital survivors. Reducing time to follow-up, to three years would have reduced the proportion lost to follow-up, but not changed any estimates on survival, considering the models chosen still included the information provided at three-years. In this chapter, with better framing of the causal question of interest, and greater care to not block causal pathways, I am able to demonstrate the probable residual causal impact after surviving critical illness on reduced long term survival. Due to the previously mentioned constraints on data availability I was unable to explore whether differences were seen for the question of disease-free survival. Considering the recommendation from ESMO to use overall survival as the most patient-centred outcome, I felt that the observed relationship seen for elective patients and overall survival was the most meaningful outcome point I was able to provide.

When describing the overall effect of critical illness both on SACT receipt and overall survival, hazard ratios provided include measures of uncertainty with credible intervals taken from the posterior distribution. In this chapter I provide point descriptions of the percentage differences in predicted survival and SACT receipt. These measures do not include full sampling from posterior distribution to provide a similar range of likely impact, and as such do not take full advantage of the nature of the Bayesian modelling undertaken. As such these point estimates should be considered illustrative, where the HR with credible intervals should be considered the more precise results.

8.8 Conclusion

In this chapter I have observed reductions in SACT receipt and long term survival (both including and excluding hospital mortality), for patients considered eligible for adjuvant SACT following curative resection of CRC with critical illness. These observed differences persist after accounting both for differences in hospital survival, and for other likely confounders. This chapter provides evidence for likely causal effects, although does not provide mediation analysis describing the likely impact of each causal pathway. Such analyses would be a natural progression for future work.

For the intensivist, oncologist, surgeon and patient: critical illness is relatively common for patients with CRC, although maybe less so than less precise initial estimates. 10% of elective admissions to critical care experience multiple days of organ support, as do 19% of emergency admissions to critical care. In hospital mortality is high for these patients with CRC and critical illness, ranging from 16-35% depending on nature of admission. These values are comparable to non-cancer patient populations with critical illness, and lower than seen among other cohorts of patients with critical illness and other solid organ cancers.

When including in-hospital mortality, unadjusted estimates of five-year survival are markedly lower than the population average for CRC of ~60%, ranging from 22-51% for those who experienced critical illness,

When conditioning on hospital survival, an observed difference remains. The largest 'well' subcohort (Elective - Monitoring) had five year survival of 70%, the estimates for survival among critical illness survivors ranged from 33-59%. When investigating the persisting causal impact of critical illness on long term survival (among hospital survivors), on patients with potentially curative disease (High Risk Stage II and Stage

III CRC who had undergone curative resection), we can estimate a highly probable (97%) clinically meaningful causal impact of critical illness on mortality for elective patients, with median HR 1.43, and a reduction in predicted absolute five-year overall survival of 9%. Emergency admissions' estimated direct effect on mortality, is an HR of 2.2. This likely overwhelms any additional impact of critical illness for patients admitted emergently, as this work fails to demonstrate any clinically meaningful difference comparing emergency patients with critical illness and emergency patients without.

One potential causal pathway that would result in this reduction in overall survival, is the causal relationship seen between surviving critical illness and reduced timely SACT receipt. Surviving critical illness is estimated to have a causal impact on timely SACT receipt, with an HR of 0.59 for elective patients for critical illness, and an HR of 0.43 for emergency patients with critical illness. These estimates of hazard result in meaningful differences in timely SACT receipt. Where observed adjuvant SACT receipt at 12 weeks post resection was 53% for all eligible patients, predicted SACT receipt for elective critical illness survivors was 41%, and for emergency critical illness survivors was 28%.

Patients with CRC and critical illness are common, they have increased in-hospital mortality, and increased risk of mortality that persists in the long-term despite surviving critical illness. They are less likely to experience timely adjuvant SACT receipt that has previously been demonstrated to provide long term survival benefit. It is possible that this difference, and multiple other causal pathways explain this meaningful difference in this patient-centred outcome of long term mortality.

Causal methods in this chapter have resulted in a revised, increased estimate of hazard of mortality for survivors of critical illness with CRC. These methods have resulted in the first provided causal estimates for the impact of critical illness on subsequent CRC care and long-term outcomes. They have also set the foundation for future work, of mediator analysis, describing causal pathways at a level of detail that would allow for future focused interventions.

Chapter 9

Reflection and Conclusion

9.1 Introduction

Throughout this thesis, each chapter has had its own discussion and conclusion. Key results and reflections will be revisited in this final chapter, rather than an exhaustive list of all results.

In this chapter I also aim to reflect on choices made throughout this thesis. Through the experience I have gained over the last four years, there are numerous decisions made that I would approach differently if starting again. I describe where the findings of this work adds to the current literature. In noting where this work contributes, I also highlight the clear next steps that could follow this work, with the aim of improving care for both patients with colorectal cancer, and critical illness survivors more generally.

9.2 Summary of findings

In this thesis I examined records kept of all patients with colorectal cancer (CRC) in Scotland diagnosed between 2006 and 2018, linking these patients to their first admission to hospital following diagnosis, stratifying them both by the nature of their admission, and the level of support that they received during their hospital stay.

With this population and its subcohorts, I described patients' characteristics, and investigated their outcomes in subsequent cancer care quality, cancer care receipt and intensity, and long term overall survival. In Chapter 8, I focused investigation onto just patients admitted to critical care, and used a more strict definition of 'critical illness' to explore further its causal impact on patient outcomes.

Of the solid organ cancers, CRC is a common cause of hospital and critical care admissions. In this thesis I identified a cohort of ~46,000 patients diagnosed in Scotland with CRC over a 12-year period. Unfortunately the majority of patients were diagnosed following clinical presentation (83%), rather than asymptomatic screening (13%). From the method of diagnosis onwards, differences in patients' cancer journeys emerge. The majority of patients diagnosed through screening are treated in hospital electively (97%), where operative intervention, and treatment in critical care for monitoring alone are the most common treatment routes for patients. 53% of patients admitted electively were admitted to critical care for monitoring ($n = 14,756$), with hospital mortality rate of 1.6% ($n = 232$). In contrast the average hospital mortality rate for all patients with CRC, defined as including hospital admission and the subsequent 30 days, was 12% ($n = 5,388$).

It is this subcohort of patients admitted electively, treated in critical care with monitoring alone, who were most consistently observed to experience the greatest cancer care quality, and most favourable long term patient-centred outcomes.

Patients were more frequently treated in critical care with monitoring alone than with organ support. Patients receiving organ support accounted for 9% of hospital admissions, and 18% of all critical care admissions. For elective patients, the ratio of those receiving monitoring alone to receiving organ support was 5.5:1 (2,687 elective patients received organ support). For patients admitted emergently, the ratio was 2.6:1 (1,367 patients received organ support).

Hospital mortality was greatest for those who received organ support, 13% for elective patients with organ support, and 32% for emergency patients with organ support.

For most of this thesis, investigation into long-term outcomes focuses on hospital survivors. Differences in screening rates were not the only differences in characteristics between subcohorts, patients admitted emergently were older, more comorbid, and more socioeconomically deprived. Looking at those who received organ support in critical care, patients were more comorbid, and underwent greater number of operations during hospital admission. Hospital length of stay was longer for those who were admitted emergently, and for those who received organ support.

Noting differences between subcohorts, it becomes apparent that multiple factors are likely relevant in a patient being treated outside of critical care. It is not simply the case that ward level subcohorts are comprised of patients 'too well' for critical care. Decisions about (in)appropriateness of treatment escalation are likely also being made. Patients treated at a ward level, particularly during emergency admissions, are older, more comorbid, less frequently treated by surgeons or receive resection, and appear likely to have greater proportion of Stage IV disease (although the large

proportion of missing data for disease stage has been recognised as a limitation of this thesis). Ward cohorts, particularly during emergency admissions, likely reflects the mix of those truly 'too well' for critical care, but also those considered 'too sick'. As such patients treated in critical care with monitoring alone were considered the baseline comparator in subsequent analyses.

This thesis is the first to use national cancer care quality performance indicators, to assess care quality for survivors of both cancer and critical illness. I observed that whilst Elective - Monitoring patients attained >75% of CRC QPI targets, elective patients who experienced organ support attained only 33%, and emergency patients with organ support attained even fewer, with 21%. Investigating timely adjuvant chemotherapy (SACT) post curative resection (QPI 11), after adjustment in multivariable analysis, I observed an association between organ support receipt and decreased attainment of QPI 11, with an OR of 0.56 of attaining QPI 11 for elective patients with organ support, and OR of 0.42 for emergency patients with organ support. Both of these estimates could be stated to have a posterior probability of close to 100% of reaching a clinically meaningful difference. However these values should also be considered non-causal associations.

Whilst QPI 11 assesses timely adjuvant SACT receipt for patients who had undergone curative resection of High Risk Stage II and Stage III disease, as a metric it has its own limitations. The version of QPI 11 that was in place when this cohort of patients were being treated, was a target of SACT receipt within 12 weeks of surgical resection. This was not in keeping with the now internationally accepted target of 8 weeks. Second QPI 11 excludes those patients aged greater than 74. In this thesis, among patients admitted to critical care following curative surgical resection for CRC, the median age was 71 (IQR 62-79). As a result in subsequent analysis I investigated SACT receipt, SACT delay, and other measures of SACT intensity for all eligible adult patients.

Patients who survived organ support in critical care had substantially lower proportions of eventual adjuvant SACT receipt following surgical resection. Among the total cohort of eligible patients, 57% received adjuvant SACT. Among elective patients who experienced organ support, 43% (n=141) received adjuvant SACT. This dropped further for emergency patients with organ support, where 35% (n=59) received adjuvant SACT. Plotting the cumulative incidence of SACT receipt, the reduced proportion in SACT receipt for those who received organ support, was observed both at 8 and 12 week timepoints. Whilst multivariable analyses were undertaken in this chapter for SACT receipt and SACT delay, such analyses were repeated with greater methodological justification in the final chapter, and I will present those results towards the end of this summary.

As well as SACT receipt and delays commencing SACT, I aimed to investigate several other proxy measures for SACT intensity. There were no observed unadjusted differences between subcohorts for these measures (proportions of patients receiving single agent versus dual agent therapy, experiencing dose delay during SACT course, or total course length) and there was evidence for no difference. In multivariable models, for patients admitted electively who experienced organ support, there was an estimated 75% probability of decreased SACT intensity in one measure (an increased likelihood of single agent therapy rather than dual agent). This result should be considered very cautiously, both due to the level of certainty in the estimate, and the limitations of the analyses.

This thesis chose to investigate both reductions in SACT receipt, and delays starting SACT, as these measures have previously been demonstrated to be associated with differences in long term survival. The key question of this thesis is whether critical illness has persisting impact on long term cancer outcomes after surviving hospital admission. As Chapters 5 and 6 demonstrated reduced likelihood of receiving planned SACT amongst survivors of critical illness, Chapter 7 aimed to investigate differences in long term survival.

Among the total cohort of hospital survivors with CRC, of all disease stages, I observed five-year (overall) survival in keeping with published Scottish estimates. Five year survival for the total cohort of hospital survivors was 52%. Patients admitted electively and admitted to critical care for monitoring alone, remained the group with best long term outcomes, with unadjusted five-year survival estimates of 70%. Those who experienced organ support in hospital had lower five-year survival, with elective patients having 61%, and emergency patients only 34%.

I first investigated patients of all disease stages, and subsequently a more homogenous cohort of patients who had received ‘curative resection and adjuvant SACT’. Within these I estimated a persisting hazard of critical illness on long term survival for the cohort of all disease stages. I did not observe any association between critical illness and long term survival among the more homogenous cohort. However, similar to the models of SACT receipt and SACT delay, several methodological limitations resulted in me undertaking further improved survival analysis in the final chapter, with results of these provided at the end of this section.

In the last chapter I made changes both to subcohort definitions, and the methods used to provide model estimates for each question of interest. Continuing to consider those who received monitoring in critical care as the ‘well’ comparator, I restricted the overall cohort to those admitted to critical care, excluding ward level patients. Accepting that some patients with organ support were potentially not ‘critically ill’, I restricted the organ support subcohort to those who received multiple days of critical care. Acknowledging that estimates of association could be more informative if using methods from causal inference, I undertook analyses that resulted in causal estimates of each question of interest.

After these changes, I observed that 12% of patients with CRC admitted to critical care met the definition of critical illness, in contrast to 18% of patients in critical care meeting the previous definition. Hospital mortality for this critical illness cohort was 22% (16% for elective patients, 35% for emergency) in contrast to 20% among those with the previous definition.

I estimated a reduced hazard of timely SACT for those who survived critical illness, when compared against patients with the same nature of hospital admission, who were admitted to critical care for monitoring, with HR 0.59 for elective patients with critical illness, and HR 0.42 for emergency patients with critical illness. Using the historic Scottish target of 12 weeks, the total eligible population had 53% predicted SACT receipt at 12 weeks. Elective patients with critical illness had 41% predicted to receive SACT at this time point, emergency patients with critical illness had predicted proportion of 28%.

I observed that critical illness has a causal influence on long term survival for patients with CRC, that persists despite restricting analysis only to hospital survivors, in a homogenous group of those who had High Risk Stage II or Stage III disease who had undergone curative resection. For elective patients who survived critical illness, estimates of HR for mortality were 1.43, with posterior probability of 97% of a clinically meaningful increase in hazard.

There was not an increase in HR of mortality for emergency patients who survived critical illness, potentially due to any effect being overwhelmed by the large increase in hazard by emergency admission itself (HR 2.21). After accounting for confounders, the well baseline of elective patients treated with monitoring in critical care, had estimated five year overall survival of 68%. The central estimate for elective patients

who experienced critical illness was 59%, an absolute reduction in predicted five-year survival of 9%. Patients admitted as an emergency treated with monitoring had predicted five-year survival of 44%, and those with emergency admission and critical illness had predicted survival of 42%.

As a reference point for the magnitude of such an impact, ESMO would categorise a treatment provided for patients with curative intent, that confers an absolute improvement of 5% on overall survival, as the highest level of substantial benefit (Grade A, Cherny et al. 2025). This chapter provides a central estimate that critical illness during elective admission, confers a reduction in overall survival, of almost double this threshold of ‘substantial’ impact.

9.3 Summary of relation to existing literature

Previous work has considered Intensive Care admission to be synonymous with critical illness. This thesis demonstrates that admission to critical care is the most common outcome for patients with planned admission to hospital, that the long term outcomes following critical care admission are not as severe as those following intensive care admission specifically, and that stratification by receipt of organ support provides more useful results. Inclusion of high dependency and intensive care, in contrast to those cohorts that use intensive care alone (such as Puxty et al. 2015) results in a greater proportion of patients admitted to higher level care, however the proportions receiving organ support are consistent between my findings, the work of Puxty et al. 2015 and the work of Dale et al. 2016.

No previous work has investigated the attainment of national cancer quality performance indicators, for patients with colorectal cancer. My findings that patients who receive organ support achieve a smaller proportion of QPIs is novel. With regards to QPI 11, and later chapters work on adjuvant SACT receipt more widely, there is some literature available for comparison. The observed probability of receiving adjuvant SACT amongst an eligible critical care population in this thesis (53%), appears consistent with the 52% estimate provided by Auclin et al. 2017, in their retrospective work investigating older patients with solid organ cancers following ICU discharge. Comparisons with their cohort are limited by multiple factors, they investigated a range of solid organ types, with gastrointestinal cancers accounting for only 30%, and 63% of their patients having metastatic disease. In the definition of the SACT-eligible cohort of this thesis, all patients had High Risk Stage II or Stage III CRC disease (i.e. no 'SACT-eligible' patients had metastatic disease). A more comparable population is provided by Kim et al. 2015, who investigated patients with Stage II and Stage III CRC and subsequent SACT receipt, almost exactly the population investigated by this thesis. I observed 70% attainment of adjuvant SACT 12 weeks following surgical resection, for elective patients treated at a ward level, Kim et al. 2015 describes 75% attainment at an earlier time point of 8 weeks. Whilst overall attainment of adjuvant SACT was lower in this thesis than seen in the study by Kim et al. 2015, the percentages are consistent with one another and differences can be potentially explained by: differences in national care quality targets (this thesis studied a Scottish population at a time when 12 weeks was the target), and differences in proportions of patients with each cancer stage (this thesis had a greater proportion of patients with High Risk Stage II disease, where the evidence of benefit of adjuvant SACT is less strong, and targets are less strict). Kim et al. 2015 provide an estimate of critical illness (ICU admission) being associated with reduced adjuvant SACT receipt, with an OR 0.42 (95% CI 0.27-0.63). This thesis provides central estimates of HR of timely SACT receipt ranging from 0.43-0.59 (depending on nature of admission), consistent

with the results from Kim et al. 2015. My work adds to Kim's, achieving consistent findings in a Scottish cohort, building on it with greater number of patients, modelling that considers both SACT receipt and SACT timing, and clear estimates of the causal impact of critical illness, rather than descriptors of association.

With regards to the association between critical illness and long-term survival for patients with CRC, this work is the first to provide observed five-year overall survival estimates (the measure recommended as the most meaningful by ESMO) for this cohort. It is also the first to provide estimates of the causal impact of critical illness on long term survival for patients with CRC. Puxty et al. 2018 reported four-year survival (including hospital mortality) for all patients with solid organ cancers following Intensive Care admission, at 39%. Their work included all solid cancer types and stages, whereas this work includes just CRC, considered to have more favourable outcomes than many other solid organ cancers. In direct comparison to the findings of Puxty et al. 2018, four-year survival in this thesis for patients with critical illness (multiple days of organ support), was 55% for elective patients with critical illness, and 27% for emergency patients with critical illness, and 45% when combining both groups into a single critical illness cohort. My findings are consistent with that of Puxty et al. 2018, reflecting the expected greater survival for CRC (when compared against other solid organ cancers), but also demonstrates the importance of stratification by nature of admission, where nature of presentation to hospital results in substantial differences in long-term survival.

In the final months of this thesis, Dahlberg et al. 2026 have published their findings on the most comparable cohort so far. In a Swedish cohort from 2010 to 2019, of patients with non-metastatic CRC undergoing elective surgical resection (n=23,891), they identified 5.6% who required unplanned ICU admission. In doing so they identified a population at least four times greater than the comparable Scottish cohort, patients who received surgical resection for the same disease stages (n = 5,256, which includes emergency resections). Their patients had an unadjusted mortality rate of 40% at

three years post resection, when including in-hospital mortality, the same value I observed at three years for what appears on first glance to be the most comparable subcohort, elective patients with multiple days of organ support (including in-hospital mortality).

