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Evaluation of clinical predictive factors on short-term outcomes for colon cancer surgery

By

Chee Mei Cheong

MBChB, MRCS, FRCS

A thesis submitted in fulfilment of the requirements for the degree of Medical Doctorate (MD), School of Medicine, Dentistry & Nursing, College of Medical, Veterinary & Life Sciences, University of Glasgow, December 2025

From research conducted in the Academic Unit of Surgery, Glasgow Royal Infirmary, Faculty of Medicine, University of Glasgow

Abstract

Colorectal cancer is the third most common cancer worldwide and the fourth most common cancer in the United Kingdom after lung, breast and prostate cancer. Surgical resection remains the primary curative treatment for most patients; however, it is associated with significant morbidity and mortality. The overall mortality following colorectal cancer resection ranges from 3% to 16%, while morbidity rates of up to 35% have been reported.

Postoperative complications may be defined as any deviation from the normal postoperative course and can be classified by severity, as described in the Clavien-Dindo classification, or by type (infective versus non-infective). Considerable efforts have been directed towards reducing postoperative complications, including the use of preoperative antibiotics, specialist surgical teams, standardised skin preparation protocols, and enhanced recovery programmes. Despite these interventions, postoperative complication rates remain substantial.

Surgical risk prediction tools such as P-POSSUM, SORT, NELA and the speciality-specific CR-POSSUM aim to estimate 30-day morbidity and mortality. However, most risk assessment models incorporate only a limited subset of patient and operative variables and therefore may not provide accurate, individual risk estimates. In addition, several prognostic tools demonstrate limited clinical utility because of their complexity and subjectivity. Other patient-specific factors that influence the risk of morbidity and mortality may not be adequately captured by existing models.

Although extensive literature has evaluated prognostic factors associated with long-term outcomes in colorectal cancer, overall survival is also strongly influenced by surgical quality and short-term postoperative outcomes. It is therefore important to examine the impact of preoperative predictive factors on postoperative complications in order to target interventions that may improve overall outcomes. Such efforts are particularly relevant given the substantial burden of postoperative morbidity and the increasing emphasis on standardised outcome measures for benchmarking surgical quality.

This thesis aims to identify clinical predictive factors associated with short-term outcomes following colon cancer surgery. In addition, it examines the relationship between the host- and tumour-related factors and postoperative infective complications and evaluates objective measures for predicting surgical site infection.

Chapter 1 provides an overview of colorectal cancer including epidemiology, carcinogenesis pathway, risk factors, clinical presentations, investigation and management of patients with colorectal cancer.

Chapter 2 reviews published literature in the form of systematic reviews reporting on short-term outcomes in colorectal cancer and presents an umbrella review identifying validated factors associated with short-term outcomes. The work contributed to a minimum dataset of mandatory, recommended and potential baseline variables for studies of patients undergoing colorectal cancer resection.

Chapter 3 examines the impact of preoperative carbohydrate loading on surgical site infection in a cohort of patients undergoing elective curative colon cancer surgery in a single tertiary unit, within an enhanced recovery setting. This reflects current practice and examines the association between carbohydrate loading, short-term outcomes and systemic inflammatory response. The results of the study showed that the routine use of preoperative carbohydrate loading does not lead to reduced surgical site infection.

Chapter 4 evaluates the association between previously validated predictive factors and short-term postoperative outcomes of a regional cohort of patients undergoing colon cancer surgery in the West of Scotland. The results showed that elevated body mass index, diabetes and open surgical approach were independently associated with infective complications and surgical site infections.

Chapter 5 examines the relationship between computed tomography-derived body composition, body mass index, diabetes and surgical site infections. Although computed tomography-derived body composition showed that greater subcutaneous fat index and visceral fat index were consistently associated with surgical site infection, BMI demonstrated the highest observed discriminatory

performance. These findings suggest that CT-derived measures of body composition did not demonstrate an apparent advantage over BMI in this cohort.

Chapter 6 examines the relationship between preoperative glycated haemoglobin and surgical site infection in patients undergoing elective colon cancer surgery. The results of the study demonstrated that preoperative glycated haemoglobin was independently associated with surgical site infections. Furthermore, the study also reported the presence of undiagnosed diabetes as well as the utility of preoperative glycated haemoglobin level along with body mass index to stratify the risk of developing surgical site infection.

Chapter 7 prospectively validates the findings regarding preoperative haemoglobin and surgical site infections. The results again support the finding that elevated preoperative glycated haemoglobin levels are associated with an increased risk of surgical site infections.

Finally, Chapter 8 provides the summary of the principal findings of this thesis, discusses their clinical implications, and outlines areas for future research.

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Author's Declaration

The work presented in this thesis was undertaken during a period of research between 2020 and 2024 in the University of Glasgow Academic Unit of Surgery at Glasgow Royal Infirmary. This was completed whilst working as a specialty registrar in General Surgery in the West of Scotland Deanery as well as a Robotic Colorectal Fellow in Northumbria Healthcare NHS Foundation Trust between 2024 and 2025.

I declare that the work presented in this thesis was undertaken by myself except where indicated below:

-The initial acquisition of basic regional data carried out prior to commencing my research by Mr David Mansouri and Mr Allan Golder

-Assistance with collection of basic local data used in Chapter 6 by Mr Tanvir Abbas and Mr Ross Dolan

-Assistance with analysis of CT scan images for body composition in the Managed Clinical Network Database provided by Mr Allan Golder

-The Managed Clinical Network Database used within this thesis was provided by the Public Benefit and Privacy Panel in Scotland

Publications

The work presented in this thesis resulted in the following published papers

Cheong CM, Golder AM, Horgan PG, Roxburgh CSD, McMillan DC. Relationship between preoperative glycated haemoglobin and surgical site infection in patients undergoing elective colon cancer surgery. Oncol Lett. 2022 Jul 5;24(3):296. doi: 10.3892/ol.2022.13416.

Cheong CM, Golder AM, Horgan PG, McMillan DC, Roxburgh CSD. Evaluation of clinical prognostic variables on short-term outcome for colorectal cancer surgery: An overview and minimum dataset. Cancer Treat Res Commun. 2022;31:100544. doi:10.1016/j.ctarc.2022.100544.

Presentations

The work presented in this thesis has resulted in the following presentations

Cheong CM, Golder AM, Horgan PG, Roxburgh CSD, McMillan DC**.** The relationship between routine preoperative clinicopathological factors and postoperative infective complications in patients undergoing elective potentially curative colon cancer resection**,** Surgical Research Society Annual Meeting, Nottingham, United Kingdom 2022 (Oral)

Cheong CM, Golder AM, Horgan PG, McMillan DC, Roxburgh CSD. Evaluation of clinical prognostic variables on short-term outcome for colorectal cancer surgery: An overview and minimum dataset. Surgical Research Society Annual Meeting, Nottingham, United Kingdom 2022 (Poster)

Cheong CM, Golder AM, Horgan PG, Roxburgh CSD, McMillan DC. The relationship between preoperative glycated haemoglobin, clinicopathological characteristics and surgical site infection in patients undergoing elective potentially curative surgery for colon cancer. ACPGBI Annual Meeting, Edinburgh, United Kingdom 2022 (Poster)

Cheong CM, Golder AM, Horgan PG, Roxburgh CSD, McMillan DC. The relationship between computed tomography-derived body composition, body mass index, diabetes, and surgical site infection in patients undergoing curative colon cancer resection. ESCP 17th Scientific Conference, Dublin, Ireland, 2023 (Poster)

Cheong CM, Abbas T, Dolan R, Mackay GJ, Horgan PG, Roxburgh CSD, McMillan DC. Effect of preoperative carbohydrate loading on surgical site infection in curative colon cancer surgery. Tripartite Colorectal Meeting, Paris, France 2025 (Poster)

Definitions/Abbreviations

AJCC	American Joint Committee on Cancer
APC	Adenomatous polyposis coli
APER	Abdominoperineal excision
ASA	American Society of Anesthesiologists
BMI	Body mass index
CI	Confidence interval
CIN	Chromosomal instability
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CIMP	CpG island methylator phenotype
CT	Computed tomography
DNA	Deoxyribonucleic acid
ERAS	Enhanced recovery after surgery
FAP	Familial adenomatous polyposis
FIT	Faecal immunochemical test
gFOBT	Guaiac faecal occult blood test
HbA1c	Glycated haemoglobin
HDI	Human development index
HPNCC	Hereditary non-polyposis colorectal cancer
HU	Hounsfield unit
MBP	Mechanical bowel preparation
MCN	Managed Clinical Network
mGPS	Modified Glasgow prognostic score
MMR	Mismatch repair
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MUST	Malnutrition universal screening tool
nCRT	Neoadjuvant chemoradiotherapy
NHSGGC	NHS Greater Glasgow and Clyde
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NLR	Neutrophil lymphocyte ratio
OAB	Oral antibiotics
poGPS	Postoperative Glasgow prognostic score
RCT	Randomised controlled trial
RR	Relative risk
SFA	Subcutaneous fat area
SIG	Systemic Inflammatory Grade
SMA	Skeletal muscle area
SMD	Skeletal muscle density
SMI	Skeletal muscle index
SIMD	Scottish index of multiple deprivation
SSI	Surgical site infection
TFA	Total fat area
TME	Total mesorectal excision
TNM	Tumour, node, metastases
VFA	Visceral fat area
WHO	World Health Organisation

Chapter 1 Introduction

1.1 Epidemiology

Colorectal cancer is the second leading cause of cancer-related death worldwide, with an estimated 1.9 million new cases diagnosed and almost 900 000 deaths in 2022. Despite a trend in the reduction of colorectal cancer mortality rate, the incidence has increased over the past four decades. According to GLOBOCAN 2022, colorectal cancer is the third most commonly diagnosed cancer worldwide after lung (12.4%) and breast cancer (11.6%)(Figure 1-1) (1).

In the United Kingdom, approximately 44 000 new cases were diagnosed annually between 2017 and 2019 (2). This represents 11 % of all new cancer cases reported annually, making it the fourth most common cancer. In females, colorectal cancer is the third most common cancer after lung and breast cancer with approximately 19 600 cases per 100 000 person-years. In males, colorectal cancer is also the third most common cancer after lung and prostate cancer with an annual incidence of approximately 24 500 per 100 000 person-years.

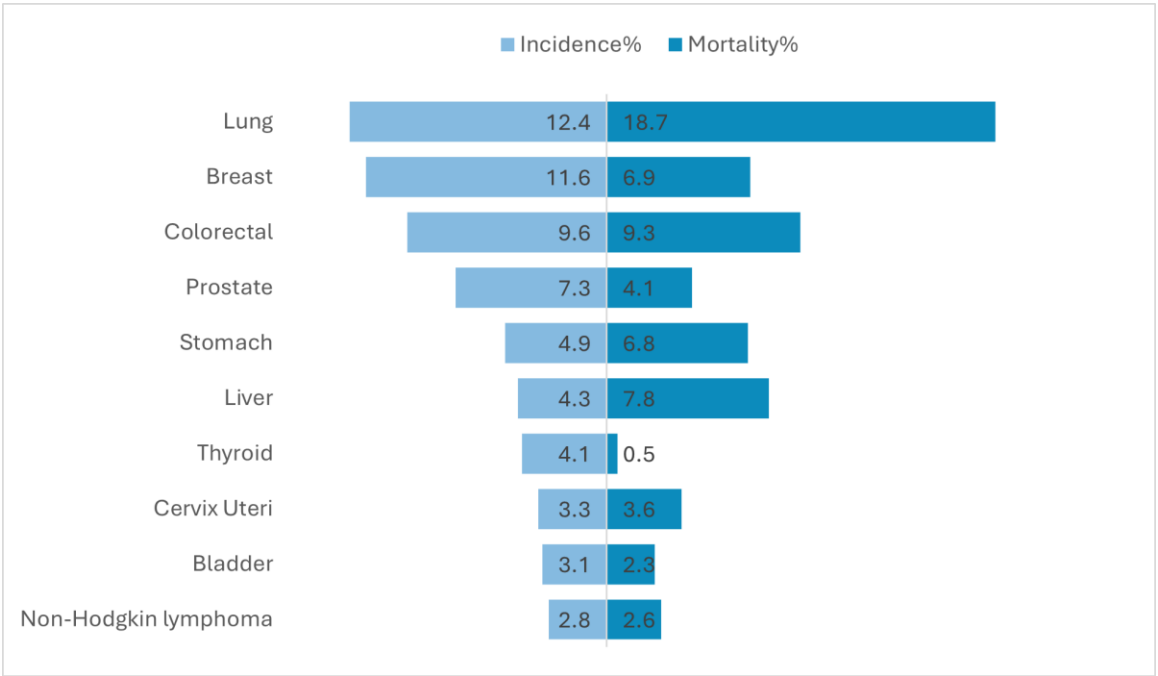


Figure 1-1 Top 10 Most common cancers worldwide in 2022

The global distribution of colorectal cancer worldwide exhibits marked geographical variation, with the highest incidence and mortality rates observed in Europe, Australia/New Zealand and North America. The combined incidences of colorectal cancer remain relatively low in most parts of Africa and South-Central Asia. Data from GLOBOCAN 2022 have suggested that these differences are partly explained by the Human Development Index (HDI), a composite metric of social and economic development (1).

The steadily rising incidence of colorectal cancer in developing countries compared to developed countries reflects lifestyle and behavioural factors, including changes in dietary patterns and increasingly sedentary lifestyles, leading to the surge in overweight and obesity (3). On the contrary, declining mortality rates in developed countries have been attributed to the implementation of organised screening programmes and advances in treatment. Countries such as North America and Japan, which introduced screening programmes in the 1990s, have demonstrated sustained reductions in colorectal mortality. Conversely, recently implemented screening programmes in developing countries may initially lead to an apparent increase in incidence due to improved detection of previously undiagnosed disease. Nevertheless, it would be difficult to quantify the influence of a particular screening programme on incidence with changing infrastructure and delivery of treatment services.

Colorectal cancer has predominantly affected older individuals, with about 40% of cancers in the United Kingdom diagnosed in people aged 75 and over each year (2). However, a concerning global increase in early-onset colorectal cancer among individuals younger than 50 years has been observed (4-6). An explanatory factor for this may represent a shift in exposure to risk factors and alterations in disease pathogenesis influencing the future cancer burden.

1.2 Colorectal carcinogenesis pathway

Colorectal cancer is a biologically heterogeneous disease that results from accrued genetic and epigenetic alterations. The genetic changes are widely studied, and tumour development is recognised to arise from either one or a combination of three principal molecular pathways: chromosomal instability (CIN) pathway, microsatellite instability (MSI) pathway and the CpG Island Methylator Phenotype (CIMP) pathway.

1.2.1 Chromosomal instability pathway

Vogelstein and Fearon first described the traditional 'adenoma-carcinoma sequence' proposed through a multi-hit genetic model for colorectal carcinogenesis (7). The entire process from adenomatous polyps progressing to dysplasia and transformation to malignancy is heavily associated with chromosomal instability.

The classical CIN pathway begins with mutation in the adenomatous polyposis coli (APC) gene on chromosome 5q21, resulting in the formation of colorectal adenoma. This is followed by activation of the K-RAS oncogene that subsequently promotes both growth and dysplastic change in the polyp. Finally, the inactivation of the tumour suppressor gene, TP53, facilitates progression to adenocarcinoma. The loss of heterozygosity contributes to the majority of sporadic tumours (85%), although cases associated with the germline mutation in the APC gene can lead to hereditary tumours (8).

However, this linear model represents an oversimplification and merely one possibility in the multistep process of colorectal carcinogenesis. Evidence suggests that KRAS and p53 mutations rarely coexist in the same tumour (9). The presence of a variety of oncogene and tumour suppressor genes such as PIK3CA, SMAD4, and DCC is more likely to explain the variation in profiles found in colorectal cancer (10). The range of mutations, inactivations and deletions is wide. Consequently, tumour development along the CIN pathway is highly variable and is postulated to occur over a period of 10 years or more, providing a significant window for early detection and intervention (11).

1.2.2 Microsatellite Instability

In contrast to CIN, microsatellite instability results from defects in the DNA mismatch repair (MMR) pathway. MSI is a hypermutable phenotype characterised by frequent somatic DNA base pair mutations. DNA microsatellites are short repeated genetic sequences that are particularly susceptible to replication errors. Under normal circumstances, these errors are corrected by the MMR pathway. Mutation in the DNA MMR gene results in a failure to correct these errors, and this feature is present in about 15% of colorectal cancers (12).

Deficient MMR can arise from inherited germline mutation in an MMR gene (MLH1, MSH2, MSH6, PMS2) as seen in Lynch Syndrome or sporadic inactivation of the MLH1 gene often associated with the CIMP pathway (subsequently described). In sporadic MSI-high-related colorectal cancer, distinct phenotypes were noted with predilection for the proximal colon, poor differentiation, abundant tumour-infiltrating lymphocytes and lower likelihood to metastasise at diagnosis (13). Approximately half of sporadic MSI tumours harbour a BRAF mutation, which facilitates cost-effective exclusion of Lynch syndrome during diagnostic evaluation.

1.2.3 CpG Island Methylator Phenotype

Serrated polyps were previously considered benign but are now thought to represent premalignant precursors to colorectal cancer that progress via the CpG island methylator phenotype described by Toyota and colleagues (14). CIMP participates in the initiation and progression of the serrated adenoma pathway as a result of DNA hypermethylation of promoter-associated CpG islands that surround tumour suppressor genes, causing transcriptional silencing of these genes (15). CIMP pathway accounts for 15% of colorectal cancers and often CIMP-high colorectal cancers are distinguished by the activation of the V600E mutation in BRAF, proximal colon location, older age onset, prevalence in females, and high levels of MSI. Together, these molecular pathways underpin the heterogeneity observed in colorectal biology and clinical behaviour.

1.3 Risk Factors

Colorectal cancer can arise from both genetic susceptibility and environmental factors. Majority of colorectal cancers are deemed to be sporadic from random genetic mutations and the influence of environmental factors, while the remainder are inherited through specific conditions that predispose to the development of colorectal cancer. The identification of both modifiable and non-modifiable risk factors influences the screening pathway and prevention of colorectal cancer.

1.3.1 Age

Age is recognised as a major risk factor in colorectal cancer. Colorectal cancer is rare under the age of 40, with more than 90% of colorectal cancer occurring in people over the age of 50. The incidence rate increases significantly with each subsequent decade (2). This may be the result of accumulation of damaged DNA over time, along with the combined influence of lifestyle factors. Nevertheless, the cause of increasing numbers of early cancers remains unknown, as accumulated adulthood exposures to risk factors cannot fully explain this rise.

1.3.2 Sex

Studies have shown higher age-standardised rates of colorectal cancer in males compared to females (16, 17). In the United Kingdom, 55% of colorectal cancers occur in men versus 45% in women. Mortality rates are also higher in males, but notably younger women (age 18-44) have better survival outcomes than men of the same age compared to older women, suggesting a protective effect of oestrogen hormone in the development of colorectal cancer(18).

1.3.3 Lifestyle factors

1.3.3.1 Diet

Diet has also been shown to strongly influence the risk of developing colorectal cancer. Long-term consumption of red meat, processed meat and high-temperature food preparation has been linked to increased risk of colorectal cancer. The exact mechanisms underlying the association between colorectal

cancer and intake of red and processed meat are uncertain, but the postulated mechanism involves mutagenic N-nitroso compounds during exogenous processing of meats and consumption of Heme iron resulting in endogenous N-nitroso compounds. A meta-analysis showed a positive correlation between red meat consumption and colorectal cancer, with a 13% risk increase per 5 servings per week (19).

While high-temperature cooking has been implicated as a contributing risk, potentially due to the production of heterocyclic amines and polycyclic aromatic hydrocarbons. These substances are mutagenic, causing alterations in DNA that increase the risk of cancer. Indeed, the World Cancer Research Fund, in conjunction with the Cancer Update Programme, has recommended restricting red and processed meat consumption for the prevention of colorectal cancer (20).

In contrast, fruit consumption and vegetable consumption were associated with reduced risk of colorectal cancer. One meta-analysis of prospective studies suggested around a 10% reduction in colorectal cancer for the highest versus lowest intake of fruits and vegetables (21). While another meta-analysis showed a decrease of 15% risk with 3 servings or more a day of fruits, similarly in vegetables (19).

Other possible dietary protective factors include intake of fibre, calcium and vitamin D. The European Prospective Investigation into Cancer and Nutrition found that dietary fibre in food could reduce the risk of colorectal cancer by 40%, particularly in left-sided cancers (22). The underlying explanation for this involves reduced transit time, dilatation of colonic contents and stimulation of anaerobic bacterial fermentation. Vitamin D signalling pathways act as an inhibitor in colorectal progression models, and Vitamin D deficiency has been demonstrated to increase the incidence of colorectal cancer (23).

Calcium participates in cell regulation that influences regulatory gene expression that plays a role in colorectal cancer carcinogenesis along with ability to bind unconjugated bile acid and free fatty acid. Epidemiology studies have suggested a higher calcium intake with lower relative risk of colorectal cancer (24). Although both Vitamin D and calcium have been indicated in reducing the incidence in colorectal cancer, the benefit of the direct effect of Vitamin D and calcium

supplementation over recommended dietary intake on colorectal cancer remains unproven in clinical trials (25).

1.3.3.2 Physical activity

Physical activity has often been related to other colorectal cancer risk, primarily obesity and cardiovascular risk. However, in the presence of colorectal cancer, physical activity has also demonstrated a protective effect independent of these confounders (26). Studies on physical activity concluded that there was a reduced risk of both proximal and distal colon cancer when comparing the most versus the least active individuals (27). Several mechanisms have been hypothesised to explain this association between physical activity and colorectal cancer, with possible mechanisms relating to hyperinsulinemia, decrease in gut transit time, changes in prostaglandin ratios, lower bile acid secretion, and altered gut flora. Several systematic reviews concluded that regular physical activity, either leisure or occupational, significantly reduced the risk of colorectal cancer in those engaging in the highest versus lowest categories of physical activity (28).

1.3.3.3 Alcohol

Excessive alcohol consumption is an established and potentially modifiable risk factor for colorectal cancer. The effect of alcohol on the development of colorectal cancer is hypothesised to be through alcohol metabolites causing DNA damage, dysregulation of the colorectal microbiome, increased intestinal permeability allowing for bacterial translocation, inflammation, immunosuppression and resulting in epigenetic dysregulation, while chronic consumption has been shown to disrupt folate metabolism important for gene regulation (29). A meta-analysis reported the dose dependent effect of alcohol and noted an interesting pattern of a J-shaped dose-response pattern associated to colorectal cancers. There was an increased risk of colorectal cancers in groups comparing non-drinkers to occasional or very heavy consumption but a protective effect in groups comparing non-drinkers to those with moderate alcohol consumption (up to 2 drinks/day) (30).

1.3.3.4 Smoking

Another potentially modifiable risk factor for colorectal cancer has been demonstrated in smokers. The causal relationship between smoking and colorectal cancer has long been demonstrated in observational studies, with an absolute increase of 10.8 cases per 100,000 person-years. A more recent study has identified differences in colorectal cancer incidence between sexes. Compared to male smokers, female smokers were at increased risk of right-sided colon and rectal cancer (31). Nevertheless, this risk reduces on cessation of smoking, making this a cost-effective preventative measure for the prevention of colorectal cancer (32).

1.3.4 Comorbidities

1.3.4.1 Obesity

High levels of body fat as characterised by higher body mass index (BMI>30 kg/m^2) or higher waist-to-hip ratio (WHR) have been associated with increased risk of colorectal cancer, although the association in body mass index appears to be greater in males versus females (33). If obesity represents overall energy imbalance, the differences in the incidences in males and females would not be evident (34). Nonetheless, the differences could be explained by the protective effect of oestrogen hormone.

Obesity contributes to tumour-promoting inflammation via secretion of proinflammatory cytokines that enhance tumour progression (35). Obesity associated colorectal cancers have also been postulated to develop as a result of genomic instability associated with the CIMP pathway, telomere dysfunction, sustained cell proliferation in defective pathways, angiogenesis for invasion and dissemination of malignant cells, and microbial alterations (36).

1.3.4.2 Inflammatory Bowel Disease

Inflammatory bowel disease is a chronic immune-related condition characterised by the recurring and remitting nature of inflammation in the gastrointestinal tract. This subsequently confers a higher risk of developing colorectal cancer in individuals with inflammatory bowel disease due to the prolonged exposure cycle

to inflammatory insults and regeneration. The relationship between ulcerative colitis and the risk of colorectal cancer has been well documented, with an estimated standardised ratio of 2.4 (37). The primary determinants include the extent and duration of disease, with cumulative risk increment over time: 2% at 10 years, 8% after 20 years and 18% after 30 years (38). Although not as well studied, Crohn's disease also increases the risk of colorectal cancer by 2.4 times compared to the average population (39).

1.3.4.3 Diabetes Mellitus

Type 2 diabetes mellitus shares many of its risk factors with colorectal cancer, including sedentary lifestyle and obesity. The changes in glucose metabolism in adipose tissue lead to insulin resistance, resulting in hyperinsulinemia and hyperglycaemia. The potential pathological mechanism for colorectal cancer includes hyperinsulinemia, insulin-like growth factor, hyperglycaemia, inflammation and decreased gut motility (40). Numerous studies have demonstrated the increased risk of developing colorectal cancer in patients with diabetes, with Wu et al. reporting an increased risk of 1.22 times higher than individuals without diabetes, along with a predisposition to right-sided cancer compared to left-sided cancer (41, 42). Similarly, the prognosis for diabetic patients with colorectal cancer was worse both from the perspective of decreased survival and increased risk of relapse(43).