In their multivariable analysis on odds of three-year mortality, where they included variables based on ‘clinical judgement and previous studies’ they reported unplanned ICU admission to have OR 2.06 (95% CI 1.78-2.38). Their reported OR is of a greater magnitude than my reported causal impact of critical illness on HR of long term overall mortality. It is important to note though, first that these are different scales (OR of death at three years versus HR of time to mortality), and second that this difference is expected. In their modelling, Dahlberg et al. 2026 included in-hospital deaths. I aimed to understand any impact of mortality that persisted after surviving hospital, and in doing so ‘blocked’ any increase hazard due to the impact of critical illness on in-hospital mortality. Similarly as noted in Chapter 8, my choice to condition on hospital survival also introduces some additional biases that risk biasing my estimate towards the null. Dahlberg et al. 2026 are not purporting to provide a causal impact of critical illness on long-term mortality in their work, but even if they had, we would expect a larger estimate of impact, as they report the total impact of critical illness on long-term mortality, and I report the impact that persists after initial survival from critical illness.

Their work has several advantages, with greater access to detail on operation specific metrics (operation duration, estimated blood loss, intraoperative complications), and sample size as noted above. However as relative limitations, they note substantial missing data on SACT receipt (and so cannot provide values for this), and excluded patients treated as an emergency. My work has the advantages of providing estimates of hazard of mortality for both elective and emergency admissions, additional stratification on severity of illness (requiring both organ support receipt, and multiple days

of organ support receipt), modelling strategies that can provide predicted survival curves after adjustment in multivariable analysis (up to five-years post resection, where Dahlberg make a single comparison of proportion surviving at three years), and clarity in the causal nature of the estimate provided.

9.4 Challenges and Lessons

This thesis gained and suffered from all the advantages and limitations of large scale analysis of routinely collected registry data, mentioned in each chapter. Use of these registries provided access to all patients diagnosed with CRC in Scotland over the study period, and information on all hospital and critical care admissions. The results of this thesis provides an example of the merits of linking previously siloed datasets and systems, highlighting the type of relevant questions that can be addressed in Scottish healthcare without new data collection being performed (avoiding the additional workforce and financial strain of collecting such data). As a limitation, information available was restricted to what had been entered within each registry, with relevant patient measures (such as frailty) not being recorded at all, and key cancer specific information (anatomic stage) having patchy recording in the national cancer registry. As a clinician working in intensive care, prior to commencing this thesis I had good levels of understanding of the limitations of routinely collected critical care information (SICSAG). Throughout this thesis I had to develop my understanding of the limitations of each other data source, often not immediately apparent at first glance. Throughout the work of this thesis I have gained a greater understanding of the relative merits of these datasets available from Public Health Scotland. This has allowed me to now provide meaningful support to the Health Board I work in, in their plans to join the federated network of trusted research environments, contributing to the West of Scotland Safehaven.

Performing all analyses in a Trusted Research Environment (TRE), provided several restrictions, in terms of statistical packages and software available. Several aspects of my work, such as code generated and model objects from analyses (posterior draws from each model), would have been useful to export for later use. However as the eDRIS TRE requires manual review of each object exported, requesting several hundred-thousand lines of code, and model objects with 40,000 samples a piece, would have been unnecessarily burdensome and unfeasible requests. Considering in the year of submission (2026) there have been widely published stories of patient sensitive information being leaked from systems that did not use TREs, it is likely that an increasing proportion of future large scale data work will be required to be performed in such an environment. The work of this thesis has provided me with the skills and experience, for me to attain my accreditation as an ONS accredited researcher, a relatively new national requirement prior to future work in TREs.

Over the course of undertaking this thesis, methods published in medical literature continue to change in prevalence. Some choices I made at the beginning of this thesis felt like stepping out on a limb, like choosing to undertake Bayesian analysis. These choices are now much less controversial. I made other choices at the beginning, to account for the perceived ‘atypical’ nature of a Bayesian thesis; such as original drafts of this thesis using predetermined thresholds for significance, and my choice initially to use univariable screening rather than methods of causal inference. These now appear to be overly conservative and cautious. I am particularly grateful for the feedback of my examiners, who rightly identified that some of these cautious choices could be described as picking the ‘worst of both worlds’ from each statistical paradigm. Their feedback allowed me to improve the presentation of each results chapter, and also undertake a final chapter with greater methodological rigour in model creation.

9.5 Additional Limitations and Future Work

Additional to the limitations raised in each chapter, this thesis is also limited by what it has not attempted to answer, questions that could be rightly raised as the more meaningful ones to ask.

The thesis identifies a cohort of patients with CRC and critical illness; I describe them and their outcomes of SACT receipt and overall survival. I note that there are differences in these outcomes, and in my final chapter I note that the impact of critical illness is likely causative. What I do not provide an rigorous answer to, is why such a causal impact exists.

In the final results section I note that mediation analysis could attempt to address each direct pathway within the total causal effect. Such an analysis would provide a likely starting point for future work. As an example this thesis did not provide thorough estimates on the direct effect of SACT omission/delay on long-term survival for critical care survivors. Considering the work of Hanna et al. 2020 it appears likely that such an effect would exist, however it has not previously been investigated in this population. As an example for SACT receipt, I noted in the previous chapter that hospital length of stay is a potential mediator, however I did not provide any mediation analysis for this.

At the beginning of the process of this thesis, I hoped to explore other patient centred outcomes, and to gain greater understanding on what routinely collected information could realistically answer for what may be seen as more qualitative metrics (such as quality of life, symptom burden, and quality of care at the end of life). A limitation of my own processes during this thesis is I undertook significant time cleaning and exploring other relevant datasets, only to be limited by time constraints (and

my own inefficiencies resulting in these time constraints) preventing these analyses being performed. As a clinician in intensive care, the key question of interest for me is not only, are you going to survive, but what does such a survival look like. Future work that explores the experiences of patients with cancer following critical illness could describe many relevant metrics: of proxy measures for symptom burden, care receipt, access to specialist support, and access to high quality palliative care. Registry data already collected across Scotland could provide new information on each of these questions. In doing so, clinicians and patients can have a richer understanding of what we are asking patients to consent to, in regards to likely and potential outcomes. Currently collected registry data across Scottish healthcare is inefficiently used, with an opportunity cost to research not performed, but also failing to make the best use of the work of the patients who provided their information, and the professionals who recorded it. I will accept, that many questions of health quality, would be better addressed by qualitative work itself, such as interviewing the survivors of cancer and critical illness. Such work would also help point towards what questions we should aim to explore with larger scale registry interrogation. Noted in the introduction of this thesis, a key descriptor of a mediating effect of critical illness on long term outcomes would likely be measures of Post-Intensive Care Syndrome (PICS). No national Scottish registry exists recording incidence of PICS for patients, and as such I was unable to explore any relationship between PICS and long-term outcomes. Future work to investigate any relationship would likely require prospective recruitment of patients with cancer who survived critical illness, potentially through collaboration with existing rehabilitation and more general ICU follow up programmes.

After identifying the differences in patient outcomes for those with critical illness and CRC, and recognising the next meaningful step is greater exploration of why and how critical illness causes such differences, the following step should be to develop interventions to meaningfully reduce such differences where possible. As a hypothetical

example, if difference in length of stay is the factor of most relevance for SACT, and SACT receipt is the most relevant factor for overall survival, it may be that increased resources in post-critical illness rehabilitation could be a meaningful intervention to reduce any difference in long-term survival.

Additional to the points made above, the goal of this thesis was to provide information useful both to clinicians and patients. The discussion so far has focused on how to gain additional information on patient-centred outcomes. Equally important though is understanding how best to communicate any information gained. Sobrero et al. 2020 aimed to better understand and communicate additional survival benefits of ever more burdensome forms of adjuvant SACT, so that a patient may best interpret where proposed treatments meet their own values, and where the point that proposed burdens outweigh proposed benefits. My thesis provides the information that it has gained, in a manner that hopefully communicates itself clearly, with predicted survival curves, and similar curves for time-to-SACT. It still though does not allow predictions of survival for an individual patient, instead again relying on the hypothetical ‘average impact of critical illness’. Qualitative work to better understand how to communicate risks and probabilities to a patient, models that provide greater stratification of predictions, or even creation of tools that allow for an individual to predict outcomes for their unique scenario, may be of merit in the future.

I began this thesis worried about the following hypothetical scenario, the commonly observed encounter with potential for conflict, where oncologists and surgeons report curative intent for a patient and estimated survival figures, an intensive care team concerned it is likely that critical illness prevents such a positive long-term outcome, and a patient stuck between the two perspectives with no clear information to support any decision. For this cohort of patients with potentially curative colorectal cancer and critical illness, this work now supports all involved in any decision-making process, reporting: the percentage of patients with critical illness who survive their hospital admission, the predicted chance of patients with critical illness receiving

their planned SACT if they survive, and their predicted long-term survival, with estimates given for the contribution of critical illness itself on such predictions. The key questions for future work remain: how can we improve equity in cancer care for survivors of critical illness?, how can we improve long-term survival?, and what is a life following critical illness with cancer like, for the person living it?

Appendices

A Methods

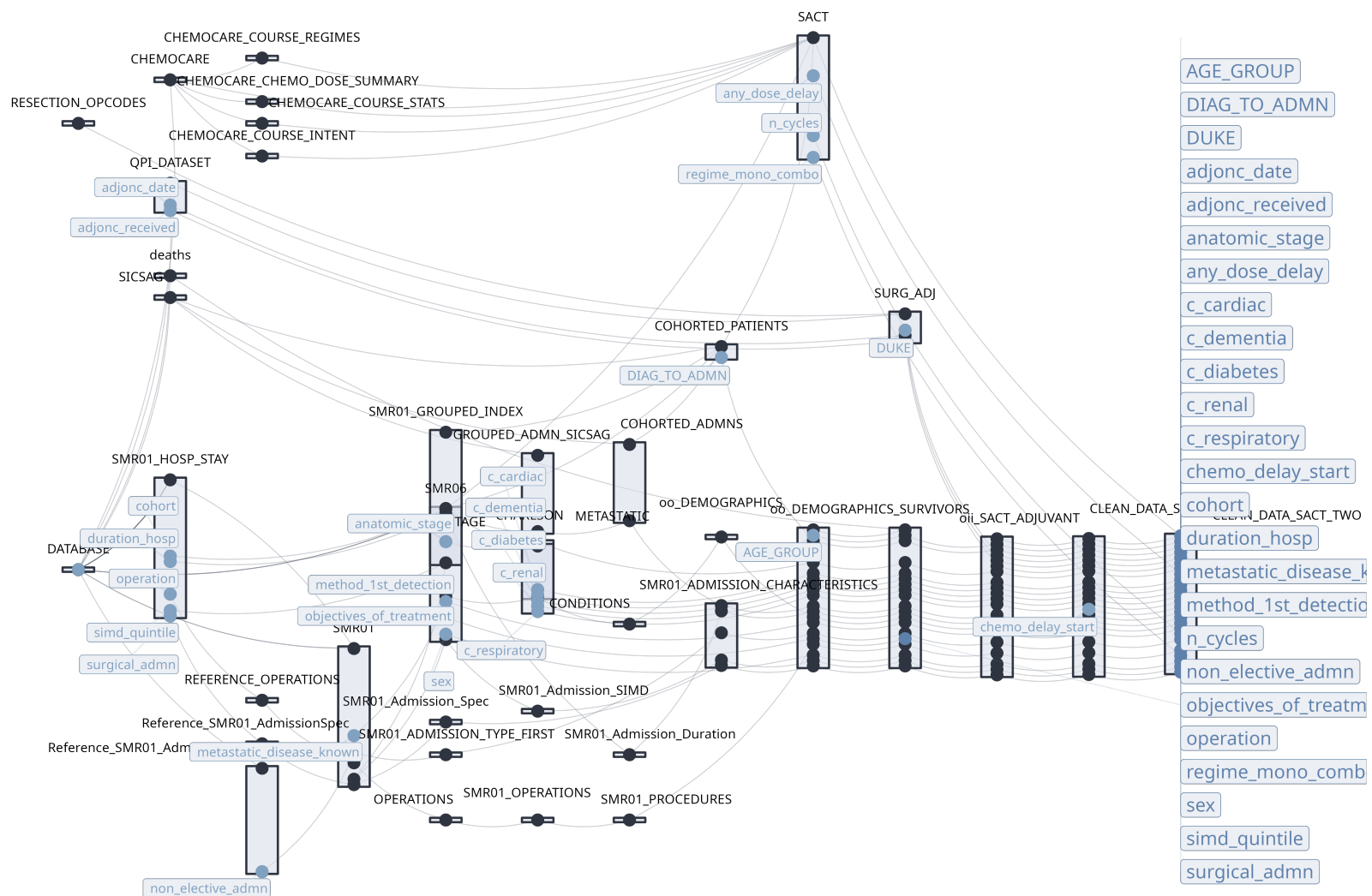


Figure A.1: Illustration Of Dataset Construction for SACT Analysis

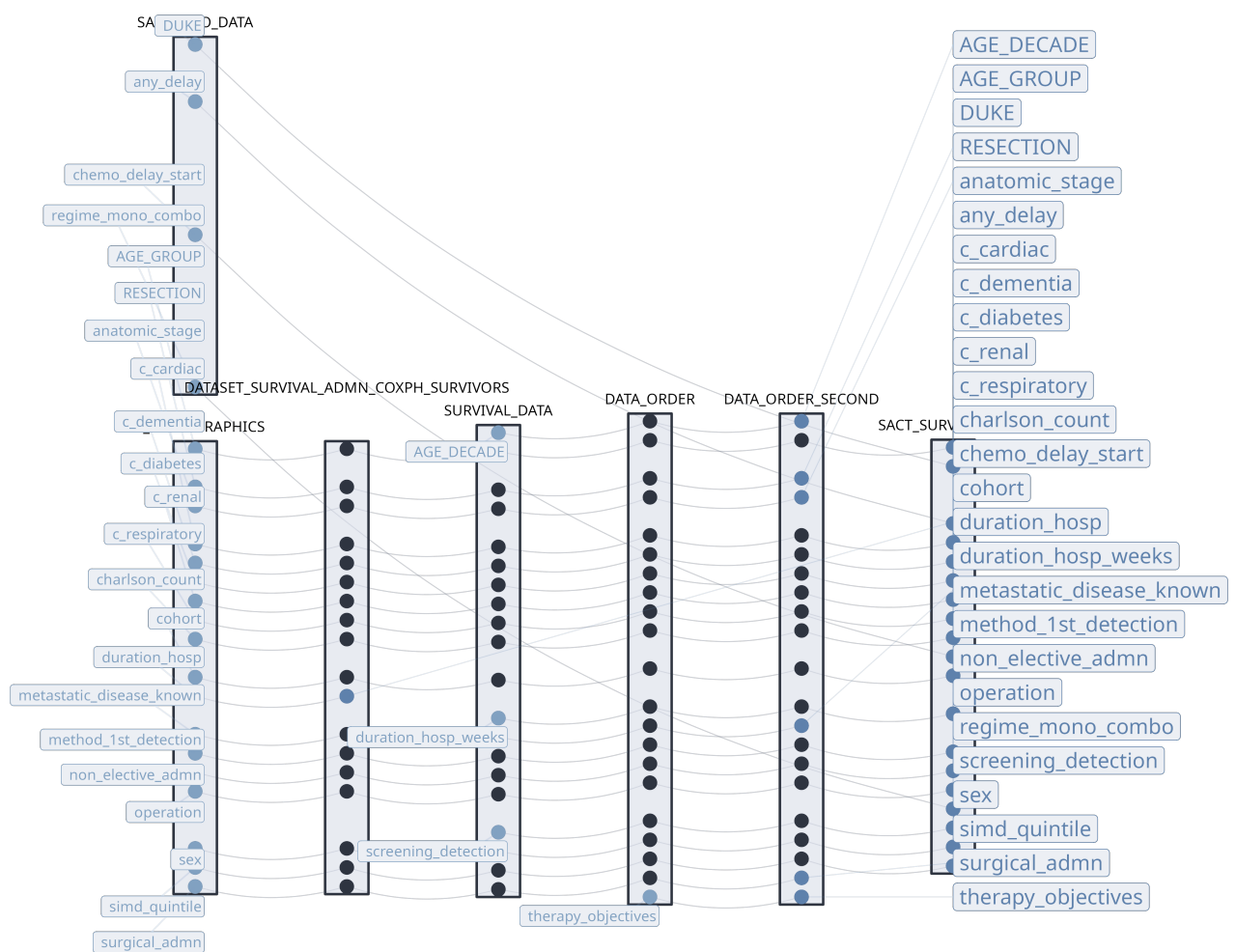


Figure A.2: Illustration Of Dataset Construction for Survival Analysis

B QPI

Table B.1: Multivariable Analysis Results - Summary of posterior probability distribution of the odds ratio for achieving QPI 11 (timely adjuvant chemotherapy), from multivariable logistic regression model using uninformative priors, for all other variables included in the model

Variable	Median	Crl	PD (%)	ROPE (%)	Increase	Decrease	Percentage Of Largest Effect
Age (years)	0.93	(0.92 - 0.95)	100.00	0.14	0.00	99.87	99.87% chance meaningful reduction
<i>per increase in age by one year</i>							
Comorbidities 1 Additional	0.54	(0.42 - 0.69)	100.00	0.00	0.00	100.00	100% chance meaningful reduction
Comorbidities 2+ Additional	0.29	(0.2 - 0.44)	100.00	0.00	0.00	100.00	100% chance meaningful reduction
<i>vs no additional comorbidity</i>							
Hospital LOS (Days)	0.93	(0.92 - 0.95)	100.00	0.00	0.00	100.00	100% chance meaningful reduction
<i>per increase in length of stay by one day</i>							
Method Diagnosis							
Clinical Presenta- tion	0.69	(0.55 - 0.87)	99.89	0.25	0.02	99.73	99.73% chance meaningful reduction
Incidental Finding	0.49	(0.29 - 0.83)	99.58	0.34	0.29	99.38	99.38% chance meaningful reduction
Other / Not Known	1.18	(0.61 - 2.29)	68.35	8.48	64.08	27.44	64.08% chance meaningful increase
<i>vs diagnosis through screening</i>							
Emergency	0.97	(0.73 - 1.29)	57.67	21.22	32.14	46.63	46.63% chance meaningful reduction
<i>vs elective admission</i>							
Female	1.33	(1.08 - 1.64)	99.67	0.86	99.05	0.08	99.05% chance meaningful increase
<i>vs male</i>							
SIMD Quintile 2	0.97	(0.73 - 1.28)	58.86	21.40	30.88	47.72	47.72% chance meaningful reduction
SIMD Quintile 3	1.30	(0.98 - 1.73)	96.56	4.24	93.98	1.78	93.98% chance meaningful increase
SIMD Quintile 4	1.14	(0.85 - 1.53)	81.49	14.42	73.53	12.05	73.53% chance meaningful increase
SIMD Quintile 5	1.67	(1.24 - 2.26)	99.96	0.07	99.93	0.00	99.93% chance meaningful increase
<i>vs SIMD Quintile 1</i>							
Stage III	2.29	(1.85 - 2.83)	100.00	0.00	100.00	0.00	100% chance meaningful increase
<i>vs High Risk Stage II</i>							
<i>Crl - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease</i>							

Table B.2: Multivariable Regression on Attaining QPI 11 - Measures of model validity

Variable	R-hat	Bulk ESS	Tail ESS
Intercept	1.00	74415	30874
cohortNoCriticalCare	1.00	49764	33057
cohortCritCareMOrganSupport	1.00	50492	32939
non_elective_admnTRUE	1.00	41809	33466
sexfemale	1.00	69395	31181
Age (years)	1.00	75375	31450
simd_quintile2	1.00	41604	32107
simd_quintile3	1.00	39766	30991
simd_quintile4	1.00	40392	32166
simd_quintile5	1.00	41791	33310
Comorbidities1	1.00	65453	32263
Comorbidities2P	1.00	69599	31199
method_1st_detectionIncidentalfinding	1.00	67754	30368
method_1st_detectionClinicalpresentation	1.00	63655	31076
method_1st_detectionOtherDNotKnown	1.00	71776	30792
duration_hosp	1.00	76635	30114
stageC	1.00	60695	31272
cohortNoCriticalCare:non_elective_admnTRUE	1.00	40919	33305
cohortCritCareMOrganSupport:non_elective_admnTRUE	1.00	45358	33098

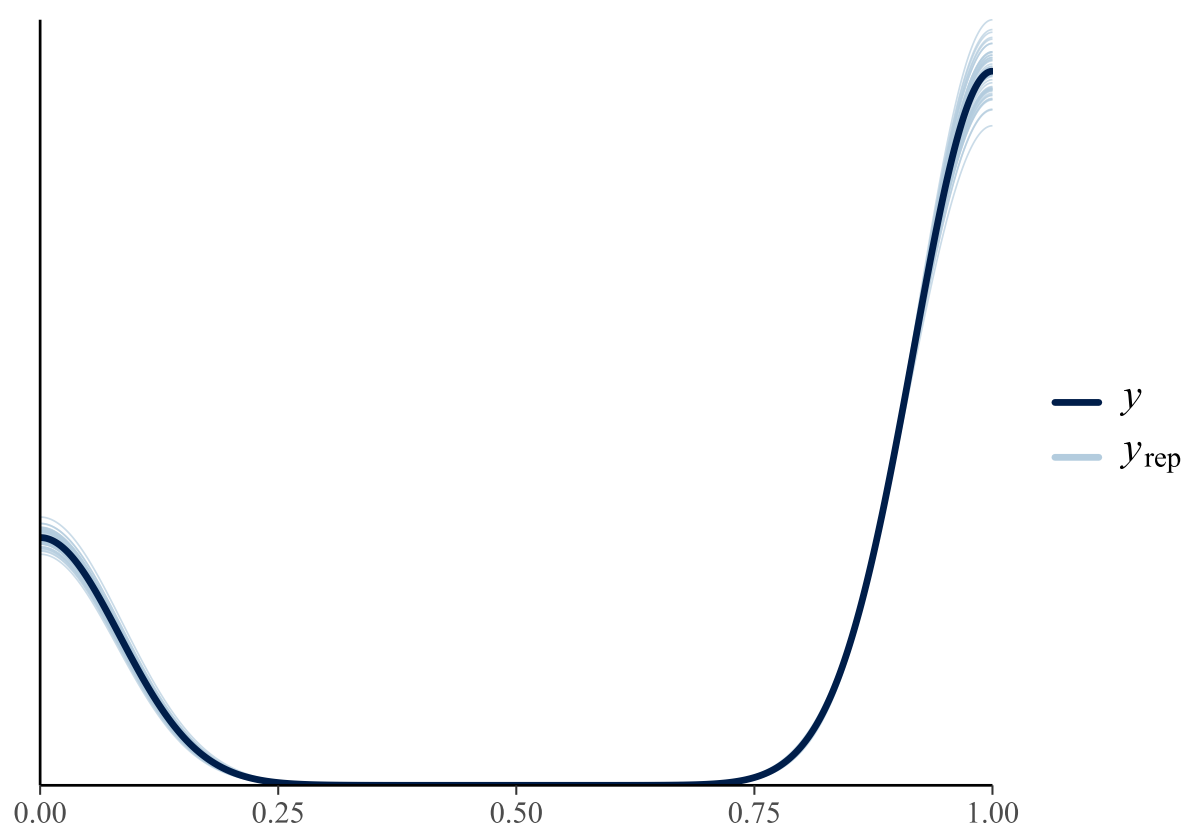


Figure B.3: Posterior predictive check of multivariable model using uninformative priors for QPI 11 attainment

Dark blue line (y) represents observed data, light-blue lines (y_{rep}) represent predictions sampled from posterior probability distributions

C SACT

C.1 Demographics Tables

Table C.3: Demographic Characteristics - Receipt of Adjuvant Chemotherapy (01A)

Demographics of Population							
Stratified By Nature of Hospital Admission and Levels of Support							
Characteristic	Overall	Elective Ward Level	Elective Monitoring	Elective Organ Support	Emergency Ward Level	Emergency Monitoring	Emergency Organ Support
	N = 3,427 ¹	N = 650 ¹	N = 1,695 ¹	N = 326 ¹	N = 170 ¹	N = 416 ¹	N = 170 ¹
Age At Diagnosis	71 (62, 79)	69 (61, 76)	70 (62, 78)	73 (65, 79)	72 (58, 80)	72 (63, 80)	73 (64, 80)
Female Sex	1,567 (46%)	305 (47%)	753 (44%)	127 (39%)	95 (56%)	218 (52%)	69 (41%)
SIMD (quintile)							
1	604 (18%)	93 (14%)	285 (17%)	67 (21%)	36 (21%)	72 (17%)	51 (30%)
2	632 (18%)	108 (17%)	321 (19%)	61 (19%)	31 (18%)	85 (21%)	26 (15%)
3	730 (21%)	156 (24%)	343 (20%)	73 (22%)	33 (20%)	88 (21%)	37 (22%)
4	717 (21%)	153 (24%)	351 (21%)	73 (22%)	32 (19%)	81 (20%)	27 (16%)
5	739 (22%)	140 (22%)	393 (23%)	52 (16%)	37 (22%)	88 (21%)	29 (17%)
Additional Charlson Co-morbidities Known							
None	2,621 (76%)	551 (85%)	1,300 (77%)	211 (65%)	131 (77%)	303 (73%)	125 (74%)
One	608 (18%)	82 (13%)	303 (18%)	77 (24%)	32 (19%)	82 (20%)	32 (19%)
Multiple	198 (5.8%)	17 (2.6%)	92 (5.4%)	38 (12%)	7 (4.1%)	31 (7.5%)	13 (7.6%)
Cardiac Disease (Charlson)	200 (5.8%)	23 (3.5%)	101 (6.0%)	31 (9.5%)	9 (5.3%)	25 (6.0%)	11 (6.5%)

Respiratory Disease	292 (8.5%)	30 (4.6%)	130 (7.7%)	50 (15%)	11 (6.5%)	52 (13%)	19 (11%)
(Charlson)							
Renal Disease (Charlson)	172 (5.0%)	20 (3.1%)	71 (4.2%)	30 (9.2%)	9 (5.3%)	28 (6.7%)	14 (8.2%)
Diabetes (Charlson)	347 (10%)	40 (6.2%)	191 (11%)	47 (14%)	16 (9.4%)	35 (8.4%)	18 (11%)
Dementia (Charlson)	23 (0.7%)	<= 5	9 (0.5%)	<= 5	<= 5	7 (1.7%)	0 (0%)
Surgical Admission	3,421 (100%)	650 (100%)	1,694 (100%)	325 (100%)	167 (98%)	416 (100%)	169 (99%)
Operations During Admission							
One	2,954 (86%)	586 (90%)	1,483 (87%)	242 (74%)	152 (89%)	367 (88%)	124 (73%)
None	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Multiple	473 (14%)	64 (9.8%)	212 (13%)	84 (26%)	18 (11%)	49 (12%)	46 (27%)
Diagnosis To Admission (days)	41 (16, 66)	46 (32, 66)	50 (34, 75)	53 (34, 76)	0 (0, 1)	0 (0, 10)	0 (0, 13)
Duration Hospital Stay (days)	9 (6, 15)	7 (5, 10)	8 (6, 12)	14 (9, 26)	14 (10, 25)	14 (10, 22)	23 (14, 41)
Duration Critical Care Stay (days)	2.00 (1.00, 4.00)	0.00 (0.00, 0.00)	2.00 (1.00, 4.00)	5.00 (3.00, 8.00)	0.00 (0.00, 0.00)	3.00 (2.00, 4.00)	5.00 (3.00, 10.00)
Critical Care Admission Was Planned	1,717 (50%)	0 (0%)	1,433 (85%)	196 (60%)	0 (0%)	76 (18%)	12 (7.1%)
APACHE II Score	13.0 (10.0, 16.0)	NA (NA, NA)	11.0 (9.0, 13.0)	14.0 (11.0, 18.0)	NA (NA, NA)	11.0 (9.0, 13.5)	16.0 (12.0, 19.0)
Vasoactive Support	444 (13%)	0 (0%)	0 (0%)	294 (90%)	0 (0%)	0 (0%)	150 (88%)
Ventilated	183 (5.3%)	0 (0%)	0 (0%)	97 (30%)	0 (0%)	0 (0%)	86 (51%)

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Renal Replacement Therapy	22 (0.6%)	0 (0%)	0 (0%)	14 (4.3%)	0 (0%)	0 (0%)	8 (4.7%)
Method of First Detection							
Clinical presentation	2,630 (77%)	442 (68%)	1,222 (72%)	241 (74%)	161 (95%)	404 (97%)	160 (94%)
Screening examination	711 (21%)	192 (30%)	426 (25%)	73 (22%)	<= 5	8 (1.9%)	<= 5
Incidental finding	73 (2.1%)	<= 5	36 (2.1%)	12 (3.7%)	<= 5	<= 5	<= 5
Other / Not Known	13 (0.4%)	<= 5	11 (0.6%)	0 (0%)	<= 5	0 (0%)	0 (0%)
Duke							
High-Risk B	1,113 (32%)	201 (31%)	534 (32%)	105 (32%)	58 (34%)	164 (39%)	51 (30%)
C	2,314 (68%)	449 (69%)	1,161 (68%)	221 (68%)	112 (66%)	252 (61%)	119 (70%)
Objectives of Treatment							
Curative Intent	3,006 (88%)	599 (92%)	1,490 (88%)	284 (87%)	138 (81%)	350 (84%)	145 (85%)
Non-curative Intent (palliative)	268 (7.8%)	37 (5.7%)	128 (7.6%)	30 (9.2%)	20 (12%)	36 (8.7%)	17 (10%)
Not Known	153 (4.5%)	14 (2.2%)	77 (4.5%)	12 (3.7%)	12 (7.1%)	30 (7.2%)	8 (4.7%)
Received Adjuvant Chemotherapy	1,946 (57%)	453 (70%)	1,011 (60%)	136 (42%)	80 (47%)	209 (50%)	57 (34%)

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¹Median (Q1, Q3); n (%)

Table C.4: Demographic Characteristics - Delay To Receipt of Adjuvant Chemotherapy (01B)

Demographics of Population Stratified By Nature of Hospital Admission and Levels of Support							
Characteristic	Overall N = 1,9426 ¹	Elective Ward Level N = 453 ¹	Elective Monitoring N = 1,011 ¹	Elective Organ Support N = 136 ¹	Emergency Ward Level N = 80 ¹	Emergency Monitoring N = 209 ¹	Emergency Organ Support N = 57 ¹
Age At Diagnosis	65 (57, 71)	65 (58, 71)	65 (58, 71)	67 (59, 73)	60 (53, 70)	65 (55, 71)	67 (58, 72)
Female Sex	913 (47%)	215 (47%)	469 (46%)	55 (40%)	42 (53%)	105 (50%)	27 (47%)
SIMD (quintile)							
1	320 (16%)	70 (15%)	157 (16%)	23 (17%)	18 (23%)	36 (17%)	16 (28%)
2	338 (17%)	75 (17%)	186 (18%)	23 (17%)	11 (14%)	36 (17%)	7 (12%)
3	430 (22%)	106 (23%)	210 (21%)	38 (28%)	15 (19%)	44 (21%)	17 (30%)
4	405 (21%)	103 (23%)	208 (21%)	31 (23%)	16 (20%)	40 (19%)	7 (12%)
5	449 (23%)	99 (22%)	249 (25%)	21 (15%)	19 (24%)	51 (25%)	10 (18%)
Additional Charlson Co-morbidities Known							
None	1,647 (85%)	404 (89%)	844 (83%)	100 (74%)	72 (90%)	180 (86%)	47 (82%)
One	264 (14%)	43 (9.5%)	144 (14%)	31 (23%)	8 (10%)	28 (13%)	10 (18%)
Multiple	35 (1.8%)	6 (1.3%)	23 (2.3%)	<= 5	0 (0%)	<= 5	0 (0%)
Cardiac Disease (Charlson)	46 (2.4%)	9 (2.0%)	31 (3.1%)	<= 5	<= 5	0 (0%)	<= 5

Respiratory Disease (Charlson)	122 (6.3%)	20 (4.4%)	63 (6.3%)	18 (13%)	<= 5	16 (7.7%)	<= 5
Renal Disease (Charlson)	26 (1.3%)	<= 5	16 (1.6%)	<= 5	0 (0%)	<= 5	<= 5
Diabetes (Charlson)	141 (7.3%)	20 (4.4%)	82 (8.1%)	17 (13%)	<= 5	13 (6.2%)	<= 5
Dementia (Charlson)	<= 5	<= 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Surgical Admission Operations During Admission	1,946 (100%)	453 (100%)	1,011 (100%)	136 (100%)	80 (100%)	209 (100%)	57 (100%)
One	1,697 (87%)	414 (91%)	883 (87%)	101 (74%)	73 (91%)	184 (88%)	42 (74%)
None	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Multiple	249 (13%)	39 (8.6%)	128 (13%)	35 (26%)	7 (8.8%)	25 (12%)	15 (26%)
Diagnosis To Admission (days)	40 (21, 60)	45 (32, 64)	46 (31, 65)	51 (35, 71)	0 (0, 9)	0 (0, 8)	0 (0, 1)
Duration Hospital Stay (days)	7.0 (5.0, 11.0)	6.0 (4.0, 8.0)	7.0 (5.0, 10.0)	10.0 (7.0, 15.0)	10.5 (8.0, 16.0)	11.0 (8.0, 16.0)	14.0 (11.0, 24.0)
Duration Critical Care Stay (days)	2.00 (0.00, 3.00)	0.00 (0.00, 0.00)	2.00 (1.00, 4.00)	4.00 (3.00, 6.50)	0.00 (0.00, 0.00)	3.00 (2.00, 4.00)	4.00 (3.00, 6.00)
Critical Care Admission Was Planned	1,008 (52%)	0 (0%)	863 (85%)	103 (76%)	0 (0%)	38 (18%)	<= 5
APACHE II Score	11.0 (8.0, 13.0)	NA (NA, NA)	11.0 (8.0, 13.0)	12.0 (9.0, 16.0)	NA (NA, NA)	10.0 (7.0, 12.0)	12.0 (9.0, 17.5)
Vasoactive Support	172 (8.8%)	0 (0%)	0 (0%)	121 (89%)	0 (0%)	0 (0%)	51 (89%)
Ventilated	53 (2.7%)	0 (0%)	0 (0%)	28 (21%)	0 (0%)	0 (0%)	25 (44%)
Renal Replacement Therapy	<= 5	0 (0%)	0 (0%)	<= 5	0 (0%)	0 (0%)	<= 5

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Method of First Detection							
Clinical presentation	1,326 (68%)	276 (61%)	630 (62%)	91 (67%)	75 (94%)	201 (96%)	53 (93%)
Screening examination	579 (30%)	169 (37%)	358 (35%)	41 (30%)	<= 5	<= 5	<= 5
Incidental finding	28 (1.4%)	6 (1.3%)	12 (1.2%)	<= 5	<= 5	<= 5	<= 5
Other / Not Known	13 (0.7%)	<= 5	11 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Duke							
High-Risk B	449 (23%)	104 (23%)	214 (21%)	28 (21%)	17 (21%)	72 (34%)	14 (25%)
C	1,497 (77%)	349 (77%)	797 (79%)	108 (79%)	63 (79%)	137 (66%)	43 (75%)
Received Adjunctive	1,946 (100%)	453 (100%)	1,011 (100%)	136 (100%)	80 (100%)	209 (100%)	57 (100%)
Chemotherapy for HRB or C							
Delays In Receiving Adjunctive Chemotherapy	506 (26%)	108 (24%)	229 (23%)	51 (38%)	25 (33%)	62 (30%)	31 (54%)
Unknown	14	1	5	1	4	3	0

¹Median (Q1, Q3); n (%)

C.2 One A

Table C.5: Multivariable Analysis Results - Summary of posterior probability distribution of the odds ratio for receipt of adjuvant chemotherapy (SACT A), from multivariable logistic regression model using uninformative priors, for all other variables included in the model

[illegible]

Table C.6: Model Validity Results - Receipt of Adjuvant Chemotherapy (SACT A)

	Rhat	Bulk ESS	Tail ESS
Intercept	~1.01	72310.43	30797.94
cohortWard Level	~1.01	60080.20	29786.86
cohortOrgan Support	~1.01	57042.04	31408.76
EmergencyTRUE	~1.01	49068.00	33128.47
Age (years)	~1.01	72232.21	31994.78
Dx To Admn (days)	~1.01	46712.15	31772.03
CRC Stage- HRB	~1.01	72121.81	30045.21
Comorbidities1 Additional	~1.01	73427.77	27299.05
Comorbidities2+ Additional	~1.01	75851.21	28817.62
Hospital LOS (Days)	~1.01	58618.80	33204.55
Method DiagnosisScreening	~1.01	72262.53	31287.39
Method DiagnosisIncidental Finding	~1.01	78178.80	30506.43
Method DiagnosisOther/Not Known	~1.01	72203.85	29023.62
Multiple Operations	~1.01	66116.58	30197.00
SIMD Quintile 2	~1.01	38244.18	32759.78
SIMD Quintile 3	~1.01	38736.13	32172.13
SIMD Quintile 4	~1.01	38255.25	30815.89
SIMD Quintile 5	~1.01	37168.88	32041.12
cohortWard Level:EmergencyTRUE	~1.01	54120.36	33493.97
cohortOrgan Support:EmergencyTRUE	~1.01	52840.84	32698.20