1.3.5 Hereditary Colorectal Cancer

The majority of colorectal cancers arise sporadically, although a proportion occurs in the context of recognised hereditary syndromes, including familial adenomatous polyposis (FAP) and Lynch syndrome (44). Other cases may occur in individuals with a family history of colorectal cancer, reflecting shared genetic susceptibility (45). Specific genetic disorders, most of which are inherited in an autosomal dominant fashion, are associated with a very high risk of colorectal cancer and have specific recommendations for screening and treatment.

1.3.5.1 Familial Adenomatous Polyposis

Familial adenomatous polyposis accounts for less than 1% of colorectal cancer. Nevertheless, the penetrance for the development of colorectal cancer is

approximately 90% by the age of 45 in those untreated (46).FAP is inherited in an autosomal dominant manner due to a germline mutation in the APC gene on chromosome 5. Classical FAP is characterised by the presence of at least 100 adenomatous polyps within the lower gastrointestinal tract. The British Society of Gastroenterology guidelines recommend that individuals with classical FAP undergo regular screening colonoscopy starting from the age of 12-14 and upper gastrointestinal endoscopy from the age of 25 due to extracolonic manifestations (47). These individuals with classical FAP should then be considered for surgical resection if polyps> 10 mm are detected, high-grade dysplasia is present, or there is a significant increase in the polyp burden between endoscopic examinations. Attenuated FAP, on the other hand, is characterised by fewer than 100 polyps, later age at presentation and lower cancer risk. Nevertheless, there remains a 70% lifetime risk of colorectal cancer (48).

1.3.5.2 Hereditary Non-Polyposis Colorectal Cancer

Hereditary non-polyposis colorectal cancer or Lynch Syndrome accounts for up to 4% of colorectal cancer. This autosomal dominant syndrome is due to germline mutations in the DNA mismatch repair gene as previously described. An estimated 90% of males and 70% of females with HNPCC develop colorectal cancer by the age of 70 (49). Although HNPCC is commonly associated with colorectal cancer, it also increases the risk of endometrial, ovarian, stomach and pancreatic cancer.

Mutations in the MLH1 and MSH2 genes are responsible for approximately 90% of Lynch syndrome. Compared to FAP, HPNCC does not have a characteristic phenotype, and therefore many diagnostic criteria have been proposed, with the Amsterdam Criteria II the best known (50).

Table 1-1 Revised ICG-HNPCC criteria (Amsterdam II)

Amsterdam criteria II
There should be at least three relatives with an HNPCC-associated cancer (CRC, cancer of the endometrium, small bowel, ureter, or renal pelvis)
One affected individual should be a first-degree relative of the other 2
At least two successive generations should be affected
At least one individual should be diagnosed before age 50
Familial adenomatous polyposis should be excluded in the CRC case(s) if any
Tumours should be verified by pathological examination

1.4 Clinical presentation

Early colorectal cancers tend to be asymptomatic and often diagnosed via screening programmes. The common presenting features of colorectal cancer include iron deficiency anaemia, changes in bowel habit, rectal bleeding and abdominal pain, although the clinical presentation varies according to tumour location and stage of diagnosis (51).

1.4.1 Symptomatic disease

Despite diagnostic advances and implementation of screening programmes, epidemiological studies have shown that colorectal cancers are predominantly diagnosed in symptomatic individuals (52, 53). Right-sided cancers tend to present with signs and symptoms of occult bleeding such as anaemia due to the degradation of blood during the passage of stool in the colon (54). Patients with right-sided cancers are also more likely to present with abdominal pain or a palpable abdominal mass. On the contrary, left-sided cancers often present with rectal bleeding, change in bowel habit or lower abdominal pain (55). The most distal of the cancers in the rectum often cause urgency, tenesmus, rectal bleeding and change in bowel habit.

Approximately 20-25% of patients with colorectal cancer have synchronous metastatic disease at initial presentation (56). Colorectal cancer can spread through lymphatic and hematogenous routes as well as direct transperitoneal dissemination. The liver and lungs are major sites of distant metastasis, although peritoneal and lymph node involvement also occur (57). Clinical presentations may therefore include symptoms related to metastatic disease such as right upper quadrant pain or jaundice in patients with hepatic involvement, breathlessness in those with pulmonary metastasis, and bone pain in patients with skeletal metastasis.

1.4.2 Bowel cancer screening

Screening for colorectal cancer are increasingly employed worldwide due to its efficacy in reducing colorectal incidence and mortality, although there remain significant geographical variations in implementation (58). A variety of tests are available for colorectal cancer screening, ranging from guaiac faecal occult blood

test(gFOBT), faecal immunochemical test (FIT), flexible sigmoidoscopy to colonoscopies.

In Scotland, individuals between the ages of 50 to 74 are invited for biennial colorectal screening. The Scottish Bowel Cancer Screening Programme was introduced in 2007, screening test in the form of a two gFOBT kit were sent out on two separate occasions. Individuals with strongly positive test were invited for colonoscopy, while negative individuals returned to the biennial schedule. However, since 2017 the screening test has changed from gFOBT to FIT with a similar biennial schedule and pathway for individuals who test positive or negative with the single FIT testing kit.

1.5 Investigation, diagnosis and staging

The diagnosis of colorectal cancer in the elective setting is determined with a combination of suspicion from clinical history, examination and investigations. These investigations can include laboratory tests, endoscopic evaluation and radiological imaging for histological confirmation and staging of the cancer.

Nevertheless, in emergency presentations, the urgency to proceed to surgery may take precedence, with histological diagnosis and disease staging taking place subsequently.

1.5.1 Blood test

There is no specific blood test for detection of colorectal cancer. Routine blood tests, including full blood count, renal function and liver function tests, are beneficial in assessing the patient's general health for microcytic anaemia that may indicate occult blood loss or specific organ dysfunction indicating the presence of metastatic disease.

Carcinoembryonic antigen (CEA) is normally produced during foetal development and is usually present in very low levels in adults. CEA is neither sensitive nor specific to individuals with colorectal cancer; instead, it is utilised as a biomarker to detect recurrence of colorectal cancer(59).

1.5.2 Quantitative faecal immunochemical test

Faecal immunochemical testing (FIT) is a highly sensitive non-invasive test that allows for the quantitative detection of microscopic blood in the faeces using antibodies to haemoglobin. It is used to assess the likelihood of colorectal cancer and to help determine which patients require further investigations, with higher concentrations associated with an increased likelihood of colorectal cancer. At a threshold of 10 μg Hb/g faeces, the NICE FIT study reported a negative predictive value of 99.6% in symptomatic patients referred to secondary care (60). The high negative predictive value supports the use of FIT as a risk stratification tool in clinical practice (61). However, a negative FIT result does not completely exclude colorectal cancer, and some patients with colorectal cancer may have faecal haemoglobin concentration below the referral threshold. Therefore, FIT should be

interpreted alongside clinical assessment and further investigations should be considered when symptoms persist, or clinical suspicion remains despite a low result.

The diagnostic performance of FIT may be improved through emerging risk stratification strategies. The COLOFIT model combines faecal haemoglobin concentration with patient age, sex, mean corpuscular volume and platelet count to estimate colorectal cancer risk and potentially reduce unnecessary investigations while maintaining cancer detection rates (62). Another approach is double FIT, which involves analysing two separate faecal samples to account for intermittent tumour bleeding. A prospective study demonstrated that double FIT increased sensitivity for colorectal cancer to 96.6% compared with 84.1% for single FIT (63). However, double FIT may increase the number of positive results and subsequent investigations. Both approaches offer potential advantages over a single FIT result, although further evaluation is required to establish their clinical utility and applicability across different patient populations.

1.5.3 Endoscopic evaluation

Endoscopic evaluation of the lower gastrointestinal tract with colonoscopy is considered the gold standard investigation for colorectal cancer. This allows for the complete evaluation of the entire large bowel, biopsy of suspicious lesions to provide histological diagnosis, as well as the benefit of potentially resecting early polyp cancers endoscopically. Despite its high effectiveness, colonoscopy does require full colonic bowel preparation and, on most occasions, the administration of intravenous sedation and analgesia for tolerability (64). The intrinsic nature of the test may form an important barrier to the uptake of colonoscopy. Generally considered a safe procedure, colonoscopy does carry risks including colonic perforation, especially in colonoscopies with polypectomies (0.8/1000), bleeding (2.4/1000), post-polypectomy syndrome (3/1000) and missed pathology with a 3-year incidence of 6.5% in the UK population (65). Individuals who experienced a failed colonoscopy should be offered a repeat colonoscopy or CT colonography.

1.5.4 Colon capsule endoscopy

Colon capsule endoscopy (CCE) is a less invasive technique compared to colonoscopy that enables the visualisation of the colonic mucosa through the ingestion of a disposable capsule containing miniature cameras. As the capsule passes through the gastrointestinal tract, it transmits images that are subsequently reviewed to identify mucosal abnormalities. CCE does not require sedation, endoscopic intubation or ionising radiation and may be considered in selected patients who are unable or unwilling to undergo colonoscopy or following incomplete colonoscopy, provided there is no anatomical obstruction or narrowing of the bowel lumen.

However, CCE requires rigorous bowel preparation and the diagnostic performance may be limited by inadequate mucosal visualisation, incomplete examination and the inability to obtain tissue samples or remove detected lesions (66). Consequently, patients with significant pathology may require subsequent colonoscopy for histological confirmation and treatment. Although CCE represents a potential alternative for colonic evaluation, current evidence does not support its routine use as first-line investigation, and its role remains dependent on clinical indication, local availability and patient suitability (67).

1.5.5 Computed tomography

In patients who have failed a colonoscopy attempt or not deemed suitable for colonoscopy, computed tomography (CT) colonography is an alternative for diagnosing colorectal cancer. This test requires the use of an osmotic laxative for bowel preparation and rectal catheter insufflation to achieve pneumocolon. CT colonography has a high sensitivity for adenoma ≥ 10mm and is considered an acceptable alternative to colonoscopy for screening, but histological sampling is not possible, requiring patients to undergo further colonoscopy if suspicious lesions are detected (68).

Preoperative staging for colorectal cancer is accomplished by means of contrast-enhanced computed tomography of the chest, abdomen and pelvis. This allows for local assessment of the tumour and detection of distant metastases.

1.5.6 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is not routinely carried out for the assessment of colonic tumours, for which contrast-enhanced CT is the primary modality to assess the extent of disease and detect distant metastasis. In contrast, high-resolution pelvic MRI is routinely utilised for local staging of rectal cancers because it provides detailed assessment of the depth of tumour invasion, involvement of the mesorectal fascia, extramural vascular invasion and regional lymph nodes. These features are important in determining the risk of local recurrence and guide the need for neoadjuvant treatment as well as the surgical approach. Rectal cancers spread by local extension, lymphatics, and the bloodstream, with the circumferential resection margin as the main determinant of local recurrence. MRI has been shown to be the only investigation accurate at predicting the circumferential resection margin in a meta-analysis assessing the accuracy of preoperative imaging (69).

MRI can also be used for further characterisation of other suspicious lesions found on staging, primarily in the liver. The MRI allows for accurate assessment of liver metastasis and amenability for management with either liver-directed therapy or resection (70).

1.6 Management of Colorectal Cancer

The management of colorectal cancer has evolved over time from a surgery-focused approach to a multimodal approach involving interventional radiology, systemic chemotherapy and radiotherapy. The Scottish Intercollegiate Guideline Network (SIGN) have recognised that all patients diagnosed with colorectal cancer should be managed within a multidisciplinary team consisting of surgeons, oncologists, pathologists, radiologists, and specialist nurses, in addition to a wider team to offer effective management (71). Indeed, a meta-analysis of observational studies has reported improved overall survival in patients managed in the multidisciplinary setting (72).

1.6.1 Neoadjuvant Therapy

The utility of neoadjuvant therapy or preoperative chemoradiotherapy has been widely adopted as gold standard in management of certain malignancies such as breast, prostate and rectal cancers. The theoretical benefits include tumour downstaging with potential for complete response and eradication of micrometastases to prevent recurrence.

1.6.1.1 Rectal cancer

In the United Kingdom, neoadjuvant chemoradiotherapy (nCRT) is offered to rectal cancer patients with circumferential margin-threatening disease where there are concerns about the immediate surgical margin, T3 or T4 disease or those with nodal disease evident on CT and MRI staging (73). Chemotherapy regimens and external radiation dosing strategies can vary.

Conventionally, a radiosensitising chemotherapy agent such as capecitabine or 5-fluorouracil (5-FU) is given simultaneously to improve the efficacy of radiotherapy. The preoperative radiotherapy regimen can be delivered as short-course (25Gy in 5 fractions daily for 5 days) or long-course therapy (50Gy in 25 fractions over a 5-week period). For those receiving short-course radiotherapy, surgery is usually scheduled within 1 week, although more recent trials have explored the option of delayed surgery up to 4 weeks (74). In long-course radiotherapy, surgery is usually delayed for 6-8 weeks to allow maximal tumour downstaging. Nevertheless, there is no clear evidence of differences in local

recurrence and overall survival between short-course radiotherapy and long-course radiotherapy, resulting in differing regional practices (75-77).