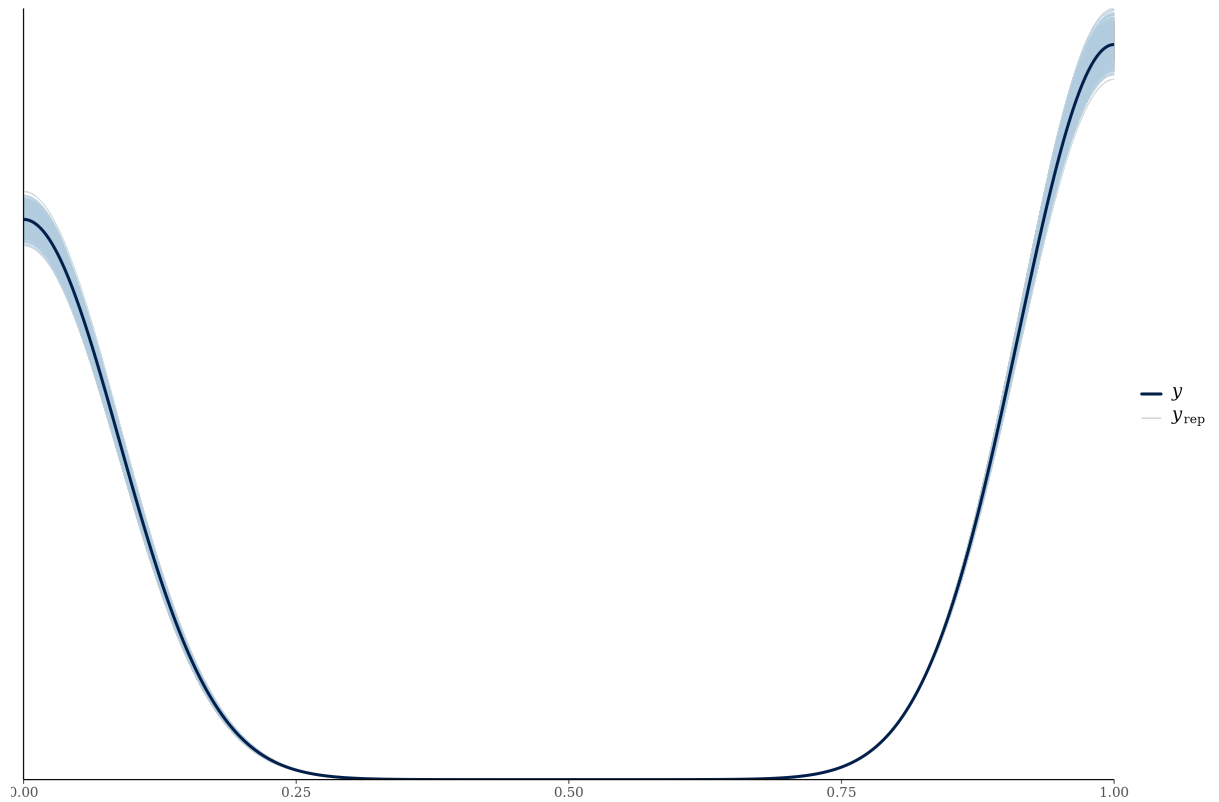
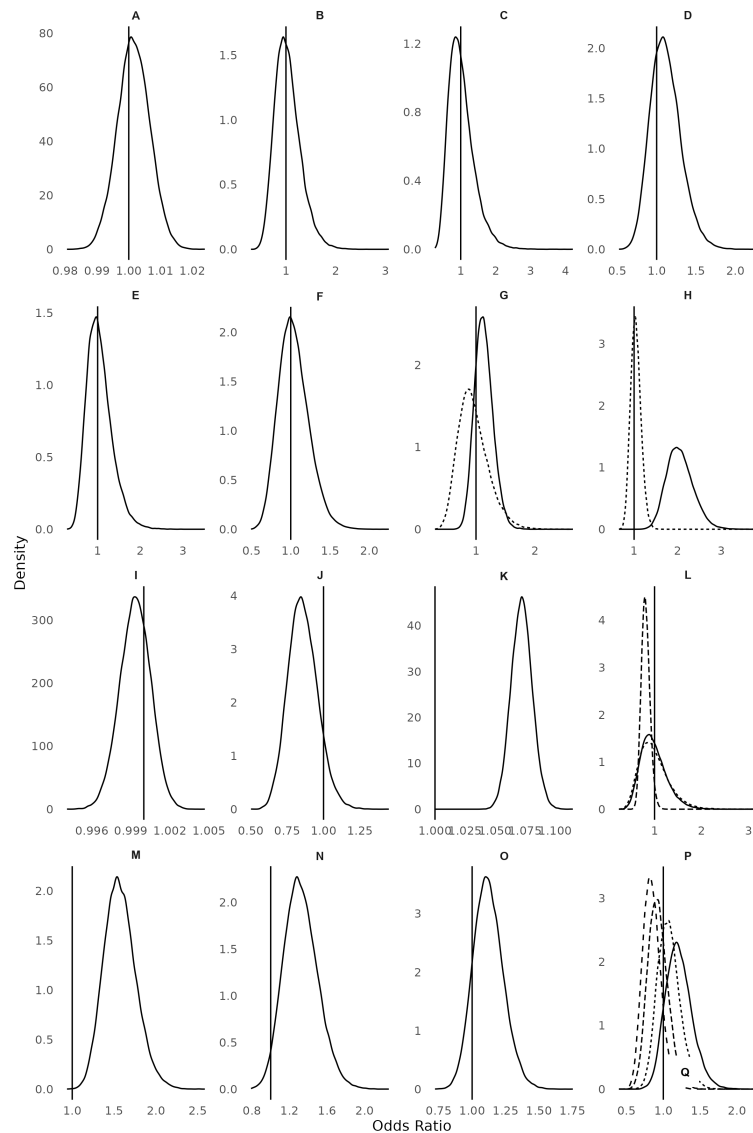


Figure C.4: Posterior predictive check of multivariable model (SACT A) using uninformative priors

Dark blue line (y) represents observed data, light-blue lines (y_{rep}) represent predictions sampled from posterior probability distributions

C.3 One B

Figure C.5 shows the results of univariable analysis for factors associated with delay to receipt of adjuvant chemotherapy.



- A** Age at diagnosis (*per* increase in age by one year)
B Cardiac comorbidity (vs No cardiac comorbidity)
C Dementia (vs No dementia)
D Diabetes (vs No diabetes)
E Renal comorbidity (vs No renal comorbidity)
F Respiratory comorbidity (vs No respiratory comorbidity)
G Charlson comorbidity count (vs Zero additional comorbidity); solid = One additional, dotted = Two plus
H Support in Hospital (vs Monitoring); solid = Organ Support, dotted = Ward Level
I Diagnosis-to-admission interval (*per* increase in interval by one day)
J Anatomic Stage High Risk II (vs Stage III)
K Duration of hospital stay (*per* increase in admission duration by one day)
L Method of first detection (vs Clinical Presentation); dashed = Screening, solid = Other/Not Known, dotted = Incidental Finding
M Non-elective admission (vs Elective admission)
N Multiple operations (vs Single operation)
O Female Sex (vs Male)
P Deprivation quintile (SIMD) (vs Q1); solid = Q2, dotted = Q3, long-dash = Q4, dashed = Q5

Figure C.5: Posterior probability distributions of the odds ratio for delay to receipt of adjuvant chemotherapy (SACT B), from univariable logistic regression models fitted to each variable. Vertical line at OR 1 (no effect). Facet key provides title and comparator for each variable

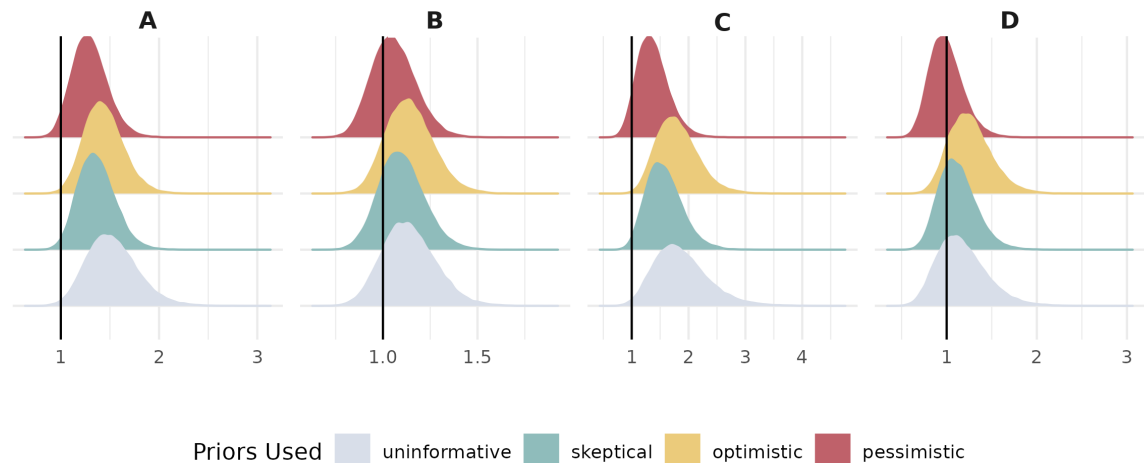
Table 6.9 provides detailed results of the univariable analysis.

Table C.7: Multivariable Analysis Results - Summary of posterior probability distribution of the odds ratio for delay to receipt of adjuvant chemotherapy (SACT B), from multivariable logistic regression model using uninformative priors, for all other variables included in the model

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease	Percentage Of Largest Effect
Hospital Stay (days) <i>per increase in duration by one day</i>	1.07	(1.05-1.09)	100.00	4.45	95.55	0.00	95.55% chance meaningful increase
CRC Detection:							
Incidental Finding	0.91	(0.52-1.57)	63.12	13.62	30.47	55.91	55.91% chance meaningful reduction
Other / Not Known	0.96	(0.51-1.77)	54.93	12.38	38.99	48.62	48.62% chance meaningful reduction
Screening Examination <i>vs diagnosis following clinical presentation</i>	0.94	(0.75-1.17)	71.06	29.20	16.33	54.47	54.47% chance meaningful reduction
Emergency Admission <i>vs Elective admission</i>	1.04	(0.78-1.39)	60.30	25.13	47.55	27.33	47.55% chance meaningful increase
Multiple Operations <i>vs Single Operation</i>	0.95	(0.71-1.27)	63.27	25.23	25.25	49.53	49.53% chance meaningful reduction
<i>CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease</i>							

C.3.1 Model Validity And Sensitivity

Figure C.6 shows the sensitivity analysis comparing different prior distributions.



- A Elective: Organ Support (vs Elective: Monitoring)
 B Elective: Ward Level (vs Elective: Monitoring)
 C Emergency: Organ Support (vs Emergency: Monitoring)
 D Emergency: Ward Level (vs Emergency: Monitoring)

Figure C.6: Sensitivity Analysis - Comparisons of posterior probability distribution of the odds ratio for delay to receipt of adjuvant chemotherapy (SACT B), from multivariable logistic regression models using different prior probability distributions
 Facet key provided for variable names and comparators

Table C.8 provides detailed results of the validity checks.

Table C.8: Validity Checks - Delay to Receipt of Adjuvant Chemotherapy (SACT B)

	Rhat	Bulk ESS	Tail ESS
Intercept	1.0000727	74258.45	32497.34
cohortWard Level	1.0001748	63021.19	32557.22
cohortOrgan Support	0.9999919	64696.88	33255.94
EmergencyTRUE	1.0003655	53900.08	33966.90
Hospital LOS (Days)	1.0001622	69957.52	32412.79
Method DiagnosisScreening	1.0001844	71723.54	31970.66
Method DiagnosisIncidental Finding	1.0001155	76668.28	31589.75
Method DiagnosisOther/Not Known	1.0004938	83947.56	28242.96
Multiple Operations	1.0001958	75454.08	31545.17
cohortWard Level:EmergencyTRUE	1.0001634	59170.55	33994.68
cohortOrgan Support:EmergencyTRUE	1.0003787	63098.74	32546.18

Figure C.7 shows the posterior predictive check for the model.

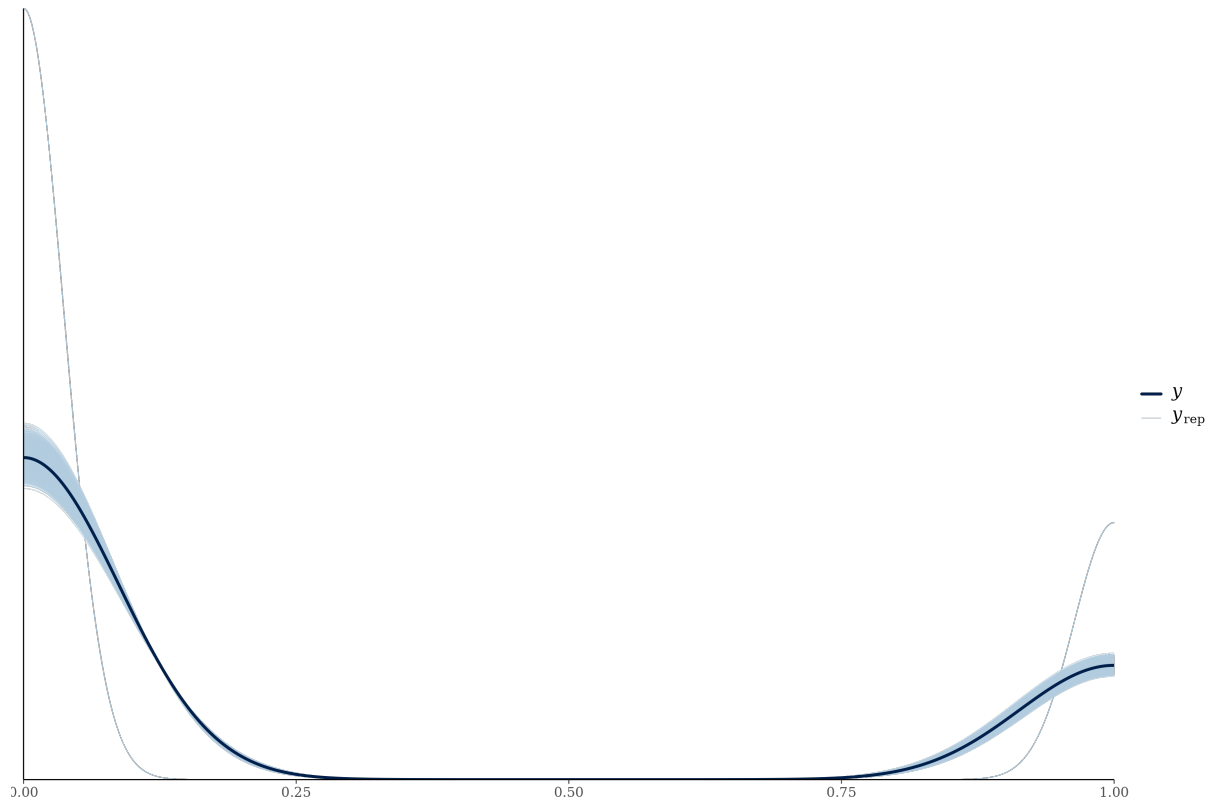


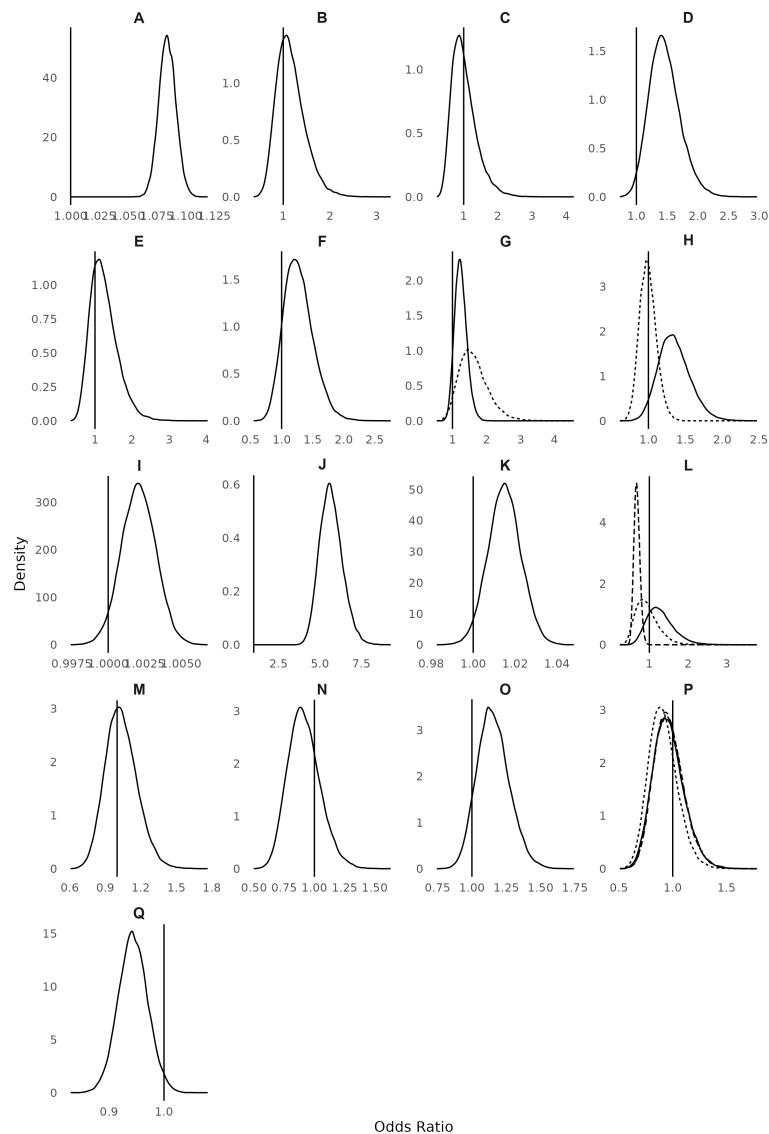
Figure C.7: Posterior predictive check of multivariable model (SACT B) using uninformative priors

Dark blue line (y) represents observed data, light-blue lines (y_{rep}) represent predictions sampled from posterior probability distributions

C.4 Two A

C.4.1 Variable Selection - Univariable Analysis

Figure C.8 shows the results of univariable analysis for factors associated with regime choice in adjuvant chemotherapy.



- A** Age at diagnosis (*per* increase in age by one year)
B Cardiac comorbidity (vs No cardiac comorbidity)
C Dementia (vs No dementia)
D Diabetes (vs No diabetes)
E Renal comorbidity (vs No renal comorbidity)
F Respiratory comorbidity (vs No respiratory comorbidity)
G Charlson comorbidity count (vs Zero additional comorbidity); solid = One additional, dotted = Two plus
H Support in Hospital (vs Monitoring); solid = Organ Support, dotted = Ward Level
I Diagnosis-to-admission interval (*per* increase in interval by one day)
J Anatomic Stage High Risk II (vs Stage III)
K Duration of hospital stay (*per* increase in admission duration by one day)
L Method of first detection (vs Clinical Presentation); dashed = Other/Not Known, solid = Screening, dotted = Incidental Finding
M Non-elective admission (vs Elective admission)
N Multiple operations (vs Single Operation)
O Female Sex (vs Male)
P Deprivation quintile (SIMD) (vs Q1); solid = Q2, dotted = Q3, long-dash = Q4, dashed = Q5
Q Surgery-to-chemotherapy interval (*per* increase in interval by one day)

Figure C.8: Posterior probability distributions of the odds ratio for receipt of single agent adjuvant chemotherapy (SACT C), from univariable logistic regression models fitted to each variable. Vertical line at OR 1 (no effect). Facet key provides title and comparator for each variable

C.4.2 Model Validity And Sensitivity

Figure C.9 shows the sensitivity analysis comparing different prior distributions.

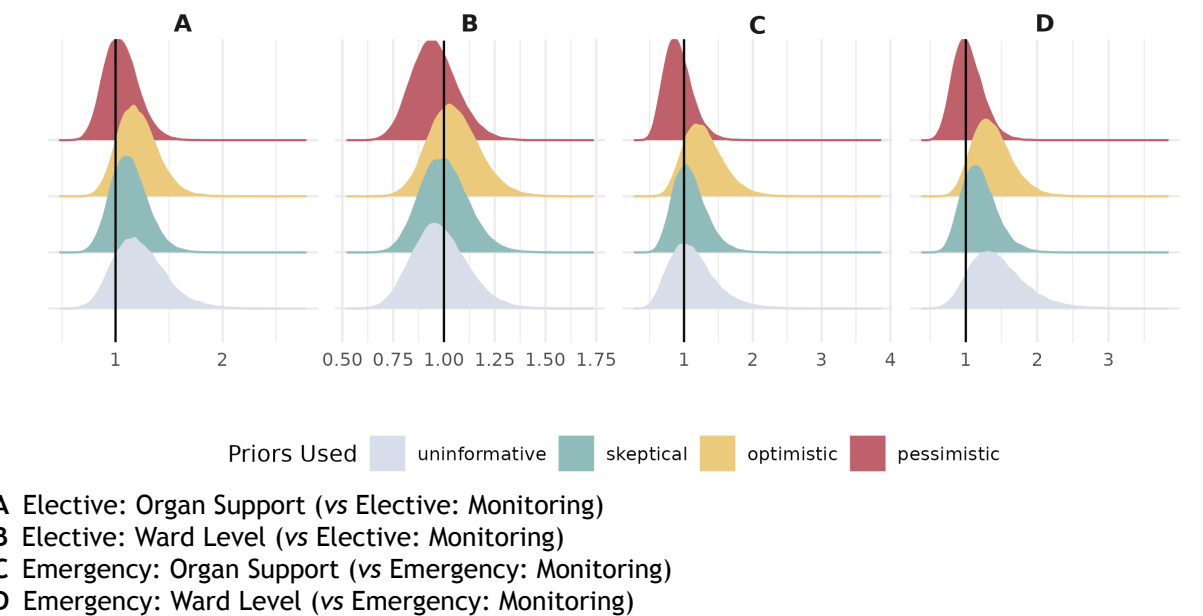


Figure C.9: Sensitivity Analysis - Comparisons of posterior probability distribution of the odds ratio for receipt of single agent adjuvant chemotherapy (SACT C), from multivariable logistic regression models using different prior probability distributions
Facet key provided for variable names and comparators

Table C.10 provides detailed results of the validity checcks.

Table C.10: Validity Checks - Regime Choice In Adjuvant Chemotherapy (SACT C)

	Rhat	Bulk ESS	Tail ESS
Intercept	1.000255	46283.34	32084.07
cohortWard Level	1.000067	48261.52	32793.41
cohortOrgan Support	1.000127	48122.92	31562.28
EmergencyTRUE	1.000180	41776.60	30233.82
Age (years)	1.000276	45852.62	31370.13
Dx To Admn (days)	1.000036	45505.99	33346.69
CRC Stage- HRB	1.000123	46200.48	31076.68
Diabetes	1.000202	50258.28	30848.31
Hospital LOS (Days)	1.000272	49778.93	32782.11
Method DiagnosisScreening	1.000335	51604.13	31309.74
Method DiagnosisIncidental Finding	1.000143	51928.89	29992.19
Method DiagnosisOther/Not Known	1.000166	50966.74	31864.31
surg_to_chemo	1.000244	48963.91	31106.62
cohortWard Level:EmergencyTRUE	1.000103	46131.44	32054.78
cohortOrgan Support:EmergencyTRUE	1.000280	47425.89	30649.77

Figure C.10 shows the posterior predictive check for the model.

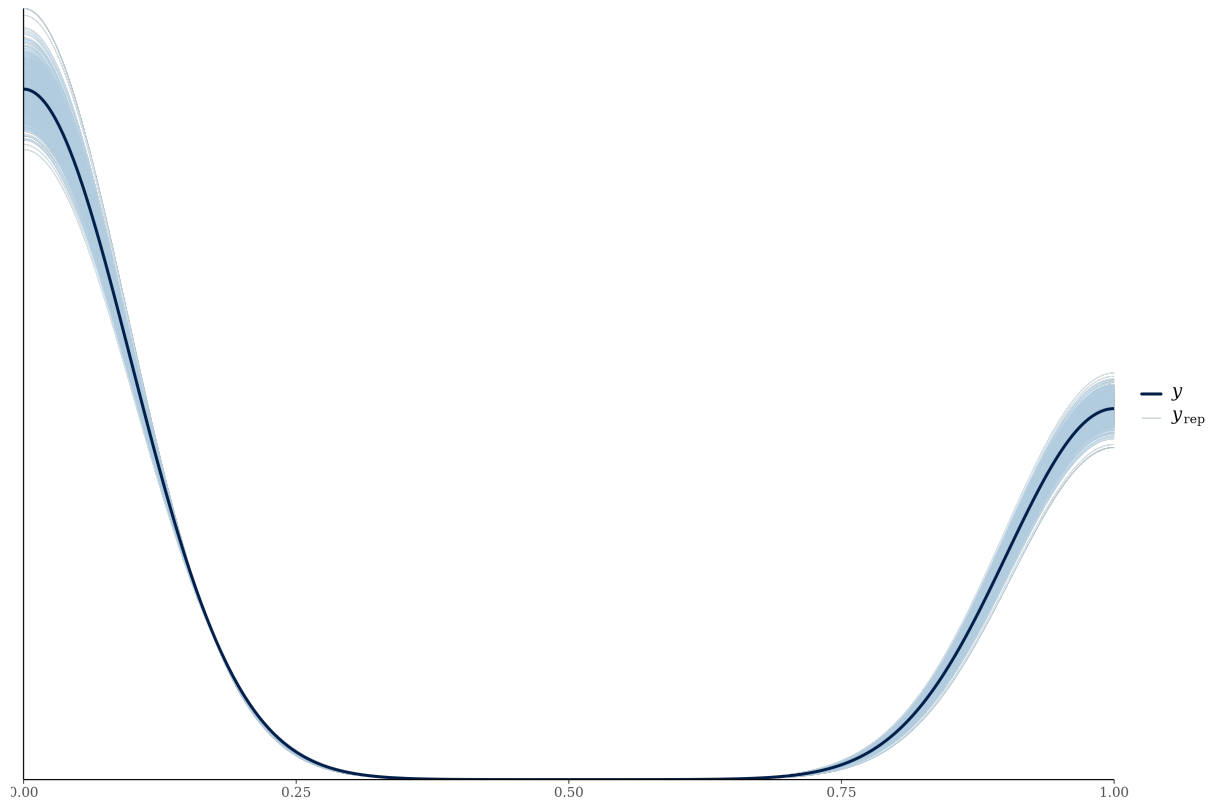


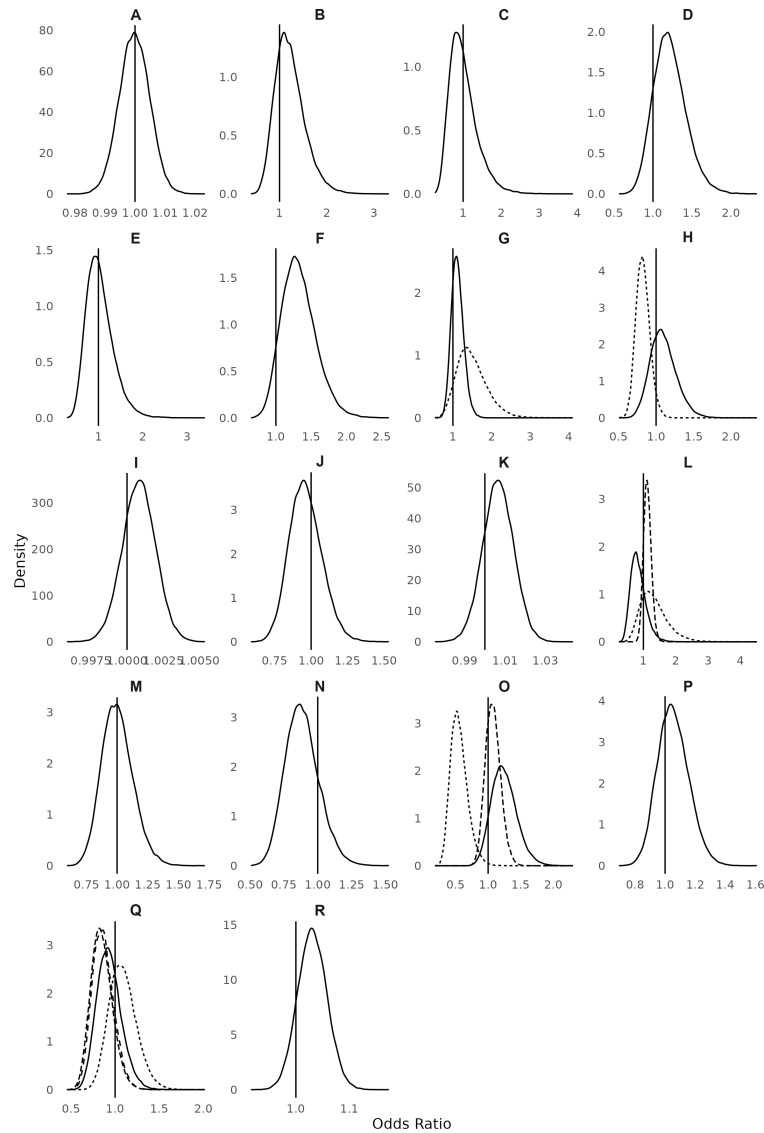
Figure C.10: Posterior predictive check of multivariable model (SACT C) using uninformative priors

Dark blue line (y) represents observed data, light-blue lines (y_{rep}) represent predictions sampled from posterior probability distributions

C.5 Two B

C.5.1 Variable Selection - Univariable Analysis

Figure C.11 shows the results of univariable analysis for factors associated with dose delay in adjuvant chemotherapy.



- A** Age at diagnosis (*per* increase in age by one year)
B Cardiac comorbidity (vs No cardiac comorbidity)
C Dementia (vs No dementia)
D Diabetes (vs No diabetes)
E Renal comorbidity (vs No renal comorbidity)
F Respiratory comorbidity (vs No respiratory comorbidity)
G Charlson comorbidity count (vs Zero additional comorbidity); solid = One additional, dotted = Two plus
H Support in Hospital (vs Monitoring); solid = Organ Support, dotted = Ward Level
I Diagnosis-to-admission interval (*per* increase in interval by one day)
J Anatomic Stage High Risk II (vs Stage III)
K Duration of hospital stay (*per* increase in admission duration by one day)
L Method of first detection (vs Clinical Presentation); dashed = Other/Not Known, solid = Screening, dotted = Incidental Finding
M Non-elective admission (vs Elective admission)
N Multiple operations (vs Single Operation)
O Regime (vs CAPOX); solid = FOLFOX, dotted = 5FU, dashed = Capecitabine
P Female Sex (vs Male)
Q Deprivation quintile (SIMD) (vs Q1); solid = Q2, dotted = Q3, long-dash = Q4, dashed = Q5
R Surgery-to-chemotherapy interval (*per* increase in interval by one day)

Figure C.11: Posterior probability distributions of the odds ratio for dose delay in adjuvant chemotherapy (SACT D), from univariable logistic regression models fitted to each variable. Vertical line at OR 1 (no effect). Facet key provides title and comparator for each variable

Table 6.18 provides detailed results of the univariable analysis.

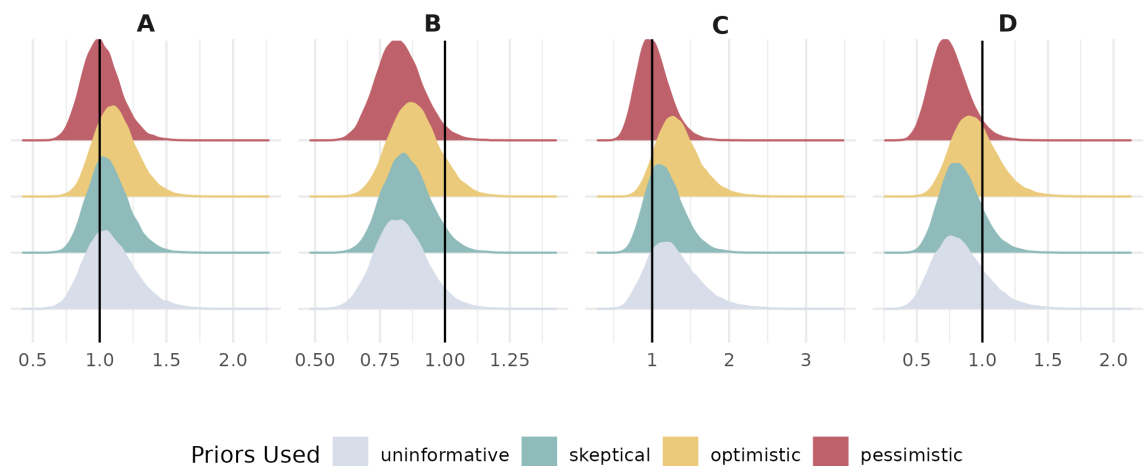
Table C.11: Multivariable Analysis Results - Summary of posterior probability distribution of the odds ratio for dose delay in adjuvant chemotherapy (SACT D), from multivariable logistic regression model using uninformative priors, for all other variables included in the model

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease	Percentage Of Largest Effect Explained
Emergency Admission <i>vs Elective admission</i>	0.97	(0.73-1.28)	58.86	26.46	28.67	44.87	44.87% chance meaningful reduction
FOLFOX	1.25	(0.92-1.69)	91.90	9.52	86.35	4.12	86.35% chance meaningful increase
5FU	0.55	(0.34-0.87)	99.56	0.64	0.25	99.11	99.11% chance meaningful reduction
Capecitabine <i>vs CAPOX</i>	1.06	(0.86-1.32)	71.58	30.76	54.43	14.80	54.43% chance meaningful increase

CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease

C.5.2 Model Validity And Sensitivity

Figure C.12 shows the sensitivity analysis comparing different prior distributions.



- A Elective: Organ Support (vs Elective: Monitoring)
 B Elective: Ward Level (vs Elective: Monitoring)
 C Emergency: Organ Support (vs Emergency: Monitoring)
 D Emergency: Ward Level (vs Emergency: Monitoring)

Figure C.12: Sensitivity Analysis - Comparisons of posterior probability distribution of the odds ratio for dose delay in adjuvant chemotherapy (SACT D), from multivariable logistic regression models using different prior probability distributions
 Facet key provided for variable names and comparators

Table C.12 provides detailed results of the validity checks.

Table C.12: Validity Checks - Dose Delay in Adjuvant Chemotherapy (SACT D)

	Rhat	Bulk ESS	Tail ESS
Intercept	1.000094	69250.22	32631.06
cohortWard Level	1.000380	63735.28	31920.60
cohortOrgan Support	1.000039	63519.08	32714.26
EmergencyTRUE	1.000050	59464.93	34013.26
regime_catFOLFOX	1.000153	68799.31	31083.20
regime_cat5FU	1.000389	70009.13	30413.88
regime_catCapecitabine	1.000292	70141.93	32963.18
cohortWard Level:EmergencyTRUE	1.000123	59714.93	33948.57
cohortOrgan Support:EmergencyTRUE	1.000076	60458.08	33931.60

Figure C.13 shows the posterior predictive check for the model.

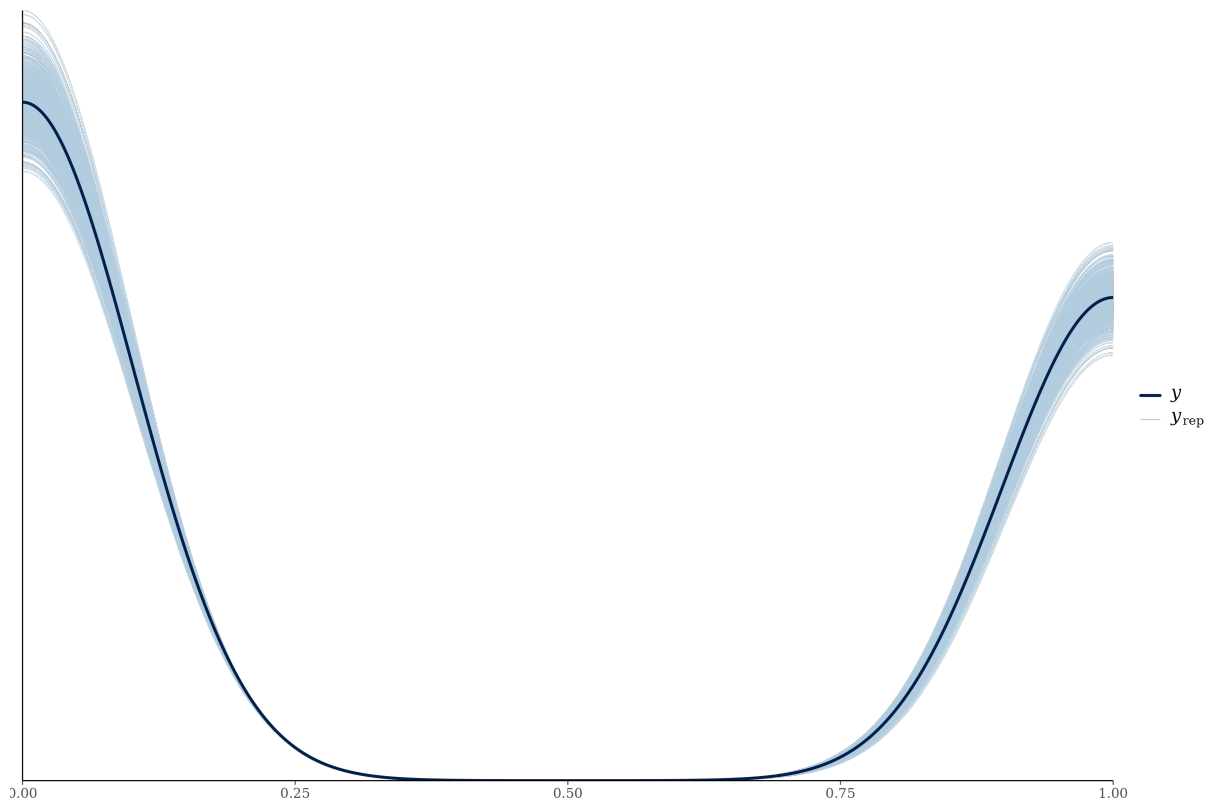


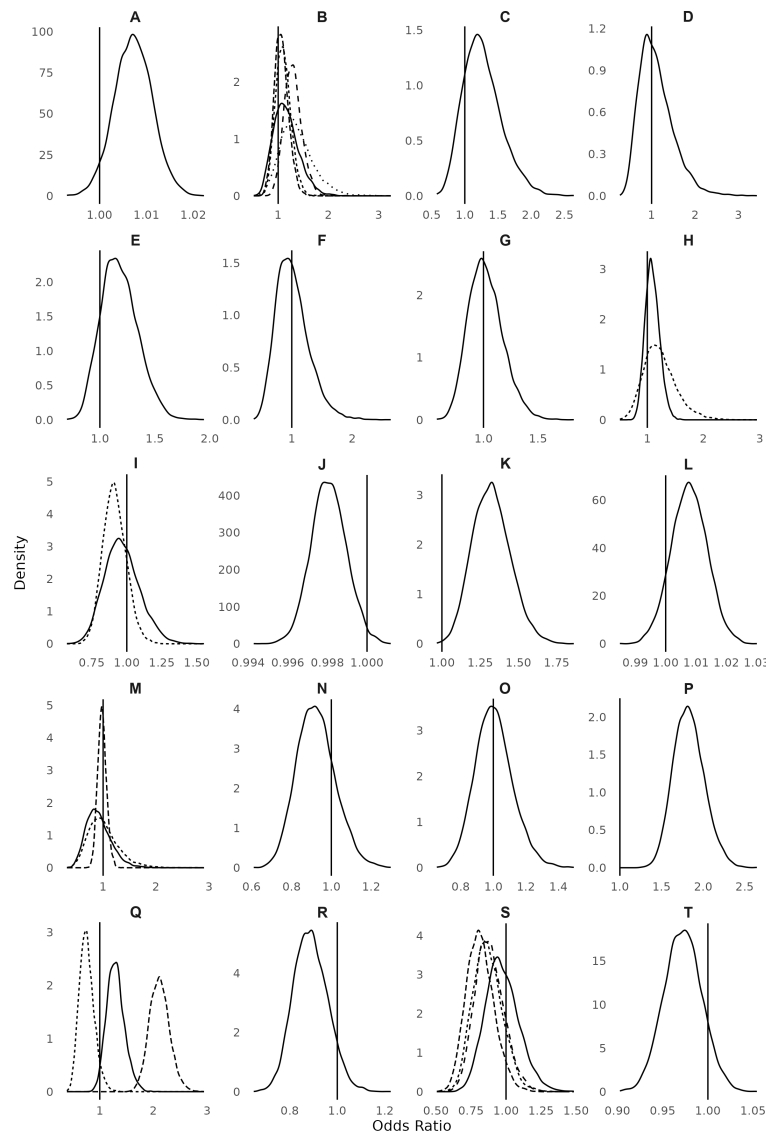
Figure C.13: Posterior predictive check of multivariable model (SACT D) using uninformative priors