Patients with early rectal disease are currently not offered neoadjuvant therapy as standard treatment. However, an increasing number of studies are assessing the outcome of combined neoadjuvant therapy and organ preservation surgery (78, 79). The STAR-TREC trial compared short-course radiotherapy along with long-course chemoradiotherapy in patients with early- and intermediate-stage rectal cancer, investigating whether response-adapted treatment could increase organ preservation without compromising oncological outcomes. Initial results have been published, demonstrating a 12-month total mesorectal excision (TME)-free survival of 78.5% with long-course chemoradiotherapy and 60.6% with short-course radiotherapy among participants who opted for organ preservation (80). The long-term outcomes are eagerly awaited as it would represent a paradigm shift in the management of early rectal cancer if the durability of organ preservation is established while offering oncological safety compared to traditional surgical resection.

Similarly, the increasing rates of complete clinical and pathological response following total neoadjuvant therapy for locally advanced rectal cancer have generated interest in non-operative management (81). The OPRA trial evaluated total neoadjuvant therapy in patients with stage II and III rectal cancer followed by response-based management, offering watch-and-wait to patients achieving complete or near-complete clinical response. At a median follow-up of 5 years, the disease-free survival was 69%, and TME-free survival was 54% among patients receiving chemoradiotherapy followed by consolidation chemotherapy (82). The phase III ACO/ARO/AIO-18.1 trial directly compares short-course radiotherapy followed by consolidation chemotherapy with long-course chemoradiotherapy followed by consolidation therapy in patients with MRI-defined intermediate and high-risk rectal cancer, incorporating selective organ preservation for patients achieving a complete clinical response (83). This trial will help clarify the role of radiotherapy fractionation within total neoadjuvant therapy and its implication for organ preservation and oncological outcomes.

1.6.1.2 Colon cancer

Neoadjuvant therapy is not considered standard treatment for resectable colon cancer in the United Kingdom at present. Currently, preoperative systemic chemotherapy is only recommended in T4 colon cancer, as there is some evidence to suggest it reduces the risk of recurrence and increases benefits of disease-free survival and overall survival (84). A meta-analysis addressed the feasibility of neoadjuvant chemotherapy in locally advanced colon cancer, although there was variation in terms of regime and duration in the studies (85). The FOxTROT 1 trial, an international randomised controlled study, demonstrated a 28% reduction in residual or recurrent disease within 2 years in patients receiving neoadjuvant chemotherapy compared to patients receiving adjuvant chemotherapy for T3 and T4 disease (86). Longer-term data are yet to be available, and perhaps the ongoing FoxTROT programme trials may yield insight into a new personalised standard of care for management of colon cancer in the future (87).

1.6.2 Surgery

Surgery remains the main modality for curative treatment of colorectal cancers. The aim of the surgical resection is removal of the tumour along with a 5cm margin of healthy proximal and distal bowel or, in the case of low rectal tumours, a 1cm distal margin. The accompanying blood supply and lymphatics are resected en bloc to offer full pathological staging. Once the tumour is removed, where possible the restoration of intestinal continuity is achieved by anastomosing the two ends of the bowel. In cases where this is not feasible, the bowel ends are exteriorised to form a stoma.

There are specific considerations, particularly in rectal cancer surgery. In early rectal cancer, local excision in the form of endoscopic or transanal minimally invasive surgery (TAMIS) may be amenable. There are obvious benefits in the form of organ preservation and avoidance of morbidity associated with standard rectal resection, but this needs to be balanced with the oncological risks (88). Kikuchi et al. reported the exponentially increased risk of lymph node involvement from 2% to 23% based on the depth of invasion of the tumour in the submucosa, dividing it into three levels from the most superficial(sm1) to the deepest layer(sm3) (89).

Inevitably, organ preservation surgery will yield a higher rate of local recurrence compared to standard rectal resection owing to residual disease and incomplete pathological staging. Active surveillance is required to detect and treat recurrent disease when salvage surgery is still amenable. Nevertheless, the local recurrence rate is comparable if the histology shows clear tumour margins, well/ moderate differentiation, no lymphatic or vascular invasion and only superficial invasion (sm1/sm2) (90). Patients therefore require adequate counselling of the oncological risk prior to embarking on organ preservation surgery.

The current gold standard for rectal cancer surgery below the peritoneal reflection was described by Heald and colleagues in 1979 (91). The total mesorectal excision (TME) technique entails removal of the rectum along the embryological plane with an intact mesorectum and has demonstrated a significant reduction in local recurrence rates (92). Another consideration for rectal surgery is the feasibility of a sphincter-sparing procedure without sacrificing the oncological margin. An anterior resection with TME principles is performed if sphincter-sparing surgery is possible; alternatively, the patient is subjected to an abdominoperineal resection and formation of an end colostomy.

1.6.2.1 Operative technique

Traditional open surgery, as the name suggests, involved making a large incision to access the bowel for cancer resections. The large incision often led to longer recovery and length of stay. Over time, the evolution of medical technology introduced minimally invasive surgery in the form of laparoscopic surgery. Several large randomised controlled trials demonstrated the non-inferiority of laparoscopic versus traditional open surgery in terms of long-term outcome and additionally improved short-term outcome with less blood loss, earlier recovery of bowel function and reduced hospital stay (93-95). Therefore, the National Institute of Clinical Excellence recommends offering a laparoscopic approach in patients undergoing colorectal cancer surgery if both options are available(73).

Since the first reported robotic surgery for colorectal cancer in 2002, the adoption of robotic surgery has increased globally. Robotic surgery offers a three-dimensional stable platform with a wide range of articulation to offer accuracy and flexibility even when operating in limited spaces. Randomised controlled trials

between robotic and laparoscopic surgery for colorectal cancer have not shown significant differences in outcomes (96). While most observational studies report lower rates of conversion to open, the longer operating times are noted in robotic versus laparoscopic surgery (97). Nevertheless, robotic surgery comes with a high operational cost, making accessibility variable.

1.6.2.2 Enhanced Recovery After Surgery

The concept of a multi-modal approach was initially introduced in the 1990s (98). Kehlet and colleagues focused on reducing the postoperative stress response in a group of elderly patients undergoing neoplastic colonic resection by introducing a combination of preoperative, perioperative, and postoperative interventions. These interventions effectively reduced the hospital stay and demonstrated effective improvements in surgical outcome in the study group and therefore started the 'Enhanced Recovery After Surgery (ERAS)' movement. The number of components adopted by each unit is specific, but regardless of the construct of the protocol, the implementation of ERAS has been shown to reduce morbidity following elective colorectal surgery (99).

Surgical trauma induces a complex physiological stress response involving hormonal, metabolic and inflammatory changes. These responses promote the mobilisation of energy substrate to meet the increased metabolic demands of surgery and recovery. However, the associated catabolic state, insulin resistance and disturbance of glucose homeostasis may contribute to postoperative morbidity. Consequently, interventions intended to attenuate the metabolic response to surgery have attracted interest as a potential means of improving short-term surgical outcomes.

Preoperative oral carbohydrate loading is a specific component of ERAS protocols that aims to reduce the metabolic consequences of prolonged preoperative fasting. Administration of oral carbohydrate drinks before surgery has been proposed to attenuate postoperative insulin resistance by maintaining a more favourable metabolic state at the time of surgery (100). As perioperative metabolic disturbances may influence postoperative outcomes, including the host response to infection, preoperative carbohydrate loading represents a potentially relevant intervention to investigate in relation to surgical site infection.

Although carbohydrate loading has been incorporated into ERAS pathways, its clinical benefits remain uncertain. A systematic review of randomised controlled trials in colorectal surgery has not consistently demonstrated improvements in glycaemic control or overall postoperative morbidity, and its specific effect on surgical site infection remains insufficiently established (101). Furthermore, because ERAS comprises multiple interventions delivered across the perioperative pathway, the contribution of individual components to postoperative outcomes cannot be readily determined by evaluating the pathway as a whole. Investigating preoperative carbohydrate loading separately therefore allows its association with surgical site infection to be examined as a distinct, potentially modifiable perioperative exposure.

1.6.3 Immunotherapy

Immune checkpoint inhibition has emerged as an important therapeutic approach in colorectal cancer, particularly in tumours exhibiting deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H). These tumours accumulate somatic mutations and express tumour-associated neoantigens, making them more susceptible to immune recognition and checkpoint blockade. Inhibition of the programmed cell death protein 1 (PD-1) pathway restores antitumour T-cell activity and has demonstrated substantial efficacy in selected patients in colorectal cancer.

In rectal cancer, Cercek et al. reported clinical complete responses following treatment with anti-PD-1 antibody dostarlimab in patients with locally advanced dMMR disease, raising the possibility of avoiding radical surgery and radiotherapy in selected patients (102). In colon cancer, the phase II NICHE-2 study demonstrated major pathological responses following neoadjuvant nivolumab and ipilimumab in locally advanced dMMR tumour, including pathological complete response in 68% of patients (103). More recently, the phase III ATOMIC trial demonstrated improved disease-free survival compared with chemotherapy alone in patients with resected stage III dMMR colon cancer (104).

In the United Kingdom, immune checkpoint inhibitors have become an established treatment option for patients with unresectable or metastatic colorectal cancer exhibiting dMMR or MSI-H. NICE recommends pembrolizumab as an option for untreated metastatic colorectal cancer and nivolumab in combination with ipilimumab as a first-line treatment option for untreated unresectable or metastatic dMMR/MSH-H colorectal cancer (73). The phase III KEYNOTE-177 trial demonstrated a 16.5-month median progression-free survival with pembrolizumab compared to 8.2 months with standard chemotherapy (105). More recently, the phase III CheckMate 8HW trial demonstrated superior progression-free survival with nivolumab plus ipilimumab compared with chemotherapy, with 24-month progression-free survival rates of 72% and 14%, respectively (106). Despite these promising findings, the benefit of immune checkpoint inhibition remains largely concentrated on dMMR/MSI-H subgroup. Further research is required to establish optimal sequencing, long-term outcomes and the role of immunotherapy in the broader colorectal cancer population.

1.6.4 Adjuvant therapy

Adjuvant therapy is offered after surgery to reduce the risk of cancer recurrence and is mostly in the form of chemotherapy. Those who are deemed to be at higher risk of recurrence are patients with serosal involvement (T4), perforated or obstructed tumours, positive lymph nodes, poorly differentiated tumours and tumours with extramural venous invasion.

Chemotherapy is usually offered as a combined therapy such as platinum-based oxaliplatin with an antimetabolite capecitabine (CAPOX) or with 5-fluorouracil and folinic acid (FOLFOX). Each of these chemotherapy agents is accompanied by specific side effect profiles and can affect the completion rate of treatment. However, studies have shown that combination therapy, regardless of duration, is likely to improve survival rates compared to monotherapy (107). The specific chemotherapeutic agent offered is inevitably dependent on the tumour biology, patient performance status, preference and comorbidities.

In rectal cancers, adjuvant radiotherapy can be offered to reduce local recurrence in positive resection margin if the patient has not already had neoadjuvant

radiotherapy. However, the benefit is less significant compared to preoperative radiotherapy.

1.6.5 Palliative Therapy

Palliative chemotherapy is reserved for patients with inoperable disease; those unfit to undergo surgical resection or inoperable metastatic disease. The aim is to offer symptom control and slow disease progression. Systematic reviews have shown that chemotherapy improves survival in patients with metastatic colorectal cancer (108, 109). Similar to adjuvant chemotherapy, the suitability for palliative chemotherapy involves balancing toxicity profiles, patient tolerability, and potential benefits. Some patients will ultimately have no further therapeutic options, and timely recognition to alter focus of care and end-of-life experience should be considered (110).

1.7 Pathology and staging

The accurate reporting of pathological staging in colorectal cancer is vital to confirm the diagnosis and particularly inform prognosis as well as individual treatment plans. The communication of the pathology information to the multidisciplinary team and patient is essential for good quality management. The Royal College of Pathologists provides guidelines for the reporting of colorectal cancer through a standardised dataset to ensure accuracy and high-quality pathology reporting (111).

1.7.1 Staging

1.7.1.1 Dukes Staging

Dukes classification system was introduced in 1932 by pathologist Cuthbert Dukes for the staging of rectal cancer (112). The principal classification of rectal cancer was divided into 3 categories based on the extent of spread. This version has undergone subsequent modifications, and the most recent model described by Astler-Coller is shown in Table 1-2 (73, 113). The simplicity of the classification provided accurate prognostic information and was used as a guide for offering adjuvant therapy until recently. The staging classification is now superseded by the TNM Classification (described below).