Dark blue line (y) represents observed data, light-blue lines (y_{rep}) represent predictions sampled from posterior probability distributions

C.6 Two C

C.6.1 Variable Selection - Univariable Analysis

Figure C.14 shows the results of univariable analysis for factors associated with course duration (weeks) of adjuvant chemotherapy.



- A** Age at diagnosis (*per* increase in age by one year)
B Age group (vs Age under 40); solid = Age 40-49, dashed = Age 50-59, dotted = Age 60-69, dotdash = Age 70-79, longdash = Age 80+
C Cardiac comorbidity (vs No cardiac comorbidity)
D Dementia (vs No dementia)
E Diabetes (vs No diabetes)
F Renal comorbidity (vs No renal comorbidity)
G Respiratory comorbidity (vs No respiratory comorbidity)
H Charlson comorbidity count (vs Zero additional comorbidity); solid = One additional, dotted = Two plus
I Support in Hospital (vs Monitoring); solid = Organ Support, dotted = Ward Level
J Diagnosis-to-admission interval (*per* increase in interval by one day)
K Anatomic Stage High Risk II (vs Stage III)
L Duration of hospital stay (*per* increase in admission duration by one day)
M Method of first detection (vs Clinical Presentation); dashed = Other/Not Known, solid = Screening, dotted = Incidental Finding
N Non-elective admission (vs Elective admission)
O Multiple operations (vs Single operation)
P Diagnosis pre-SCOT trial results (vs post trial publication)
Q Regime (vs CAPOX); solid = FOLFOX, dotted = 5FU, dashed = Capecitabine
R Sex (vs Male)
S Deprivation quintile (SIMD) (vs Q1); solid = Q2, dotted = Q3, long-dash = Q4, dashed = Q5
T Surgery-to-chemotherapy interval (*per* increase in interval by one day)

Figure C.14: Posterior probability distributions of the odds ratio for course duration of adjuvant chemotherapy (SACT E), from univariable logistic regression models fitted to each variable. Vertical line at OR 1 (no effect). Facet key provides title and comparator for each variable

Table 6.22 provides detailed results of the univariable analysis.

Table C.13: Multivariable Analysis Results - Summary of posterior probability distribution of the odds ratio for course duration of adjuvant chemotherapy (SACT E), from multivariable logistic regression model using uninformative priors, for all other variables included in the model

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease
Age (years)	1.00	(0.99-1.01)	76.71	100.00	0	0
<i>per increase in age by one year</i>						
CRC Stage-HRB	1.03	(0.83-1.28)	60.68	34.01	43.07	22.92
<i>vs Stage III</i>						
Emergency	0.93	(0.72-1.19)	72.63	26.39	16.11	57.5
<i>vs Elective admission</i>						
Pre-SCOT Trial	2.07	(1.67-2.54)	100.00	0.00	100	0
<i>vs post trial publication</i>						
FOLFOX	1.38	(1.05-1.8)	99.04	2.01	97.66	0.33
5FU	0.67	(0.45-1.01)	97.38	2.43	1.73	95.84
Capecitabine	2.67	(2.15-3.32)	100.00	0.00	100	0
<i>vs CAPOX</i>						
SIMD Quintile 2	0.96	(0.75-1.25)	61.06	28.53	25.71	45.79
SIMD Quintile 3	0.86	(0.67-1.1)	88.93	15.39	5.37	79.24
SIMD Quintile 4	0.79	(0.62-1.01)	96.88	6.02	1.25	92.73
SIMD Quintile 5	0.85	(0.66-1.08)	90.95	13.55	4.2	82.25
<i>vs SIMD Quintile 1</i>						
<i>CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease</i>						

C.6.2 Model Validity And Sensitivity

Figure C.15 shows the sensitivity analysis comparing different prior distributions.

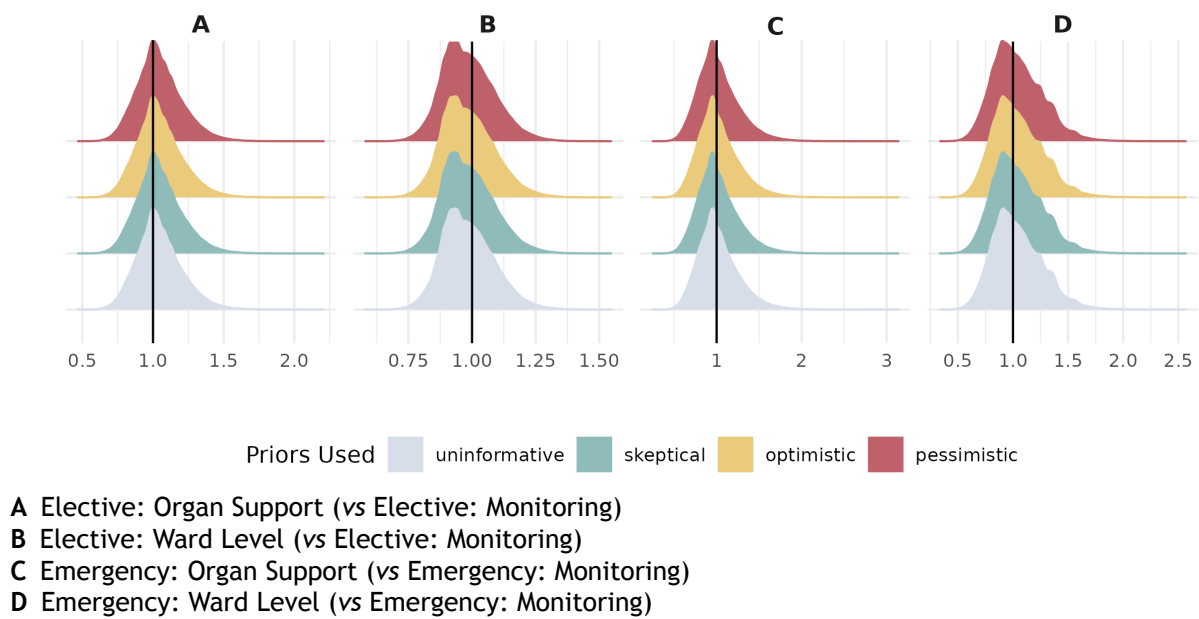


Figure C.15: Sensitivity Analysis - Comparisons of posterior probability distribution of the odds ratio for course duration of adjuvant chemotherapy (SACT E), from multivariable logistic regression models using different prior probability distributions
Facet key provided for variable names and comparators

Table C.14 provides detailed results of the validity checks.

Table C.14: Validity checks - Number of Weeks of Adjuvant Chemotherapy (SACT E)

	Rhat	Bulk ESS	Tail ESS
Intercept[1]	1.177410	36.63865	17.06902
Intercept[2]	1.062115	93.61995	178.98730
Intercept[3]	1.050801	113.63985	516.59386
Intercept[4]	1.053072	108.92693	446.21492
Intercept[5]	1.056501	102.55168	324.53248
Intercept[6]	1.068474	85.33903	164.09517
Intercept[7]	1.070900	82.47613	151.98354
Intercept[8]	1.091698	64.79505	83.59847
Intercept[9]	1.074748	78.04803	158.35020
Intercept[10]	1.041564	137.83056	4524.50884
Intercept[11]	1.028368	203.60211	44349.20705
Intercept[12]	1.014975	388.86405	76871.28233
cohortWard Level	1.025064	226.42494	100859.57253
cohortOrgan Support	1.036344	22096.67552	61209.74465
EmergencyTRUE	1.022066	1540.17927	95925.25396
Age (years)	1.044532	131.11930	549.17750
Dx To Admn (days)	1.024828	309.97962	1339.09472
CRC Stage- HRB	1.021841	266.57807	120714.55836
Hospital LOS (Days)	1.008360	957.91772	49436.41841
pre_scot	1.016045	586.82776	88712.89985
regime_catFOLFOX	1.011878	3319.56302	115783.09015
regime_cat5FU	1.016759	1606.26099	63372.18457
regime_catCapecitabine	1.022557	1799.36371	92346.63191
Sex	1.094325	62.01389	103.79397
SIMD Quintile 2	1.024837	579.75024	50294.31244
SIMD Quintile 3	1.024777	232.39392	84931.29748
SIMD Quintile 4	1.089334	65.34202	669.19775
SIMD Quintile 5	1.029794	8767.76650	86050.93074
cohortWard LevelEmergencyTRUE	1.030149	187.67430	467.95469
cohortOrgan SupportEmergencyTRUE	1.034222	11587.48374	96787.77730

Figure C.16 shows the posterior predictive check for the model.

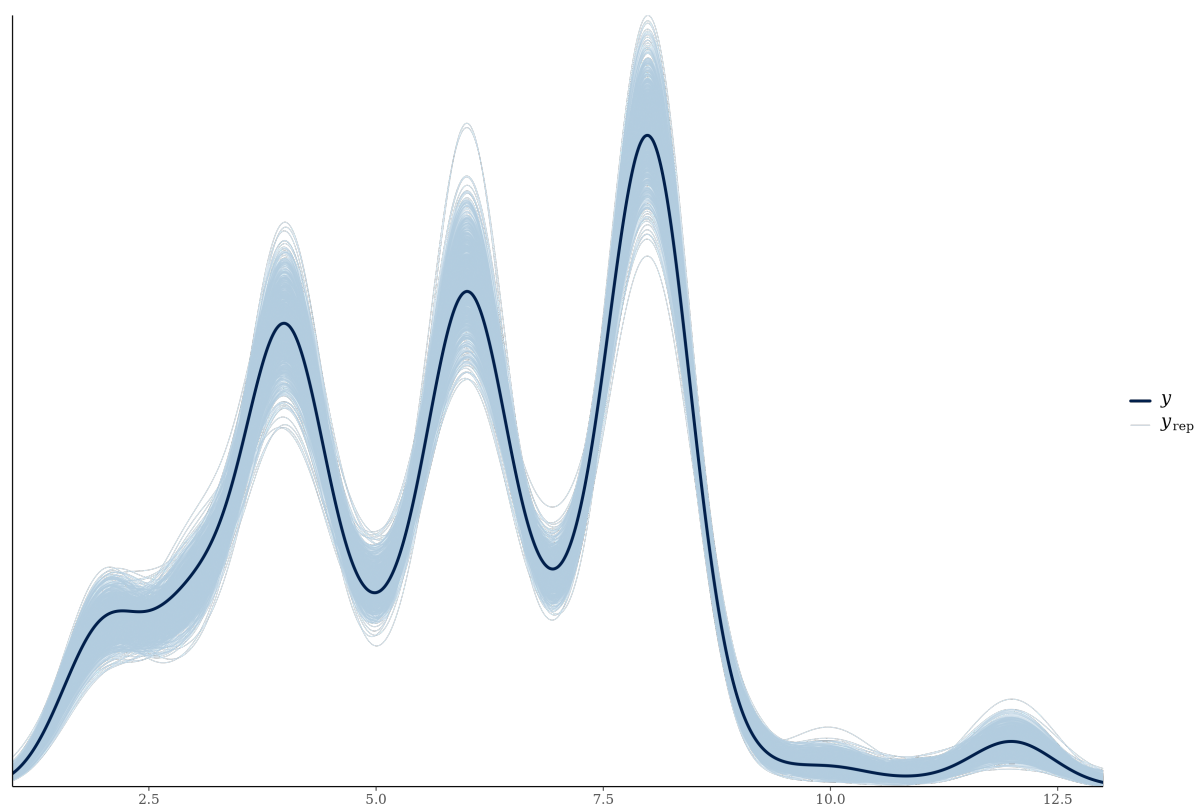


Figure C.16: Posterior predictive check of multivariable model (SACT E) using uninformative priors

Dark blue line (y) represents observed data, light-blue lines (y_{rep}) represent predictions sampled from posterior probability distributions

D Survival

D.1 Overall Survival Including Post Operative Mortality

Table D.15: Estimated survivorship across all patients with colorectal cancer

Characteristic	Overall N = 43,773	Elective			Emergency		
		Ward Level N = 10,189	Monitoring N = 14,756	Organ Support N = 2,687	Ward Level N = 11,185	Monitoring N = 3,589	Organ Support N = 1,367
Hospital Survivorship Survived	38,385 (88%)	9,606 (94%)	14,524 (98%)	2,338 (87%)	7,836 (70%)	3,156 (88%)	925 (68%)
Kaplan 5 Year Survivorship KM Estimate	52%	54%	70%	61%	23%	40%	34%
Total 5 Year Survivorship (Inc. Hospital Mortality) KM Estimate	46%	51%	69%	53%	16%	35%	23%

D.2 Total Cohort Multivariable Analysis

Table D.16: Multivariable Analysis Results - Summary of posterior probability distribution of the hazard ratio for five-year overall survival (total cohort), from multivariable survival model using uninformative priors, for all other variables included in the model

Variable	Median	CrI	PD (%)	ROPE (%)	Increase	Decrease	Percentage Of Largest Effect
Age <40	0.83	(0.76 - 0.9)	100.00	0.77	0.00	99.23	99.23% chance meaningful reduction
Age 40-49	0.66	(0.57 - 0.77)	100.00	0.00	0.00	100.00	100% chance meaningful reduction
Age 50-59	0.91	(0.86 - 0.96)	99.95	30.93	0.00	69.07	69.07% chance meaningful reduction
Age 70-79	1.21	(1.16 - 1.26)	100.00	0.00	100.00	0.00	100% chance meaningful increase
Age ≥ 80	1.36	(1.3 - 1.43)	100.00	0.00	100.00	0.00	100% chance meaningful increase
<i>vs age 60-69</i>							
Surgical Resection - False	1.31	(1.24 - 1.38)	100.00	0.00	100.00	0.00	100% chance meaningful increase
<i>vs curative resection in admission</i>							
Comorbidity Count: 1	1.12	(1.07 - 1.16)	100.00	11.60	88.40	0.00	88.4% chance meaningful increase
Comorbidity Count ≥ 2	1.21	(1.15 - 1.28)	100.00	0.01	99.99	0.00	99.99% chance meaningful increase
<i>vs zero additional comorbidity</i>							
Admission Duration 2-3 Weeks	1.10	(1.06 - 1.15)	100.00	30.90	69.11	0.00	69.11% chance meaningful increase
Admission Duration 3-4 Weeks	1.34	(1.28 - 1.41)	100.00	0.00	100.00	0.00	100% chance meaningful increase
Admission Duration ≥ 4 Weeks	1.52	(1.45 - 1.6)	100.00	0.00	100.00	0.00	100% chance meaningful increase
<i>vs admission duration <1 week</i>							
Diagnosis Incidental Finding	0.93	(0.85 - 1.02)	93.34	62.81	0.03	37.16	37.16% chance meaningful reduction
Diagnosis Other/Not Known	0.99	(0.86 - 1.14)	53.62	75.03	9.72	15.25	15.25% chance meaningful reduction
Diagnosis Screening Examination	0.59	(0.55 - 0.63)	100.00	0.00	0.00	100.00	100% chance meaningful reduction
<i>vs diagnosis following clinical presentation</i>							
Emergency Admission	1.73	(1.63 - 1.83)	100.00	0.00	100.00	0.00	100% chance meaningful increase
<i>vs Elective admission</i>							
Operations Multiple	0.98	(0.93 - 1.04)	70.61	98.34	0.04	1.62	1.62% chance meaningful reduction
Operations None	1.26	(1.19 - 1.33)	100.00	0.00	100.00	0.00	100% chance meaningful increase
<i>vs one operation</i>							
SIMD Quintile 2	0.97	(0.92 - 1.02)	90.66	98.51	0.00	1.49	1.49% chance meaningful reduction
SIMD Quintile 3	0.94	(0.9 - 0.98)	99.57	80.40	0.00	19.60	19.6% chance meaningful reduction
SIMD Quintile 4	0.99	(0.94 - 1.03)	72.56	99.79	0.00	0.21	0.21% chance meaningful reduction
SIMD Quintile 5	0.97	(0.92 - 1.01)	92.00	97.57	0.00	2.43	2.43% chance meaningful reduction
<i>vs SIMD Quintile 1</i>							
Surgical Admission	0.90	(0.86 - 0.94)	100.00	11.76	0.00	88.24	88.24% chance meaningful reduction
<i>vs medical admission</i>							
Therapy Objectives Non Curative / Palliative	6.12	(5.89 - 6.35)	100.00	0.00	100.00	0.00	100% chance meaningful increase
Therapy Objectives Not Known	2.01	(1.89 - 2.13)	100.00	0.00	100.00	0.00	100% chance meaningful increase
<i>vs curative intent</i>							