Table 1-2 Modified Dukes (Astler-Coller) Classification and Survival

Stage	Tumour Extent	Lymph Nodes	5-Year Survival
A	Tumour limited to mucosa	No	>90%
B1	Tumour invades muscularis propria	No	≈ 85%
B2	Tumour penetrates through bowel wall	No	≈ 70–80%
C1	Same as B1	Yes (positive nodes)	≈ 60%
C2	Same as B2	Yes (positive nodes)	≈ 35–45%
D	Distant metastasis present	±	< 5–30%

1.7.1.2 TNM Staging

The Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) introduced the tumour, node and metastasis (TNM) staging system in 1987. This is now a globally accepted standard for classification of cancers. Since the introduction, the classification system has been regularly updated, and the latest version, the 8th edition, is shown in Table 1-3 and Table 1-4 (114).

Cancer staging is considered the most important prognostic indicator in the management of colorectal cancer, and additionally, treatment decisions are now often based upon TNM classification. The current TNM staging has refined the classification of high-risk factors to identify those who may require adjuvant therapy, but controversy has arisen due to the non-hierarchical prognostic nature of the staging system (115). A large study by Bhutiani et al. has found that in patients with high tumour stage, the tumour category had a higher impact than the nodal category. Therefore, paradoxically, higher survival is seen in Stage III cancer compared to Stage II cancer. The changes in TNM staging over time should be taken into consideration when analysing survival results in the future.

In addition to TNM Staging, prefixes may indicate whether staging is based on radiological information (e.g., cTNM), pathological staging (e.g., pTNM), neoadjuvant therapy administered (e.g., yTNM), or whether the tumour is recurrent (e.g., rTNM).

Table 1-3 UICC TNM 8th Edition Classification of colorectal tumours

pT	**Primary tumour**
pTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour
pT1	Tumour invades submucosa
pT2	Tumour invades muscularis propria
pT3	Tumour invades the subserosa or into non-peritonealised pericolic or perirectal tissues
pT4	Tumour perforates visceral peritoneum (4a) and/or directly invades other organs or structures (4b)
pN	**Regional lymph nodes**
pN0	Regional lymph nodes cannot be assessed
pNX	No regional lymph node metastatic disease
pN1	Metastatic disease in 1–3 regional lymph nodes
pN1a	Metastasis in 1 regional lymph node
pN1b	Metastases in 2–3 regional lymph nodes
pN1c	Tumour deposit(s), i.e. satellites, in the subserosa, or in non-peritonealised pericolic or perirectal soft tissue without regional lymph node metastatic disease (tumour deposits are ignored if there is nodal metastatic disease)
pN2	Metastatic disease in 4 or more regional lymph nodes
pN2a	Metastases in 4–6 regional lymph nodes
pN2b	Metastases in 7 or more regional lymph nodes
pM	**Distant metastatic disease**
pM1	Distant metastatic disease
pM1a	Metastasis confined to 1 organ without peritoneal metastases
pM1b	Metastases in more than 1 organ
pM1c	Metastases to the peritoneum with or without other organ involvement

Table 1-4 AJCC TNM Stage Grouping

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1–T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1–T2	N1 / N1c	M0
	T1	N2a	M0
Stage IIIB	T3–T4a	N1 / N1c	M0
	T2–T3	N2a	M0
Stage IIIC	T4a	N2a	M0
	T3–T4b	N2b	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

1.7.2 Pathology

1.7.2.1 Macroscopic core items

The Royal College of Pathologists set out guidelines for the standard dataset required, and these are shown in Table 1-5 (111).

Table 1-5 Macroscopic core items

Data item	Details recorded
Nature of specimen and type of operation	Type of resection, e.g. right hemicolectomy, anterior resection or abdominoperineal excision (APER)
Site of tumour	Anatomical location of the primary tumour
Maximum tumour diameter	Maximum dimension of the tumour in millimetres
Distance to the nearer longitudinal resection margin	Clearance from the tumour to the nearest proximal or distal resection margin
Tumour perforation	Presence or absence of macroscopic tumour perforation
Relationship to the peritoneal reflection	Relationship of the tumour to the anterior peritoneal reflection; rectal tumours only
Plane of surgical excision	Quality of the surgical excision plane, particularly for anterior resection and APER specimens
Distance from the dentate line	Distance from the tumour to the dentate line; APER specimens only

The type of operation, nature and site of specimen should ordinarily be recorded by the operating surgeon. In tumour specimens that straddle two sites, the greatest bulk of tumour should be recorded, e.g. sigmoid versus rectum.

Although tumour diameter does not influence the staging of cancer, the measurement is taken from the luminal size to allow for correlation of preoperative investigations and measurement of response to preoperative therapy if neoadjuvant treatment was given.

The distance of the tumour from the nearer longitudinal margin is examined histologically if it is within 30mm of the resection margin macroscopically, otherwise it is assumed that the longitudinal margin is not involved.

Tumour perforations are classified specifically as the macroscopically visible defect through the tumour and regarded as pT4a disease. Tumour perforations in the peritoneal cavity are a well-known adverse prognostic factor (116). Therefore, the reporting excludes clinical classification of bowel perforation upstream from tumours as a result of obstruction or full-thickness defects that occur during handling of the specimen outside the peritoneal cavity. Similarly, findings suggestive of tumour perforation such as peritumoral abscess, faecal material or foreign body giant cells located in mesentery or serosal surface are not sufficient to define perforation in the absence of a macroscopic defect.

In rectal cancers, the relationship to the peritoneal reflection is an important indicator, as tumours below the peritoneal reflection have higher rates of local recurrence. As previously discussed, the current gold standard resection for rectal cancer is the total mesorectal excision, and the grade of the specimen is reported based on violation of the mesorectal plane.

Similarly, in patients undergoing APER, the plane of surgical excision around the anal canal and below the mesorectum is examined. The APER is associated with poorer outcomes compared to anterior resections for higher rectal cancer due to local recurrences attributed to higher rates of positive circumferential resection margin or intraoperative full-thickness defects. A systematic review by How et al. reported higher local recurrence rates after APER in most studies, demonstrating a significant difference, whereas there was no consistent difference in distant recurrences observed (117).

In low rectal tumours undergoing APER, the distance from the dentate line is recorded to indicate the location of the tumour in relation to the internal sphincter and assess the appropriateness of the extent of resection.

1.7.2.2 Microscopic core items

Aside from the macroscopic core items, the Royal College of Pathologists also recommend specific microscopic dataset that can offer prognostic information. These are shown in Table 1-6.

Table 1-6 Microscopic core data items

Data item	Details recorded
Histological tumour type	Histological classification and subtype, e.g. adenocarcinoma, mucinous carcinoma or signet-ring cell carcinoma
Grade of differentiation	Degree of tumour differentiation
Maximum extent of local invasion	Pathological T stage (pT), including depth of extramural spread for pT3 tumours
Response to preoperative therapy	Histological tumour regression grade, where neoadjuvant treatment has been administered
Resection margin status	Proximal and distal longitudinal margins and circumferential resection margin (CRM)
Lymph node status	Number of lymph nodes examined, number involved and highest lymph node status
Tumour deposits	Presence or absence of tumour deposits
Venous invasion	Presence or absence of venous invasion
Lymphatic invasion	Presence or absence of lymphatic invasion
Perineural invasion	Presence or absence of perineural invasion
Histologically confirmed distant metastatic disease	Histological evidence of metastases in submitted specimens, where applicable
Separate abnormalities	Other relevant pathological findings, such as synchronous carcinomas, polyps, inflammatory bowel disease or diverticulosis
Block index	Identification of sampled tissue blocks, including representative blocks suitable for molecular testing

Although nearly all colorectal cancers are adenocarcinomas with no specific subtype in origin, the WHO classification does recognise specific subtypes: mucinous carcinoma, signet ring carcinoma, medullary carcinoma, serrated adenocarcinoma, micropapillary adenocarcinoma and adenoma-like adenocarcinoma (118). Specific differentiations have an association with microsatellite instability, especially in mucinous, signet and medullary carcinoma.

The grade of differentiation has been shown to be an independent prognostic factor in colorectal cancer, although the inter-observer agreement in assessment remains poor (119). The current TNM staging recommends the use of four grades: grade 1- well differentiated, grade 2- moderately differentiated, grade 3- poorly differentiated and grade 4- undifferentiated. For consistency, WHO classification also recommends grading should be based on the least differentiated tumour component.

The maximum extent of local invasion determines the T category in the TNM staging as previously shown in Table 1-3. While in pT3 cancers, the maximum distance of tumour spread beyond the bowel wall measured from the outer margin of muscularis propia is documented. In some studies, the subclassification of pT3a versus pT3b based on a 5mm cutoff has shown a better prognostic profile with lower recurrence (120).

The AJCC currently recommends a four-tier system in evaluation of the response to preoperative therapy with scores ranging from 0-3 based on complete response to poor or no response, with the highest score. Patients with complete pathological response have better long-term outcomes than those with poor or no response with preoperative therapy (121).

The reporting of the resection margin includes both longitudinal margins as well as the circumferential resection margin. The longitudinal resection margin is recorded as previously described under macroscopic core items, while the circumferential resection margin requires> 1 mm. The resection margins are classified as R0 (no residual tumour), R1 (microscopic residual tumour) and R2(macroscopic residual tumour). R1 and R2 resections are predictive of local recurrence and poor survival, and this may dictate the role of adjuvant therapy (122).

The current TNM staging recommends evaluation of at least 12 lymph nodes for proper staging (123). However, as recommended by the Royal College of Pathologists, all lymph nodes should be histologically examined, as the number of nodes offers the N category staging irrespective of site in the specimen. A lymph node is considered involved if there is evidence of tumour deposit> 0.2 mm, and the highest lymph node closest to the main vascular ties is also identified, as these play a role as prognostic factors. Equally, in patients with preoperative therapy, the lymph node assessment is vital to assess for signs of regression.

Tumour deposits (satellites) are discrete microscopic and macroscopic nodules of cancer in the subserosa, in non-peritonealised pericolic or perirectal soft tissue without the histological evidence of residual lymph node, vascular or neural tissue. Based on the TNM 8th Edition, the identification of tumour deposits does not alter the T category but does alter the N category (see Table 1-3). A systematic

review reported that the presence of tumour deposits was detected in 22% of colorectal cancer cases and is associated with poor outcomes, presence of lymph node metastasis and extramural venous invasion (124).

For reporting purposes, if tumour deposits are present with identifiable vessel wall on staining, it should be classified as venous invasion (VI) or lymphatic invasion (L1) and similarly perineural invasion (Pn1) if neural structures are identified. It is well recognised that extramural venous invasion is an independent prognostic indicator, but studies have also shown lymphatic invasion and perineural invasion have adverse prognostic significance (125-127).

Distant metastatic disease can sometimes be present within the primary tumour specimen, e.g. in the presence of omental and peritoneal involvement, and these should be recorded. On occasion, metastatic disease is detected in lymph nodes away from the primary specimen and should be recorded as per TNM staging in Table 1-3.

Aside from reporting the primary cancer, the pathologist also examines for any pathological abnormalities in the submitted resection specimen, and these should be recorded especially in the presence of polyps, synchronous carcinoma, ulcerative colitis, Crohn's disease, diverticulosis, obstructive colitis and non-tumour perforation.

Documentation of the sampling process has become an important process in pathological reporting. Block index becomes a helpful resource when further review or molecular testing is required.

Additionally, other core items may be included in the pathology reporting, including tumour budding, poorly differentiated clusters, tumour stromal percentage and peritumoral inflammation.

1.8 Inflammation and cancer

1.8.1 Host response

Inflammation is the body's response to tissue damage and plays an important role in tissue homeostasis. The immune system, made up of innate and adaptive immunity, generates an inflammatory response in the form of immune or cellular changes that result in tissue repair, regeneration and remodelling. Chronic inflammation, either due to persisting causes or failure of the regulatory mechanism to shut down, has been linked to various steps involved in tumorigenesis.

Hanahan and Weinberg first described the six hallmarks of cancer, including sustained proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis and activating invasion and metastasis (128). Subsequently, it was found that inflammation had both pro- and anti-tumour effects, as the immune response that historically reflected responses to eradicate tumours also has a paradoxical effect (129).

Indeed, tumour-promoting inflammation was described as inadvertently support cancer hallmark capabilities by supplying bioactive molecules to the tumour microenvironment, growth factors, survival factors to limit cell death, proangiogenic factors and extracellular matrix-modifying enzymes (128). The presence of this inflammatory response has also been associated with adverse long-term outcomes (130).

1.8.2 Innate Immunity

The innate immunity represents the first line of defence against pathogens. This includes the physical, chemical and cellular barriers. This system of protection is non-specific and forms an immediate response that consists of both cellular and humoral components.

The cellular recruitment involves activation of macrophages, neutrophils, eosinophils, basophils, mast cells, natural killer cells and dendritic cells that uses pattern recognition molecules to remove pathogen (131). The humoral

component, on the other hand, consists of complement systems, acute phase proteins, e.g. C-reactive protein (CRP) and cytokines.