CrI - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease

Variable	$\hat{R}$	Bulk ESS	Tail ESS
Intercept	~1.00	27152.74	27344.584
cohortNoCriticalCare	~1.00	24294.62	10149.973
cohortCritCareMOrganSupport	~1.00	33467.95	29542.177
non_elective_admnEmergency	~1.00	24514.83	28169.029
Age <40	~1.00	39888.04	29003.461
Age 40-49	~1.00	45948.98	26895.474
Age 50-59	~1.00	34284.48	29859.626
Age 70-79	~1.00	28449.74	29799.990
Age ≥ 80	~1.00	30516.31	28334.826
Surgical Resection - False	~1.00	36778.24	26120.448
Comorbidity Count: 1	~1.00	41208.69	29303.280
Comorbidity Count ≥ 2	~1.00	43800.04	29131.311
Admission Duration 2 - 3 Weeks	~1.00	32500.60	30557.336
Admission Duration 3 - 4 Weeks	~1.00	31851.36	27567.999
Admission Duration ≥ 4 Weeks	~1.00	32906.51	30483.585
Diagnosis Screening Examination	~1.00	46386.25	29303.505
Diagnosis Incidental Finding	~1.00	48606.06	27748.203
Diagnosis Other/NotKnown	~1.00	15525.11	5892.654
Operations None	~1.00	33048.90	28013.741
Operations Multiple	~1.00	37280.46	20000.167
SIMD Quintile 2	~1.00	23659.61	25202.446
SIMD Quintile 3	~1.00	27080.17	27090.664
SIMD Quintile 4	~1.00	23840.04	10505.658
SIMD Quintile 5	~1.00	23844.82	23929.202
Surgical Admission	~1.00	41330.07	23540.059
Therapy Objectives Non Curative / Palliative	~1.00	34319.43	28839.724
Therapy Objectives Not Known	~1.00	40400.74	23165.707
cohortNoCriticalCare:non_elective_admnEmergency	~1.00	20913.11	7661.781
cohortCritCareMOrganSupport:non_elective_admnEmergency	~1.00	29940.78	29398.678
stend_1	~1.00	22452.78	26481.356

Table D.17: Multivariable Regression Summary - Measures of model validity

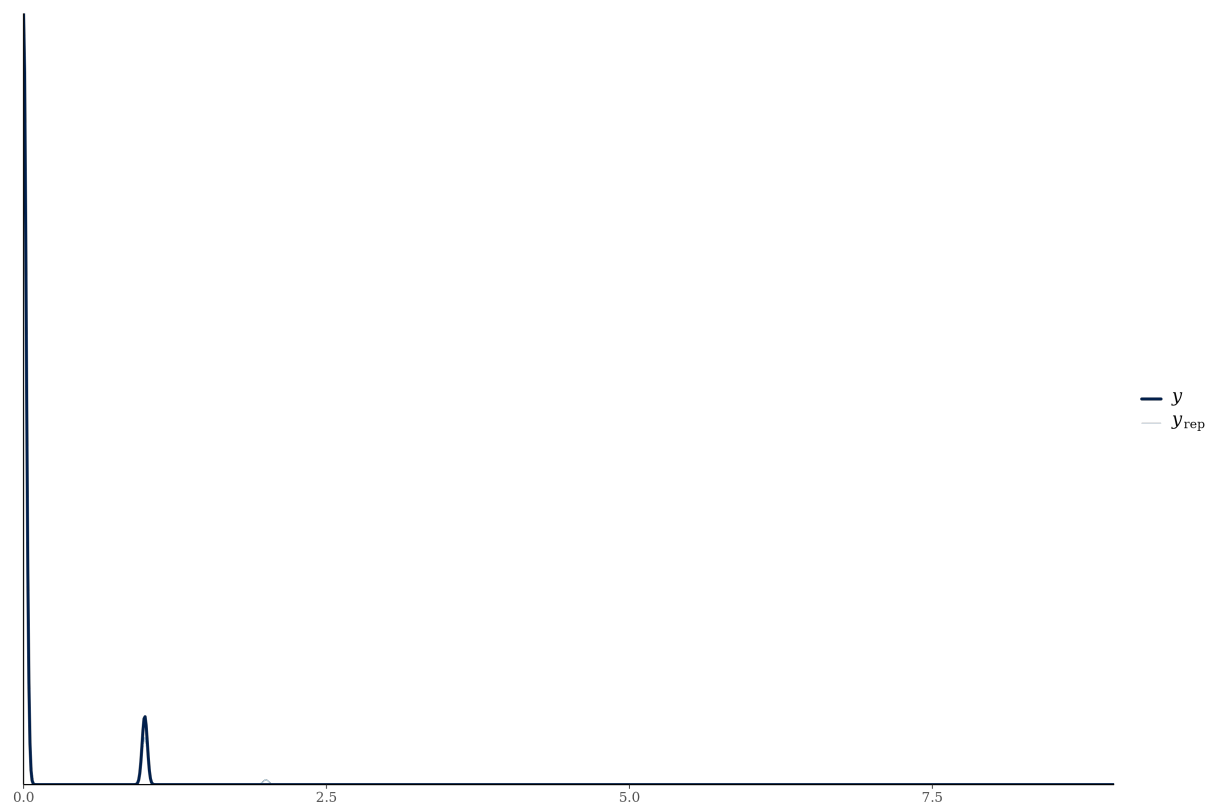


Figure D.17: Posterior predictive check of multivariable model (Survival Total) using uninformative priors

Dark blue line (y) represents observed data, light-blue lines (y_{rep}) represent predictions sampled from posterior probability distributions

D.3 SACT Cohort Multivariable Analysis

Table D.18: Multivariable Analysis Results - Summary of posterior probability distribution of the hazard ratio for five-year overall survival among patients who received adjuvant SACT, from multivariable survival model using uninformative priors, for all other variables included in the model

Variable	Median	Crl	PD (%)	ROPE (%)	Increase	Decrease	Percentage Of Largest Effect
Age < 40	0.87	(0.54 - 1.36)	72.72	43.15	10.98	45.87	45.87% chance meaningful reduction
Age 40 - 49	0.81	(0.47 - 1.35)	78.63	33.59	8.98	57.43	57.43% chance meaningful reduction
Age 50 - 59	0.88	(0.64 - 1.22)	76.96	53.66	5.70	40.64	40.64% chance meaningful reduction
Age 70 - 79	1.65	(1.22 - 2.23)	99.91	1.03	98.97	0.00	98.97% chance meaningful increase
Age ≥ 80	1.21	(0.63 - 2.27)	71.38	30.09	55.68	14.22	55.68% chance meaningful increase
<i>vs age 60-69</i>							
Stage High-Risk B	0.80	(0.55 - 1.14)	88.86	35.34	2.18	62.48	62.48% chance meaningful reduction
<i>vs Anatomic Stage III</i>							
Delay During SACT	1.64	(1.26 - 2.15)	99.99	0.39	99.61	0.00	99.61% chance meaningful increase
<i>vs no delay during chemotherapy</i>							
Renal Disease	1.14	(0.62 - 2.04)	67.07	33.87	49.42	16.72	49.42% chance meaningful increase
<i>vs no renal comorbidity</i>							
Delay Starting SACT	0.94	(0.69 - 1.26)	66.25	65.18	8.95	25.86	25.86% chance meaningful reduction
<i>vs no delay commencing chemotherapy</i>							
Admission 2 - 3 weeks	1.03	(0.76 - 1.38)	57.00	66.80	22.76	10.45	22.76% chance meaningful increase
Admission 3 - 4 weeks	0.93	(0.61 - 1.37)	64.70	51.80	14.17	34.03	34.03% chance meaningful reduction
Admission ≥ 4 weeks	1.33	(0.86 - 2.05)	89.88	23.42	74.36	2.22	74.36% chance meaningful increase
<i>vs admission duration <1 week</i>							
Emergency Admission	1.81	(1.28 - 2.54)	99.95	0.50	99.50	0.00	99.5% chance meaningful increase
<i>vs Elective admission</i>							
Screening Diagnosis	0.86	(0.63 - 1.16)	83.91	49.33	2.88	47.80	47.8% chance meaningful reduction
<i>vs non-screening diagnosis</i>							
Female Sex	1.08	(0.83 - 1.41)	70.67	65.00	30.91	4.08	30.91% chance meaningful increase
<i>vs male</i>							

Crl - 95% Credible Interval, PD - Probability of Direction, Increase/Decrease - Percentage of clinically meaningful increase/decrease

Variable	$\hat{R}$	Bulk ESS	Tail ESS
Intercept	~1.01	42721.77	30322.62
Ward Level	~1.01	45905.38	29638.24
Organ Support	~1.01	44802.80	30217.74
Emergency Admission	~1.01	39168.54	31862.42
Age ~ 40	~1.01	50241.70	30110.99
Age 40 - 49	~1.01	52529.43	29451.32
Age 50 - 59	~1.01	43765.67	28520.95
Age 70 79	~1.01	44022.87	30630.92
Age ≥ 80	~1.01	56932.24	29299.75
Stage High-Risk B	~1.01	50017.19	28165.67
Delay During SACT	~1.01	54570.84	29810.21
Renal Disease	~1.01	52460.90	28232.11
Delay Starting SACT	~1.01	50310.38	30013.65
Admission 2 - 3 weeks	~1.01	40410.99	28492.20
Admission 3 - 4 weeks	~1.01	41070.40	29022.35
Admission $\geq 4weeks$	~1.01	39202.56	30346.81
Screening Diagnosis	~1.01	52738.81	29136.04
Female Sex	~1.01	51865.72	29254.66
cohortNoCriticalCare:non_elective_admnEmergency	~1.01	37719.74	28954.39
cohortCritCareMOrganSupport:non_elective_admnEmergency	~1.01	44161.37	31177.35
stend_1	~1.01	48610.28	28061.37

Table D.19: Multivariable Regression Summary - Measures of Model Validity - SACT

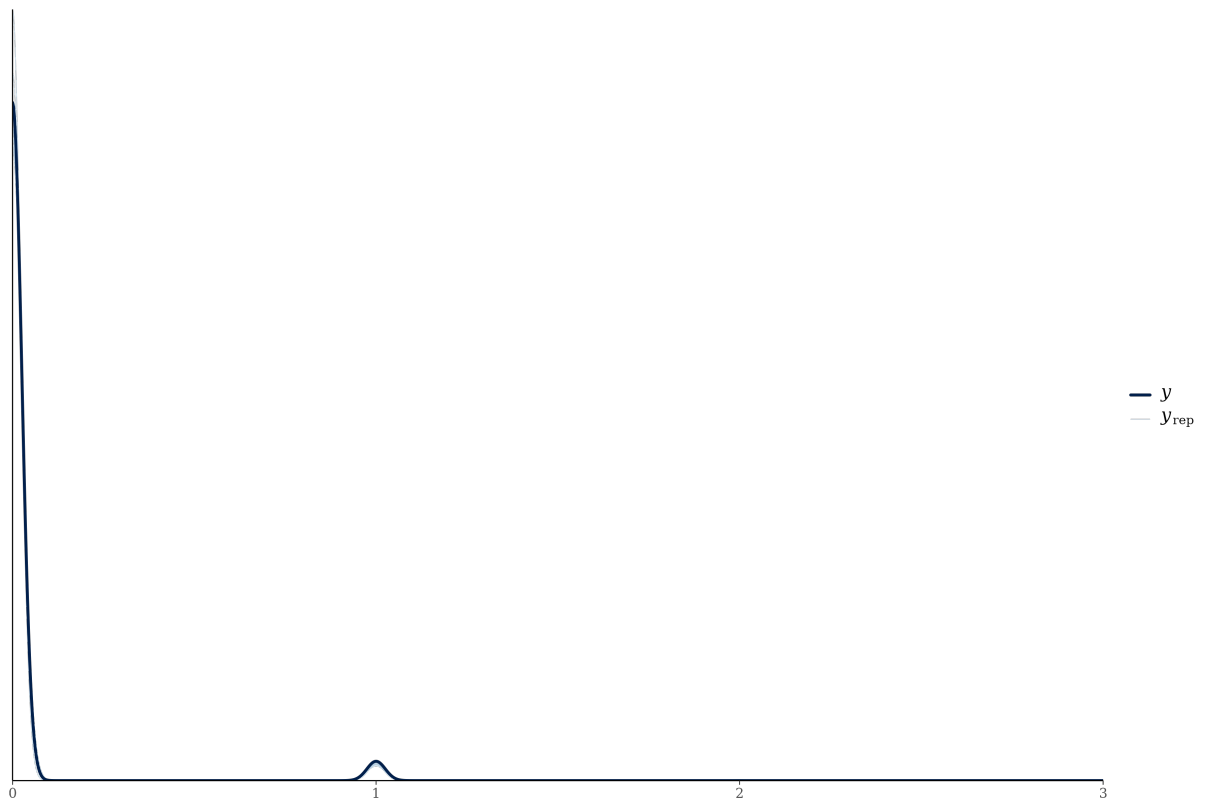


Figure D.18: Posterior predictive check of multivariable model (Survival SACT-eligible) using uninformative priors

Dark blue line (y) represents observed data, light-blue lines (y_{rep}) represent predictions sampled from posterior probability distributions

E Critical Illness

E.1 Kaplan-Meier Survival Including In-Hospital Mortality

The following Kaplan-Meier curves provide context for the discharge-conditional survival comparator presented in Section 8.4.3. They show long-term survival for the SACT-eligible cohort *including* patients who died during the index hospital admission, both as a single population curve and stratified by days of organ support.

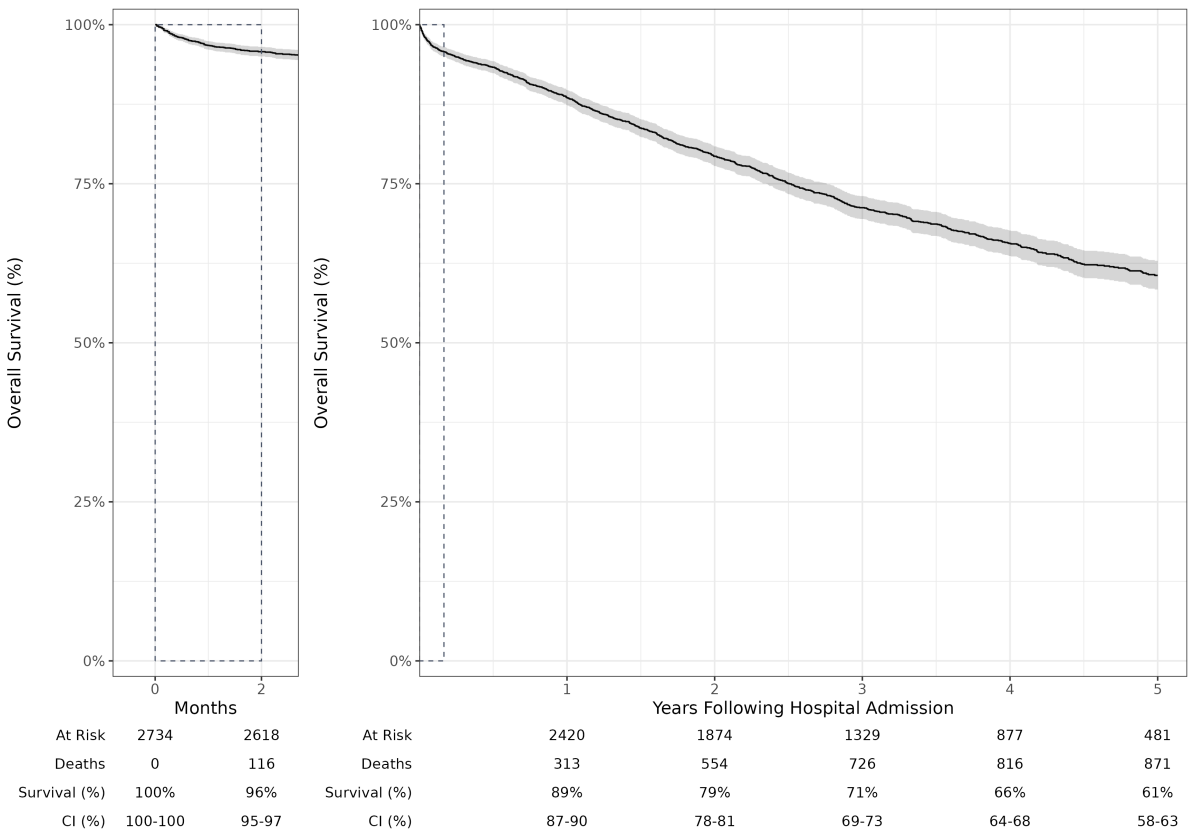


Figure E.19: Kaplan-Meier long-term survival for the SACT-eligible cohort admitted to critical care, single population curve, including in-hospital mortality.