The complement system consists of a variety of proteins that act in sequence to form the complement cascade that can be activated through three different pathways: classical, alternative and lectin pathways (132). Immune protection is achieved via identifying targets with soluble pattern recognition molecules that are subsequently eliminated by humoral and cellular effectors. The cytokines act as messengers by recruiting the cellular component to the site of inflammation.

1.8.3 Adaptive Immunity

The interaction of the humoral and cellular components from the innate immune system activates the adaptive immune system. The ability to confer protection against infection comes from the memory developed from previous antigen exposure and the ability to produce a specific response against it.

The adaptive immunity involves both antibody responses (B cell) and cell-mediated responses (T cell). The B cells are activated to produce immunoglobulins as a response to antigen-presenting cells. These antibodies subsequently circulate, detect and bind to the specific antigens that triggered the response. The antibody binding also triggers the complement cascade that results in the eventual phagocytosis and destruction.

In cell-mediated immunity, T cells are converted to activated effector T cells after encountering antigen-presenting cells. These cells can further differentiate into cytotoxic T cells that result in elimination of pathogens by direct apoptosis, and T-helper cells that primarily function to activate macrophages and B cells to produce antibodies.

1.8.4 Local inflammatory response

The presence of tumours with dense infiltration of both the innate and adaptive immune response that mimic wound healing has been noted in previous reports (133). Tumour growth is dependent on the interaction between the tumour cells and the microenvironment. The tumour microenvironment is a complex system consisting of immune cells, stromal cells, blood vessels, and extracellular matrix

(134). Tumour cells are thought to stimulate significant molecular, cellular and physical changes to support tumour growth and progression. It has been recognised that the host immune response plays an important determinant in the outcome (128).

The infiltration of lymphocytes around the cancer is associated with improved cancer-specific outcomes in colorectal cancer regardless of tumour stage (130). Conversely, the presence of local infiltrate characterised by the innate immune response has been reported to have adverse outcomes, possibly attributed to the tumour promoting inflammation (135). Although several scoring systems, including the Galon Immunoscore, the Klintrup-Makinen grade and the Glasgow Microenvironment score, are available to stratify the local inflammatory responses, the complexity of immunohistochemistry, difficulties in reliable reproducibility and associated cost limit the clinical use (136-138).

1.8.5 Systemic inflammatory response

Systemic inflammatory response represents an exaggerated immune reaction to tissue injury. While inflammation is a normal regulatory process, systemic inflammation results in the widespread release of the inflammatory cascade with the aim to isolate and eliminate the insult. However, the importance of inflammation in tumour growth and progression has previously been described as a result of chronic inflammation. In many forms of cancer, systemic inflammatory responses have been significantly related to the risk of metastasis (139).

Several cytokines are involved with the systemic inflammatory response. Interleukin-6 is a proinflammatory cytokine that increases the production of acute phase proteins, notably CRP, decreases albumin production, promotes development of megakaryocytes into platelets, boosts thrombopoietin synthesis and has also been implicated in neutrophil recruitment.

CRP is an acute phase protein that is synthesised by hepatocytes as a response to inflammatory cytokines, primarily IL-6. CRP acts by activating the complement system by binding to Fc receptors, which further enhances the inflammatory response, and also acts as an opsonin for various pathogens. Albumin is a negative acute phase protein synthesised by the liver. The concentration of albumin is

known to decrease in the presence of inflammation as a result of increased demand for amino acids for acute phase synthesis.

The systemic inflammatory response can be measured in various ways using acute phase proteins such as the modified Glasgow Prognostic Score (mGPS) or haematological markers such as the neutrophil-to-lymphocyte ratio (NLR) (140, 141). The mGPS has been extensively validated. This cumulative score is based on thresholds of CRP and albumin, although the inflammatory components weigh more heavily. The score is calculated as follows with CRP<10mg/L scores 0, CRP>10mg/L and albumin≥35 g/L scores 1 and CRP>10mg/L and albumin<35g/L scores 2 (142).

The NLR is another prognostic score that has been reported to predict outcomes in cancer. The NLR is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, with a threshold of 5 used to distinguish between those with low versus high NLR(140). In patients who have undergone curative colorectal cancer resection, the presence of an enhanced inflammatory response as measured by an elevated NLR or mPGS is associated with poorer outcomes (143).

The Systemic Inflammatory Grade (SIG) was developed to provide a combined assessment of the preoperative systemic inflammatory response by incorporating the mGPS and NLR (144). For the calculation of SIG, the NLR is categorised into three groups: 0 (NLR<3), 1 (NLR 3-5) or 2 (NLR>5). The mGPS is scored from 0-2 according to CRP and albumin concentrations. These two measures are then combined to classify patients into five grades from SIG 0 to SIG 4, representing an increasing systemic inflammatory response (Table 1-7). By integrating biochemical markers of inflammation and nutritional status with a measure of the circulating inflammatory cell profile, SIG provides a broader assessment of the host systemic inflammatory response than either mGPS or NLR alone. Its prognostic value for overall and cancer-specific survival across all TNM stages was evaluated in a cohort of 1,700 patients, with SIG demonstrating superior prognostic value compared to mGPS and NLR individually (144). These findings support the potential role of SIG as a prognostic marker in colorectal cancer, although its relationship with postoperative outcomes requires separate evaluation.

Table 1-7 Measurements of Systemic Inflammatory Grade

mGPS	Score
CRP ≤ 10	0
CRP > 10 and albumin ≥ 35	1
C-RP > 10 and albumin < 35	2
NLR	
NLR < 3	0
NLR 3–5	1
NLR > 5	2
Systemic Inflammatory Grade (SIG)	
SIG 0	mGPS 0 and NLR < 3
SIG 1	mGPS 0 and NLR 3–5 or mGPS 1 and NLR < 3
SIG 2	mGPS 0 and NLR > 5 or mGPS 2 and NLR < 3 or mGPS 1 and NLR 3–5
SIG 3	mGPS 1 and NLR > 5 or mGPS 2 and NLR 3–5
SIG 4	mGPS 2 and NLR > 5

1.9 Complications Following Surgery for Colorectal Cancer

1.9.1 Short-term outcomes

Surgical resection remains, for most of the population, the primary curative mode of treatment; however, it carries with it potential morbidity and mortality. The overall mortality rate following colorectal cancer resection ranges between 3% and 16% (145) while morbidity rates have been reported up to 35% (146). Postoperative complications are associated with poorer quality of life, prolonged hospital stay, higher readmission rates and increased mortality (147, 148).

Postoperative complications can be defined as "any variation from the normal postoperative course" and can be classified in a number of ways. The classification of complications plays an important role in clinical and research practice as it allows the ability to directly compare, compile outcomes such as those in meta-analysis and demonstrate linkage between risk factors and specific postoperative complications.

1.9.1.1 Classification by Type

Complications have more commonly been classified by type. Nevertheless, the classification of postoperative complications in this manner remains largely subjective due to variations in definition. The World Health Organisation have reported as many as 41 different definitions for surgical site infection in their global guidelines for prevention of surgical site infection (149). Although a single definition would be of value, they have recognised that there is no objective gold standard test and variation in pre-existing regional guidelines would be a challenge. Postoperative complications are therefore usually included in a descriptive manner in most literature, such as those shown in Table 1-8.

Table 1-8 Types of complications and accepted definitions

Type	Location	Complication	Description
Infective	Surgical site infection	Superficial incision	Involves only skin and subcutaneous tissue, presence of purulent drainage or positive bacterial culture or signs of infection
		Deep incisional	Affects deep soft tissue such as muscle and fascia, presence of purulent drainage from deep incision or wound dehiscence or systemic inflammatory response
		Organ/Space	Occurs in any part of the anatomy other than the incision itself, purulent drainage from drain placed in organ/space or abscess/ infection identified on imaging
	Remote site infection	Urinary tract infection	Lower urinary tract symptoms or fever with positive urinalysis or urine culture
		Pneumonia	Fever above 38.5 or systemic inflammatory response syndrome associated with positive chest X-ray findings
		Bloodstream infection	Systemic inflammatory response syndrome with positive blood culture
Non-Infective	Surgical site	Haemorrhage	Bleeding requiring radiological or operative intervention
	Wound	Seroma	Sterile superficial wound collection without fever or cellulitis
		Dehiscence	Deep or superficial separation of wound without fever, pus or cellulitis
	Cardiac	Myocardial infarction	Chest pain with associated ECG changes or raised cardiac enzymes
		Arrhythmia	New, resting ECG changes requiring medical intervention
	Vascular	Deep vein thrombosis	Deep venous thrombus confirmed radiologically
		Pulmonary embolism	Pulmonary venous thrombus confirmed radiologically
		Stroke	Persisting focal neurological deficit with radiological evidence of cerebral vascular territory infarction

	Urinary	Renal failure	Oliguria/ anuria with decreasing eGFR based on the RIFLE or AKIN criteria
		Urinary retention	Inability to void urine requiring urinary catheterisation
	Gastrointestinal	Ileus	Paralytic/ non mechanical small bowel obstruction

1.9.1.2 Classification by severity

The initial description of postoperative complications based on severity in terms of minor and major also created a subjective interpretation. The Clavien-Dindo classification described in 1992 offers a standardised system for evaluating complications (150). This classification of complications was based on the type of therapy needed to correct the complication. This principle of the classification allowed for simple, objective and reproducible application across multiple specialities (151).

Table 1-9 Clavien-Dindo scale of surgical complication (adapted from Dindo et al. 2004)

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, or radiological interventions
Grade II	Complications requiring pharmacological treatment beyond those allowed for Grade I
Grade III	Complications requiring surgical, endoscopic, or radiological intervention
Grade IIIa	Intervention not requiring general anaesthesia
Grade III b	Intervention requiring general anaesthesia
Grade IV	Life-threatening complications requiring intensive care management
Grade IV a	Single organ dysfunction
Grade IV b	Multi-organ dysfunction
Grade V	Death of the patient

1.9.2 Long-term outcomes

Although the prognosis in colorectal cancer is predominantly determined by tumour staging, it is well recognised that other factors such as the previously

described systemic inflammatory response have a significant impact independent of the TNM staging. Similarly, postoperative complications not only affect short-term outcomes but have also been reported to impact long-term outcomes.

Khuri et al. reported that the occurrence of 30-day complications reduced the median patient survival by 69% across 8 different types of operations in a large national cohort (152). Law et al. studied a cohort of patients undergoing radical resection for colorectal cancer and reported that the presence of postoperative complications was an independent factor associated with worse 5-year overall survival and high recurrence rates (153). Regardless of the type or severity of complication, McSorley et al. have demonstrated that infective complications have a negative impact on overall survival and disease-free survival after surgery for colorectal cancer (154).

Therefore, extensive research efforts have been focused on identifying factors contributing to postoperative complications. These efforts are necessary to address the significant postoperative morbidity in this population as well as the emerging emphasis on standardised outcome measures to compare surgical quality across hospitals.

1.10 Summary and Aims

The aim of the present thesis was to

1) Determine a minimum data set of prognostic variables affecting short-term outcome following colorectal cancer surgery.

2) Examine the current practice of preoperative carbohydrate loading on surgical site infection in curative colon cancer surgery

3) Examine the relationship between routinely reported clinicopathological factors on postoperative infective complications following colon cancer surgery.

4) Examine the relationship between independent clinicopathological risk factors on surgical site infection following curative colon cancer surgery

5) Examine the effect of objective measurement of independent clinicopathological risk factor on surgical site infection following curative colon cancer surgery

6) Prospective validation of objective measurement for clinicopathological factor on surgical site infection in patients undergoing surgery for colon cancer

Chapter 2 Evaluation of clinical prognostic variables on short-term outcome for colorectal cancer surgery: An overview and minimum dataset

2.1 Introduction

Colorectal cancer is the second leading cause of cancer death worldwide, with an estimate of 1.8 million new cases diagnosed and almost 900 000 deaths in 2018. Despite a trend for reduction in the rate of colorectal cancer mortality, the incidence has increased over the last four decades. The World Health Organisation International Agency for Cancer Research estimates a global incidence of colorectal cancer of 30 million by 2040 (155). In the United Kingdom, 42 081 new cases were diagnosed in 2017 (2). This represents 11 % of all new cancer cases reported in 2017, making it the fourth most common cancer.

Surgical resection remains, for most of the population, the primary curative mode of treatment; however, it carries with it potential morbidity and mortality. The overall mortality rate following colorectal cancer resection ranges between 3% and 16%, while morbidity rates have been reported up to 35% (145, 146). Extensive research efforts have been focused on identifying factors contributing to postoperative complications. These efforts are necessary to address the significant postoperative morbidity in this population as well as the emerging emphasis on standardised outcome measures to compare surgical quality across hospitals.

Postoperative complications can be defined as “any variation from the normal postoperative course” and classified by severity, such as those described in the Clavien - Dindo classification (150, 156) or by type (infective versus non-infective). The classification of complications plays an important role in clinical and research practice as it allows the ability to directly compare, compile outcomes such as those in meta-analysis and demonstrate linkage between risk factors and specific postoperative complications.

Risk predictive tools such as P-POSSUM, SORT, NELA and the speciality-specific CR-POSSUM provide an estimate of the 30-day morbidity and mortality risk to allow

better-informed decision-making before surgery (157-160). Nevertheless, most surgical risk assessment tools utilise only some of the information available about the patient's health and the proposed surgery to provide estimates of risk and may not serve as an individual patient-specific estimate. There may be other patient-specific or surgical factors that influence the risk of death significantly which are not accounted for.

Previous studies have reported that host factors (age, gender), tumour factors (cancer stage) and surgical factors (technical approach) play a role in affecting the short-term outcomes in surgery (161). Surgery stimulates the release of pro-inflammatory cytokines that trigger a systemic inflammatory response (162). Recent studies have demonstrated an association between postoperative systemic inflammatory response, postoperative complications, and long-term survival (37, 163). Studies have also reported that the presence of a preoperative systemic inflammatory response predisposes to postoperative complications for patients undergoing colorectal cancer surgery, which in turn has an effect on the long-term survival outcome (154, 164-167).

The systemic inflammatory response can be measured using acute phase proteins such as the modified Glasgow Prognostic Score (mGPS) or haematological markers such as the neutrophil-to-lymphocyte ratio (NLR) (140, 141). In patients who have undergone curative colorectal cancer resection, the presence of an enhanced inflammatory response as measured by an elevated NLR or mPGS is associated with poorer outcomes (143).

In order to reduce postoperative complications and therefore improve both short-term and long-term outcomes, it is important to identify which factors are associated with postoperative complications. The aim of the present review was to identify prognostic host and other preoperative variables that are associated with postoperative complications. This will enable a minimum data set of prognostic variables to facilitate comparison of clinical management of colorectal cancer.

2.2 Methods

On an initial search of available literature, a large number of studies (n > 14 000) were identified. It was clear that several variables were already examined on multiple occasions and included in systematic reviews. Therefore, the approach taken was to examine systematic reviews of all validated variables rather than the individual publications. This overview of systematic reviews was conducted to assess the relationship between the host and other factors and short- term postoperative complications.

The literature search was carried out in PubMed, Cochrane Database of Systematic Reviews (CDSR) and Web of Science (WoS) databases from inception to 8 September 2020. The following search term was used in free text and medical subject heading (MeSH) "(colon or colorectal) AND (cancer or neoplasm) AND (surgery or resection or operation) AND (complication or morbidity) AND (outcome)".

The titles and abstracts of all systematic reviews returned by the search were examined for relevance. Only systematic reviews were included. Reviews not available in English and reviews published in abstract form only were excluded. Where there were multiple reviews from the same group, only the most recent paper was included.

The full text of each systematic review deemed potentially relevant was obtained. Systematic reviews which included studies with non-cancer patients were also eligible if they made up less than 50% of the study population. Reviews were excluded if characteristics of individual studies were not reported. Once further exclusions outlined below were carried out, the bibliography of relevant reviews was hand searched to include additional systematic reviews.

To be included, a systematic review had to examine the relationship between short-term outcomes and colorectal cancer surgery in terms of either 30-day mortality, infective complications, non-infective complications, or severity of complications defined by the Clavien-Dindo classification. Reviews on surgical factors were excluded to focus on host and preoperative factors. Any uncertainties were resolved through discussion with the senior author (DM).

This umbrella review has been performed in accordance with PRISMA guidelines (Figure1). The data extraction in the form of a table was used to summarise study results. The following information from eligible systematic reviews was extracted: author, review aims, databases searched, years included, study design, number of studies included, total study population, outcome measures (30-day mortality, infective complications, non-infective complications or Clavien-Dindo classification) and outcomes of risk of bias assessments.

The systematic reviews were grouped according to their clinical characteristics, reporting on either host or preoperative factors. The factors identified across the included reviews were compared according to reported association with short-term postoperative outcomes. The evidence was reviewed qualitatively, taking into consideration the consistency with which each factor was reported across 30-day mortality, infective and non-infective complications. Given the heterogeneity in the variables assessed and reported outcomes, a meta-analysis of the systematic review was not undertaken. A narrative review was performed to synthesise existing systematic reviews.

Based on this synthesis, a proposed dataset of preoperative baseline variables was developed and categorised into minimum, recommended and potential variables. Variables consistently associated with 30-day mortality, 30-day morbidity, infective complication or non-infective complication were included in the minimum dataset, while those with less consistent evidence were assigned to recommended or potential categories. The proposed dataset was intended to provide a structured framework for collecting preoperative variables and facilitate more consistent evaluation of clinical predictive factors in future colorectal studies.

2.3 Results

2.3.1 Literature search

The initial search strategy identified 698 systematic reviews whose titles and abstracts were reviewed. Four further reviews were identified from searching the bibliography of included reviews, and duplicates were removed (n=3). At screening, 513 reviews were excluded, of which were not in English (n=9), were not relevant to the topic or included pathologies other than colorectal cancer (n=504). This led to a review of 186 full publications; of these, excluded reviews included reviews that did not assess short-term outcomes (n = 16), reviews of operative factors (n=94), reviews which included more than 50% benign colorectal disease (n=29), and reviews which did not specify study population (n=14). A total of 47 articles were included in this overview.

2.3.2 Age

Four reviews examined the relationship between age and short-term outcomes (Table 2-1). One review included mostly open colorectal resections, as open surgery was the norm during the period of study (168), one review included only laparoscopic resections (169), one review included two randomised controlled trials with sub-analysis on age, comparing outcomes of laparoscopic versus open surgery (170) and one review examined the risk factor for anastomotic leak (171). Nine short-term outcomes were reported across all systematic reviews.

Three reviews (168-170) examined the association between age and 30-day mortality, two (168, 169) of which reported no association, including the most recent of the reviews (169).

Two reviews (169, 170) examined the association between age and overall morbidity; both reviews reported an increase in overall morbidity in the elderly population. Three reviews (168, 169, 171) examined the association between age and anastomotic leak; all reviews reported no association. Two reviews (168, 169) examined the association between age and pulmonary complications; the more recent (169) of the two reported no association. One review (169) examined the association between age and wound infection; the review reported no association.

One review (168) examined the association between age and cerebrovascular complications; the review reported an increase in cerebrovascular complications in the elderly population. Two reviews (168, 169) examined the association between age and cardiac complications; the more recent of the two reported no association. One review (168) examined the association between age and venous thromboembolism; the review reported no association. One review (169) examined the association between age and postoperative ileus; the review reported no association.

Therefore, age was inconsistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

2.3.3 Sex

Two reviews examined the relationship between sex and short-term outcomes (Table 2-2). One review (172) examined the association with surgical site infection, and one review (171) examined the association with risk factors for anastomotic leak. Two short-term outcomes were reported across all systematic reviews.

One review (172) examined the association between sex and surgical site infections; the review reported an increased risk of surgical site infections in males. One review (171) examined the association between sex and risk of anastomotic leak; the review reported an increased risk of anastomotic leak in males.

None of the reviews examined the association between sex and non-infective complications.

Therefore, sex was inconsistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

2.3.4 Diabetes

Two reviews examined the relationship between diabetes and short-term outcomes (Table 2-3).

Four short-term outcomes were reported across all systematic reviews.

One systematic review (173) examined the association between diabetes and 30-day mortality; the review reported increased 30-day mortality in diabetics.

One review (173) examined the association between diabetes and anastomotic leak; the review reported increased risk of anastomotic leak in diabetics. One review (172) examined the association between diabetes and surgical site infections; the review reported increased surgical site infections in diabetics.

One review (172) examined the association between diabetes and cardiovascular complications; the review reported increased cardiovascular complications in diabetics.

Therefore, diabetes was consistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

2.3.5 Body composition and nutritional status

(Body mass index, visceral obesity, and sarcopenia)

Nine reviews examined the relationship between body composition or nutritional status and short-term outcomes (Table 2-4). Four reviews examined the association with body mass index (171, 172, 174, 175), two reviews examined the association with visceral obesity (176, 177), one review examined the association with sarcopenia (178), one review examined the association with both sarcopenia and visceral obesity (179) and one review examined the association with a preoperative prognostic nutritional index (180). Seven short-term outcomes were reported across all systematic reviews.

Two reviews (178, 179) examined the association between sarcopenia and 30-day mortality; the reviews reported increased 30-day mortality with sarcopenia.

One review (175) examined the association between body mass index and overall morbidity; the review reported increased overall morbidity with high body mass index. Three reviews (176, 177, 179) examined the association between visceral obesity and overall morbidity; all reviews reported increased overall morbidity

with visceral obesity. Two reviews (178, 179) examined the association between sarcopenia and overall morbidity; both reviews reported increased overall morbidity with sarcopenia. One review (180) examined the association between prognostic nutritional index and overall morbidity; the review reported increased overall morbidity with low prognostic nutritional index. Two reviews (174, 175) examined the association between body mass index and wound infections; both reviews reported increased wound infection with high body mass index. Two reviews (177, 179) examined the association between visceral obesity and wound infections; one review (177) reported increased wound infection with visceral obesity while the other review (179) was inconclusive. One review (178) examined the association between sarcopenia and wound infection; the review reported no association. One review (172) examined the relationship between body mass index and surgical site infections; the review reported increased surgical site infection with higher body mass index. Two reviews (171, 175) examined the association between body mass index and anastomotic leak; one review (175) reported increased anastomotic leaks with higher body mass index. Two reviews (177, 179) examined the association between visceral obesity and anastomotic leak; one review reported increased anastomotic leaks with visceral obesity (177), while the other review was inconclusive (179). One review (178) examined the association between sarcopenia and anastomotic leak; the review reported no association. One review examined the relationship between body mass index and intra-abdominal collection; the review reported increased intra-abdominal collections with higher body mass index (174). One review examined the relationship between preoperative prognostic nutritional index and severe complications; the review reported an increased risk of serious complications with a low prognostic nutritional index (180).

None of the reviews examined the association between body composition and non-infective complications.

Therefore, body composition was consistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

2.3.6 Functional Status

(ASA, Functional capacity, Frailty)

Four systematic reviews examined the relationship between functional status and short-term outcomes (Table 2-5). Two reviews (171, 172) examined the relationship with the American Society of Anesthesiologists physical status classification system (ASA), one review (181) examined the relationship with frailty, and one review (182) examined the relationship with functional capacity testing. Eight short-term outcomes were reported across all reviews.

One review (182) examined the association between functional capacity and 30-day mortality; the review reported no association. One review (181) examined the association between frailty and 30-day mortality; the review reported no association.

One review (164) examined the association between functional capacity and overall morbidity; the review reported reduced overall morbidity with good functional capacity. One review (181) examined the association between frailty and overall morbidity; the review reported increased overall morbidity with frailty. One review (172) examined the association between ASA and surgical site infection; the review reported increased surgical site infections with higher ASA status. One review (182) examined the association between functional capacity and infective complications; the review reported reduced infective complications with good functional capacity. One review (181) examined the association between frailty and postoperative sepsis; the review reported an increased risk of postoperative sepsis with frailty. One review (172) examined the association between ASA and anastomotic leak; the review reported a reduction in anastomotic leak with lower ASA status. One review (182) examined the association between functional capacity and pulmonary complications, the review reported reduced pulmonary complication with good functional capacity.

One review (182) examined the association between functional capacity and wound dehiscence; the review reported reduced wound dehiscence with good functional capacity. One review (181) examined the association between frailty and readmissions; the review reported increased readmissions with frailty.

Therefore, ASA status, frailty and functional capacity were inconsistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

2.3.7 Mechanical Bowel Preparation

Eight systematic reviews (183-190) examined the relationship between mechanical bowel preparation and short-term outcomes (Table 2-6). All these reviews compared mechanical bowel preparation versus no preparation. Five short-term outcomes were reported across all reviews.

Five reviews (184-186, 188, 189) examined the association between 30-day mortality and mechanical bowel preparation, all reviews reported no association.

One review (189) examined the association between overall morbidity and mechanical bowel preparation; the review reported no association. Seven reviews (184-190) examined the association between wound infections and mechanical bowel preparations; six of the reviews (184-189) reported no association between wound infections and mechanical bowel preparation. Eight reviews (183-190) examined the association between anastomotic leak and mechanical bowel preparation; seven reviews (183-188, 190) reported no association. Five reviews (184, 186-189) examined the association between intra-abdominal collection and mechanical bowel preparation; all reviews reported no association. Three reviews (184, 185, 188) examined the association between reoperation and mechanical bowel preparation; all these reviews reported no association.

None of the reviews examined the association between mechanical bowel preparation and non -infective complications.