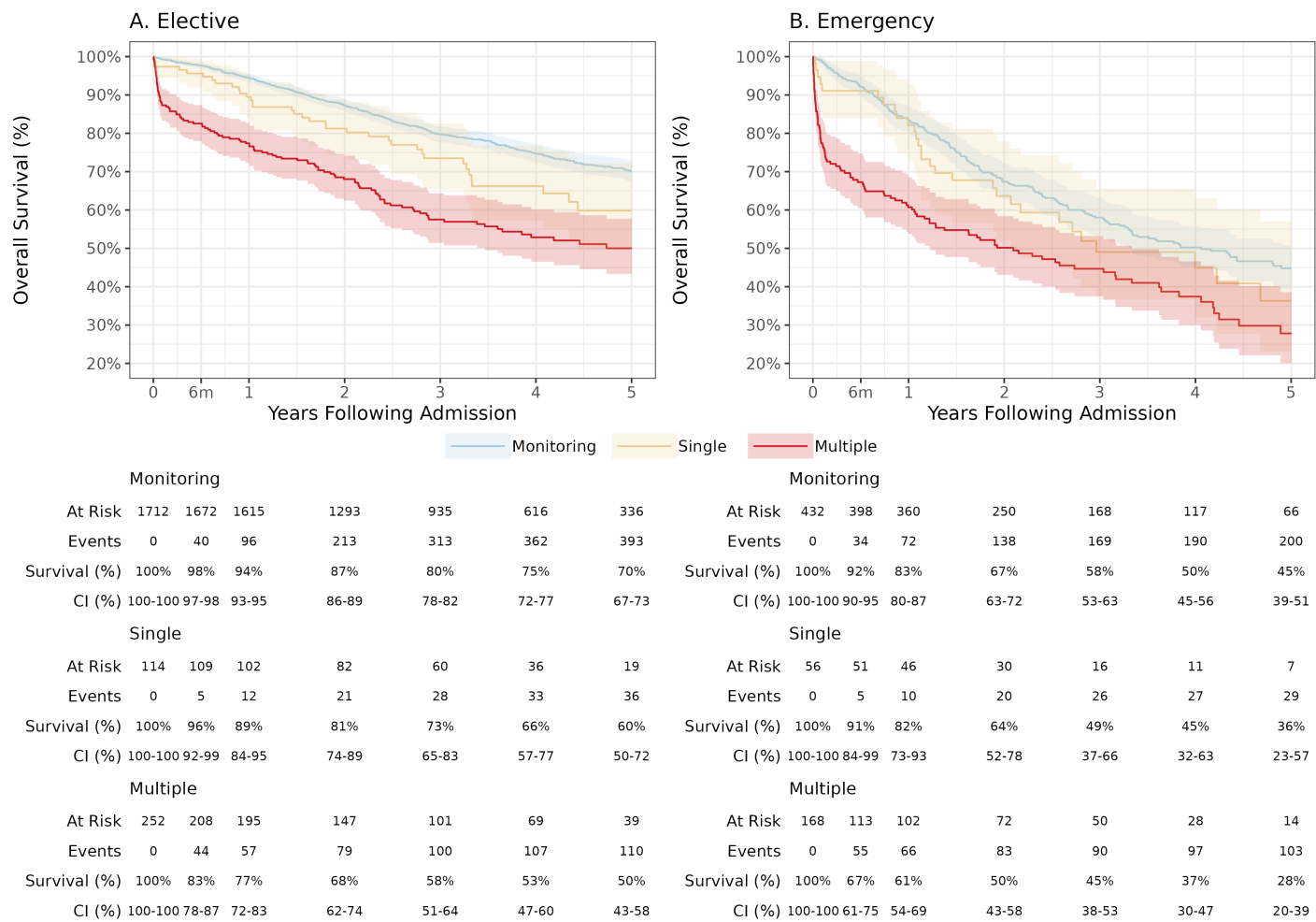
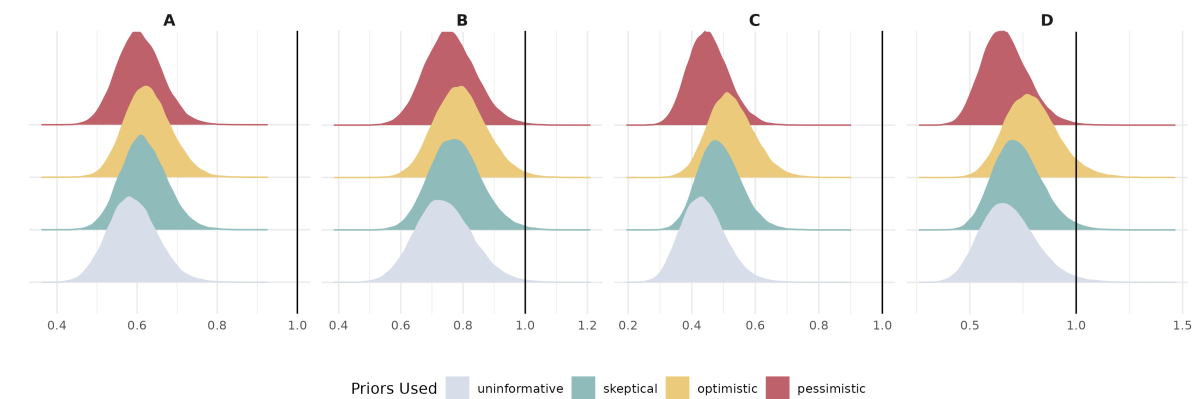


Figure E.20: Kaplan-Meier long-term survival for the SACT-eligible cohort, stratified by days of organ support, including in-hospital mortality.

Table E.20: Multivariable Analysis Results - Summary of posterior probability distribution of the hazard ratio for receipt of adjuvant SACT, from multivariable time-to-event model using uninformative priors, for all other variables included in the model

[illegible]

E.2 Sensitivity Analysis



- A Elective: Multiple days organ support (vs Monitoring in Critical Care)
- B Elective: Single day organ support (vs Monitoring in Critical Care)
- C Emergency: Multiple days organ support (vs Monitoring in Critical Care)
- D Emergency: Single day organ support (vs Monitoring in Critical Care)

Figure E.21: Sensitivity Analysis - Comparisons of posterior probability distribution of the hazard ratio for receipt of adjuvant SACT, from multivariable time-to-event models using different prior probability distributions
Facet key provided for variable names and comparators

Table E.21: Sensitivity Analysis - Summary of comparisons of posterior probability distribution of the hazard ratio for receipt of adjuvant SACT, from models using different prior probability distributions

variable	res_uninf	res_skep	uninf_skep	res_opt	uninf_opt	res_pess	uninf_pess
elec_multiple	0.59 (0.48 - 0.71)	0.61 (0.51 - 0.73)	-0.03 (-0.19 - 0.14)	0.62 (0.52 - 0.74)	-0.04 (-0.2 - 0.13)	0.6 (0.5 - 0.72)	-0.02 (-0.18 - 0.14)
elec_single	0.74 (0.57 - 0.93)	0.77 (0.63 - 0.95)	-0.04 (-0.27 - 0.2)	0.79 (0.64 - 0.96)	-0.05 (-0.29 - 0.19)	0.76 (0.61 - 0.93)	-0.02 (-0.26 - 0.22)
emerg_multiple	0.43 (0.31 - 0.59)	0.48 (0.37 - 0.63)	-0.05 (-0.24 - 0.14)	0.52 (0.4 - 0.67)	-0.09 (-0.28 - 0.11)	0.45 (0.34 - 0.59)	-0.02 (-0.2 - 0.17)
emerg_single	0.67 (0.46 - 0.96)	0.72 (0.53 - 0.97)	-0.05 (-0.37 - 0.3)	0.78 (0.57 - 1.05)	-0.11 (-0.45 - 0.25)	0.66 (0.48 - 0.9)	0.01 (-0.3 - 0.36)

E.3 Receipt of Adjuvant SACT: Model Validity and Posterior Predictive Check

Table E.22: Model validity check - adjuvant SACT receipt.

	Rhat	Bulk_ESS	Tail_ESS
Intercept	1.000112	30356.19	29596.67
days_organ_supportSingle	1.000071	43849.88	30122.30
days_organ_supportMultiple	1.000045	42110.22	30303.47
nature_admnEmergency	1.000138	44310.98	32323.71
AGE_GROUP40M49	1.000206	33149.66	29282.15
AGE_GROUP50M59	1.000498	18873.70	25065.02
AGE_GROUP60M69	1.000171	18136.87	23984.23
AGE_GROUP70M79	1.000453	18594.72	23673.43
AGE_GROUP80P	1.000011	27606.18	30073.06
DUKEHRB	1.000124	54223.65	29776.47
charlson_count1	1.000403	46969.92	29294.08
charlson_count2P	1.000288	49510.79	29166.29
c_dementiaTRUE	1.000193	51313.70	29029.27
simd_quintile2	1.000400	29341.94	31679.46
simd_quintile3	1.000290	27180.25	29888.14
simd_quintile4	1.000336	27366.60	30049.46
simd_quintile5	1.000350	26469.40	29721.06
sex	1.000258	51244.65	30578.01
days_organ_supportSingle:nature_admnEmergency	1.000154	40862.39	29403.32
days_organ_supportMultiple:nature_admnEmergency	1.000268	38177.52	31005.07
stend_1	1.000348	54077.74	29581.98

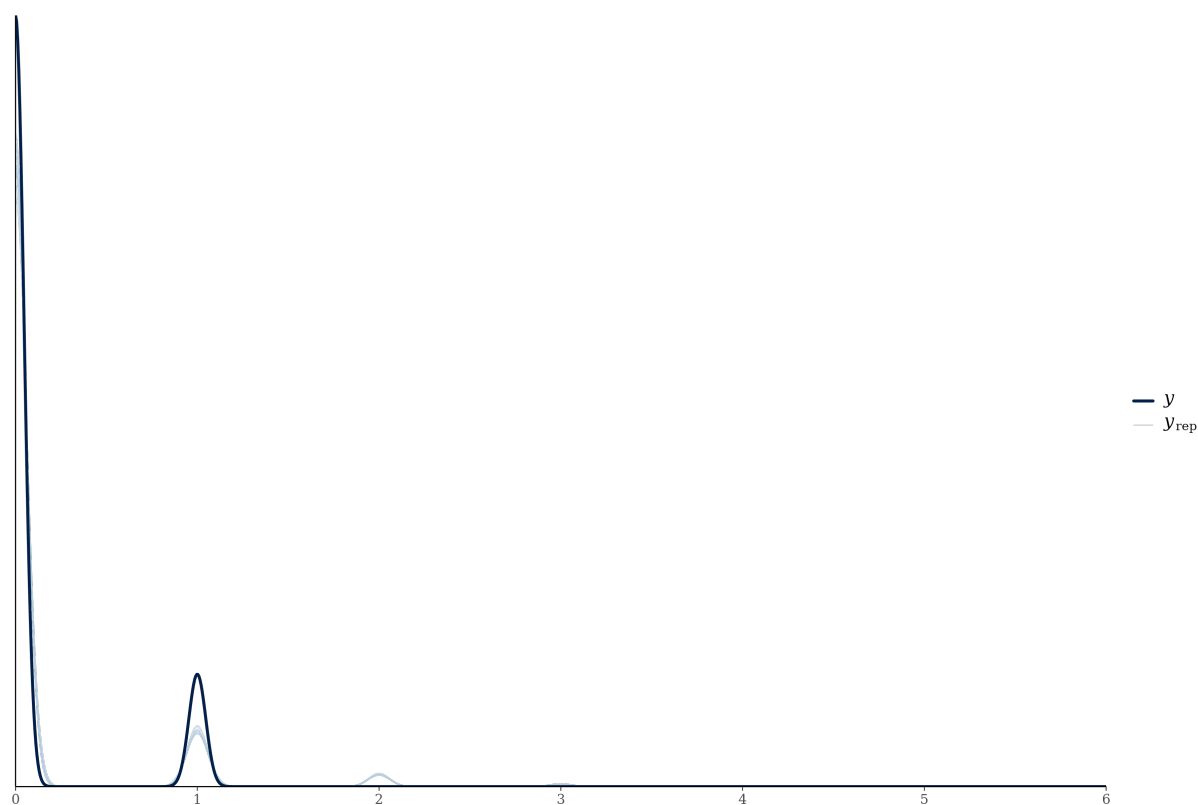


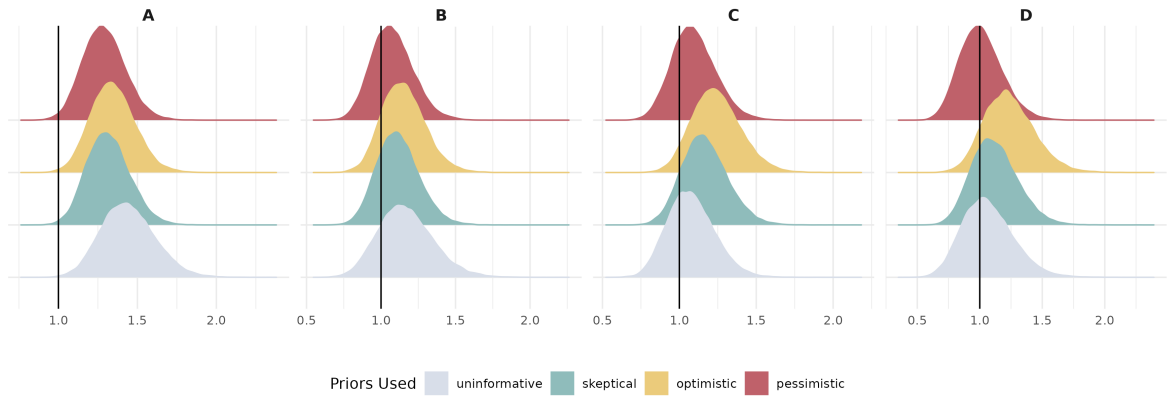
Figure E.22: Posterior predictive check of multivariable model (SACT receipt) using uninformative priors

Dark blue line (y) represents observed data, light-blue lines (y_{rep}) represent predictions sampled from posterior probability distributions

Table E.23: Multivariable Analysis Results - Summary of posterior probability distribution of the hazard ratio for five-year overall survival, from multivariable survival model using uninformative priors, for all other variables included in the model

[illegible]

E.4 Five-Year Survival: Model Validity and Posterior Predictive Check



- A** Elective: Multiple days organ support (vs Elective monitoring in critical care)
B Elective: Single day organ support (vs Elective monitoring in critical care)
C Emergency: Multiple days organ support (vs Emergency monitoring in critical care)
D Emergency: Single day organ support (vs Emergency monitoring in critical care)

Figure E.23: Sensitivity Analysis - Comparisons of posterior probability distribution of the hazard ratio for five-year overall survival, from multivariable survival models using different prior probability distributions
Facet key provided for variable names and comparators

Table E.24: Sensitivity Analysis - Summary of comparisons of posterior probability distribution of the hazard ratio for five-year overall survival, from multivariable survival models using different prior probability distributions
Facet key provided for variable names and comparators

variable	res_uninf	res_skep	uninf_skep	res_opt	uninf_opt	res_pess	uninf_pess
elec_multiple	1.43 (1.14 - 1.79)	1.31 (1.07 - 1.6)	0.12 (-0.29 - 0.56)	1.34 (1.09 - 1.63)	0.09 (-0.33 - 0.53)	1.28 (1.05 - 1.57)	0.15 (-0.26 - 0.58)
elec_single	1.15 (0.84 - 1.56)	1.11 (0.86 - 1.41)	0.05 (-0.39 - 0.52)	1.14 (0.89 - 1.46)	0.01 (-0.43 - 0.49)	1.07 (0.83 - 1.37)	0.09 (-0.35 - 0.55)
emerg_multiple	1.07 (0.81 - 1.4)	1.16 (0.9 - 1.48)	-0.09 (-0.5 - 0.32)	1.23 (0.96 - 1.57)	-0.16 (-0.59 - 0.26)	1.08 (0.84 - 1.39)	-0.02 (-0.43 - 0.39)
emerg_single	1.05 (0.71 - 1.5)	1.11 (0.8 - 1.51)	-0.06 (-0.58 - 0.49)	1.22 (0.88 - 1.66)	-0.17 (-0.72 - 0.39)	1 (0.71 - 1.38)	0.05 (-0.45 - 0.59)

Table E.25: Model validity check five-year all-cause mortality.

	Rhat	Bulk_ESS	Tail_ESS
Intercept	1.000296	30581.89	28051.82
days_organ_supportSingle	1.000040	46102.07	30040.30
days_organ_supportMultiple	1.000096	43117.10	27256.20
nature_admnEmergency	1.000266	44166.92	25015.50
AGE_GROUP40M49	1.000030	48314.19	28403.02
AGE_GROUP50M59	1.000183	29036.29	29948.53
AGE_GROUP60M69	1.000214	24657.36	28132.78
AGE_GROUP70M79	1.000178	23523.66	26452.85
AGE_GROUP80P	1.000217	23575.15	26352.02
DUKEHRB	1.000140	55697.75	28227.64
charlson_count1	1.000265	59220.58	27671.44
charlson_count2P	1.000381	53645.82	27558.32
c_dementiaTRUE	1.000439	53510.05	28123.23
simd_quintile2	1.000133	37690.35	31312.19
simd_quintile3	1.000038	37283.11	31286.13
simd_quintile4	1.000138	38100.96	31762.63
simd_quintile5	1.000132	37385.13	31165.38
sex	1.000439	56403.26	23170.09
days_organ_supportSingle:nature_admnEmergency	1.000008	43022.85	30749.38
days_organ_supportMultiple:nature_admnEmergency	1.000090	38686.80	23238.80
stend_1	1.000372	37309.36	29882.45

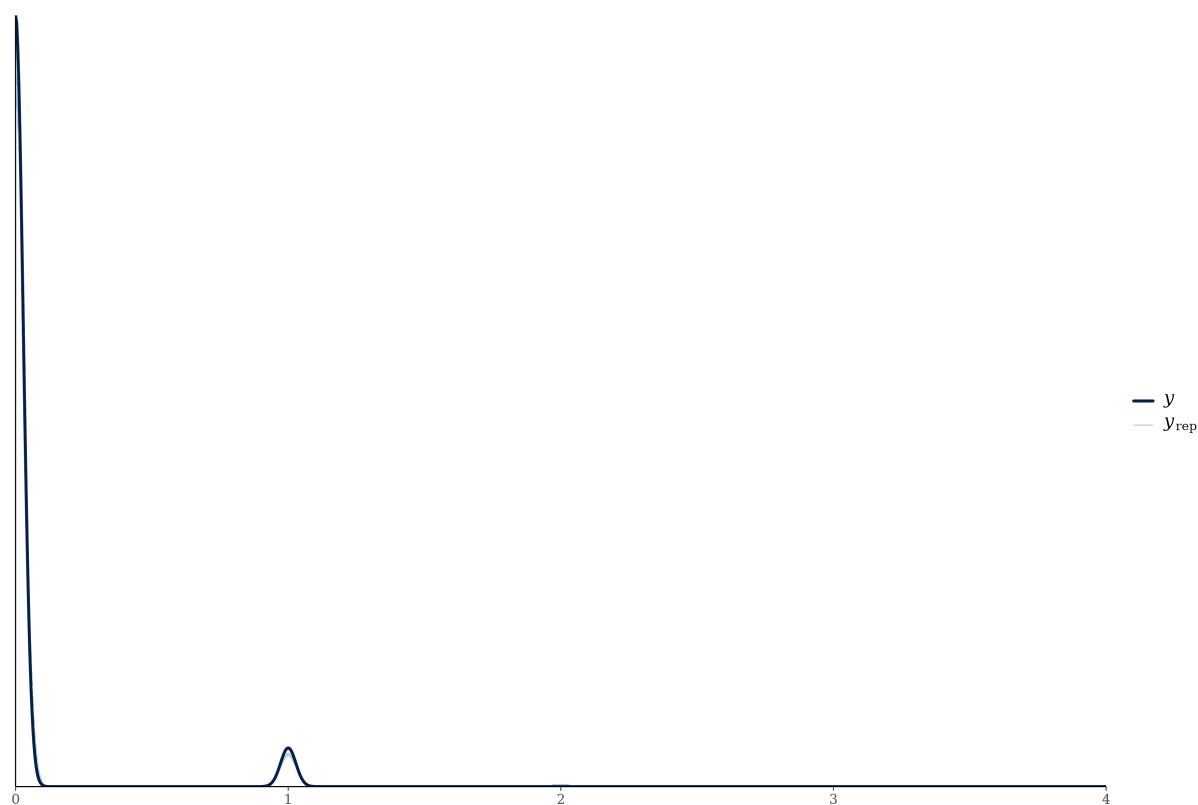


Figure E.24: Posterior predictive check of multivariable model (survival) using uninformative priors

Dark blue line (y) represents observed data, light-blue lines (y_{rep}) represent predictions sampled from posterior probability distributions

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