Therefore, mechanical bowel preparation was inconsistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

2.3.8 Antibiotic prophylaxis

Two reviews examined the relationship between antibiotic prophylaxis and short-term outcomes (Table 2-7). One review (191) examined the relationship between antibiotic prophylaxis in colorectal surgery, and one review (192) examined the

relationship between oral antibiotics and short-term outcomes in the presence of mechanical bowel preparation and systemic antibiotics. Three short-term outcomes were reported across all studies.

None of the reviews examined the association between antibiotic prophylaxis and 30-day mortality.

One review (191) . examined the association between antibiotic prophylaxis and wound infection; the review reported reduced wound infection with antibiotic prophylaxis. One review (192) examined the association between oral antibiotic prophylaxis and wound infection in the presence of mechanical bowel preparation and systemic antibiotics; the review reported a reduction in wound infections with oral antibiotics. One review (192) examined the association between oral antibiotic prophylaxis and intra-abdominal collection along with surgical site infections in the presence of mechanical bowel preparation and systemic antibiotics; the review reported no significant difference in intra-abdominal collection and a reduction in surgical site infection with oral antibiotic prophylaxis.

None of the reviews examined the association between antibiotic prophylaxis and non-infective complications.

Therefore, antibiotic prophylaxis was inconsistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

2.3.9 Anaemia

(Blood transfusion, Iron and Erythropoietin)

Five systematic reviews examined the association between management of anaemia and short-term outcomes (Table 2-8). Three reviews (193, 194) examined the association between blood transfusion and short-term outcomes. Two reviews (195, 196) examined the association between iron therapy and blood transfusion requirement. One review (197) examined the association between erythropoietin and short-term outcomes. Nine short-term outcomes were reported across all studies.

One review (197) examined the association between 30-day mortality and erythropoietin; no association was reported.

One review (193) examined the association between overall morbidity and blood transfusions; the review reported increased overall morbidity with blood transfusion. Two reviews (193, 194) examined the association between infective complications and blood transfusion; both reviews reported an association between increased infective complications and blood transfusion. One review (193) examined the association between anastomotic leak and pulmonary complications with blood transfusion; the review reported increase in both anastomotic leak and pulmonary complications with blood transfusion. Two reviews (193, 194) examined the association between reoperation and blood transfusion; both reviews reported increased reoperation with blood transfusions.

Two reviews (195, 196) examined the association between iron therapy and blood transfusion requirement; the more recent (195) of the two reported an association between a reduction in blood transfusion requirement and iron therapy. One review (193) examined the association between blood transfusion and cardiac complications; the review reported an increase in cardiac complications with blood transfusion. One review (197) examined the association between erythropoietin and thrombotic complications; the review reported no association.

Therefore, blood transfusion, iron and erythropoietin were inconsistently associated with short-term outcomes in patients undergoing colorectal cancer surgery.

2.3.10 Enhanced recovery programmes

Seventeen reviews examined the relationship between enhanced recovery programmes and short-term outcomes (Table 2-9). Five reviews (198-202) examined the association of enhanced recovery programmes versus conventional care, two review (203, 204) examined the association with physical prehabilitation, three reviews (205-207) examined the association with probiotic use, two reviews (208, 209) examined the association with chewing gum use, two reviews (210, 211) examined the association with nutritional prehabilitation, two review (212, 213) examined the combined effect of physical and nutritional

prehabilitation and one review (214) examined the association with immunonutrition. Eleven short-term outcomes were reported across all studies.

Four reviews (198-200, 202) examined the association between enhanced recovery programme and 30-day mortality; all reviews reported no association. One review (210) examined the association between nutritional intervention and 30-day mortality; the review reported no association. One review (208) examined the association between gum chewing and 30-day mortality; the review reported no association.

Five reviews (198-202) examined the association between enhanced recovery programme and overall morbidity; four reviews (198, 199, 201, 202) reported reduced overall morbidity with enhanced recovery programmes. Two reviews (203, 204) examined the association between physical prehabilitation and overall morbidity; both reviews reported no association. Two reviews (210, 211) examined the association between nutritional prehabilitation and overall morbidity; both reviews reported reduced overall morbidity with nutritional prehabilitation. Two reviews (212, 213) examined the association between combined prehabilitation (physical and nutritional) with overall morbidity; one review (212) showed reduced overall morbidity with combined prehabilitation. One review (209) examined the association between gum chewing and overall morbidity; the review reported no association.

Three reviews (205-207) examined the association between probiotic use and infective complications; all three reviews reported reduction in infective complications with probiotic use. One review (214) examined the association between immunonutrition and infective complications; the review reported reduced infective complications with immunonutrition. Two reviews (198, 201) examined the association between enhanced recovery programmes and wound infections; both reviews reported no association. Three reviews (205-207) examined the association between probiotic use and wound infections; two (205, 207) of the reviews reported no association. Two reviews (198, 201) examined the association between enhanced recovery programmes and anastomotic leaks; both reviews reported no association. Two reviews (206, 207) examined the association between probiotic use and anastomotic leak; both reviews reported no association. One review (211) examined the association between nutritional

prehabilitation and anastomotic leak; the review reported no association. Two reviews (206, 207) examined the association between probiotic use and pulmonary complications; both reviews reported reduction in pulmonary complications. One review (206) examined the association between probiotic use and urinary tract infection; the review reported no association. One review (198) examined the association between enhanced recovery programmes and reoperation; the review reported no association. One review (209) examined the association between gum chewing and reoperation; the review reported no association.

Four reviews (199-202) examined the association between enhanced recovery programmes and readmission; all reviews reported no association. One review (209) examined the association between gum chewing and readmission; the review reported no association. One review (210) examined the association between nutritional prehabilitation and readmission; the review reported no association. One review (198) examined the association between enhanced recovery programme and postoperative ileus; the review reported reduction in postoperative ileus with enhanced recovery programme. One review (208) examined the association between gum chewing and postoperative ileus; the review reported no association.

Therefore, enhanced recovery programmes were inconsistently associated with short-term outcomes in patients undergoing colorectal cancer surgery.

2.3.11 Steroid use

One review examined the relationship between steroid use and short-term outcomes (Table2-10). The review (171) examined the association with anastomotic leak. One short-term outcome was reported in the review.

No review examined the association between steroid use and 30-day mortality. One review (171) reported increased anastomotic leak with steroid use. No review examined the association between steroid use and non-infective complications.

Therefore, steroid use is inconsistently associated with short-term outcomes in patients undergoing colorectal cancer resection.

2.4 Discussion

The present overview has identified several factors that are associated with the risk of developing infective complications, including male sex, diabetes, high body mass index, visceral obesity, poor functional status, use of blood transfusion and steroids. While the presence of antibiotic prophylaxis, probiotic and immunonutrition use in enhanced recovery programme was associated with reduction in infective complications. With reference to non-infective complications, the present overview identified that diabetes, poor functional status, and blood transfusions were associated with the risk of developing non-infective complications. Finally, the overview has identified factors that are consistently associated with 30-day mortality following colorectal cancer surgery, including diabetes and sarcopenia. Therefore, these factors (in particular, those associated with 30-day mortality) should be included in a minimum dataset for future studies of postoperative outcomes in patients undergoing surgery for colorectal cancer.

In contrast, the present overview identified several factors that, on systematic review, were not consistently associated with postoperative outcomes, including mechanical bowel preparation. Certain factors reported mixed outcomes associated with either 30-day mortality or infective or non-infective outcomes such as functional status, blood transfusions and enhanced recovery programmes. These factors may be considered in addition to the minimum set of factors.

The presence of diabetes has commonly been associated with higher incidences of postoperative complications in cancer and non-cancer patients (215, 216). The findings of the present overview is in keeping with a recent meta-analysis by Tan et al. which have shown a higher rate of surgical site infection (OR 1.98; 95% CI 1.64-2.39; $p<0.001$) and anastomotic leak (OR 2.41; 95% CI 1.84-3.16; $p<0.001$) in diabetic compared to non-diabetic patients following surgery for both malignant and benign colorectal disease (217). The inflated risk of short-term complications in diabetic patients may relate in part, to associated comorbidities such as hypertension, coronary heart disease, renal disease and metabolic effects of hyperglycaemia (218). Nevertheless, the diagnosis of diabetes is a nexus to a cluster of comorbidities associated with poor postoperative outcomes. The prevalence of diabetes and impaired glucose tolerance has been steadily

increasing over the decades and can be readily treated prior to surgery (219). In patients with colorectal cancer, identification of diabetes is of considerable importance, understanding the relationship between hyperglycaemia and colorectal cancer resection could aid in risk reduction of short-term outcomes especially in patients who have untreated or undiagnosed diabetes. Frisch et al. reported an increased risk of 30-day mortality with hyperglycaemia greater in non-diabetic patients compared to known diabetics for general and non-cardiac surgery patients while an observational study by Kotagal et al, reported a higher risk of adverse event in non-diabetic patients compared to diabetic patents following surgery in the presence of hyperglycaemia (OR 1.63, 95% CI 1.27-2.10 for blood glucose > 180mg/dL) (220, 221).

The National Institute for Health and Care Excellence (NICE) recommends the use of a suitable validated risk stratification tool to supplement clinical assessment preoperatively (222). Nevertheless, diabetes is not universally taken into consideration by all risk assessment tools such as the P-POSSUM. The current recommendation by the World Health Organisation for the diagnosis of diabetes is one of the four options including a random venous plasma glucose concentration (≥ 11.1 mmol/l), a fasting plasma glucose concentration (≥ 7.0 mmol/l), a two-hour plasma glucose concentration (≥ 11.1 mmol/l) after an oral glucose tolerance test or haemoglobin A1c (≥48 mmol/mol or 6.5%) (223, 224). Several guidelines such as those from the NICE as well as the Joint Association of British Clinical Diabetologists recommend preoperative HbA1c levels within three months of surgery to identify diabetics who would benefit from optimisation but the National Confidential Enquiry into Patient Outcome and Death reports that only 64.6% of diabetics had levels check within 3 months of attending the preoperative assessment clinic and of those 16% had HbA1c levels above the range recommended for surgery (HbA1c > 69 mmol/mol or >8.5%) (225-227). Conversely, the guidelines do not recommend routine checks of HbA1c in patients not known to be diabetic (225). The International Federation of Diabetes estimates that 49.7 % of people living with diabetes worldwide are undiagnosed in 2017, while the prevalence of diabetes in the surgical population is estimated at 15% (219). Kwon et al. found that general surgery patients with perioperative hyperglycaemia were associated with a nearly two-fold increase in the rate of surgical site infection and mortality in both diabetic and non-diabetic patients (228). This therefore raises

the question of the proportion of patients who may benefit from management of hyperglycaemia prior to surgery.

In the present overview, various measurements of body composition have been identified as a prognostic variable for different short-term outcomes. Sarcopenia has been associated with increased 30-day mortality and overall morbidity. While body mass index and visceral obesity have been associated with wound infection, these associations are likely a result of complex interactions between host factors, metabolic and endocrine changes in the presence of cancer, including systemic inflammation, insulin resistance and alterations in hormones. In the presence of increasing obesity prevalence in the global population, body mass index is likely to no longer represent the best indicator of cancer cachexia (229, 230). Computed tomography assessment of body composition to characterise sarcopenia or visceral obesity is ideally required to offer a better measure (231, 232). Cachexia is an important measurement of the physiologic reserve in cancer patients. The mechanism behind cancer cachexia is poorly understood, but the effect is magnified by the subsequent surgical insult and therefore a potentially measurable and targetable prognostic area.

Preoperative anaemia is a potentially relevant predictor of short-term postoperative outcomes in patients undergoing colorectal cancer surgery. Its assessment may provide information about the patient's physiological reserve, underlying nutritional status or chronic inflammation (233-235). Preoperative anaemia may also reflect chronic tumour-related blood loss and has the potential to be modified through appropriate investigation and treatment before surgery. However, its prognostic value must be interpreted cautiously, as anaemia may also reflect advanced disease, comorbidity or chronic disease, including chronic kidney disease, that independently influence postoperative outcomes(236, 237). Furthermore, the severity of anaemia, the timing of haemoglobin measurement and the underlying cause may vary between studies, limiting comparisons.

The available systematic reviews have largely focused on interventions intended to correct preoperative anaemia. Iron therapy, erythropoietin and blood transfusion should also be considered separately from anaemia itself. These interventions may influence perioperative haemoglobin levels and transfusion requirements, but their use is determined by clinical circumstances and may

therefore introduce confounding by indication when their association with postoperative complications is assessed. In particular, confounding by association between blood transfusion and adverse outcomes may arise because patients requiring transfusion may have more severe anaemia or poorer physiological reserves, which themselves may increase the risk of postoperative complications. Similarly, the potential benefits of iron therapy or erythropoietin in selected patients do not establish that their use is consistently associated with improved postoperative outcomes across all patients undergoing colorectal resection. Evidence supporting the effect of these interventions on short-term postoperative outcomes is inconsistent and therefore included in addition to the minimum set of factors.

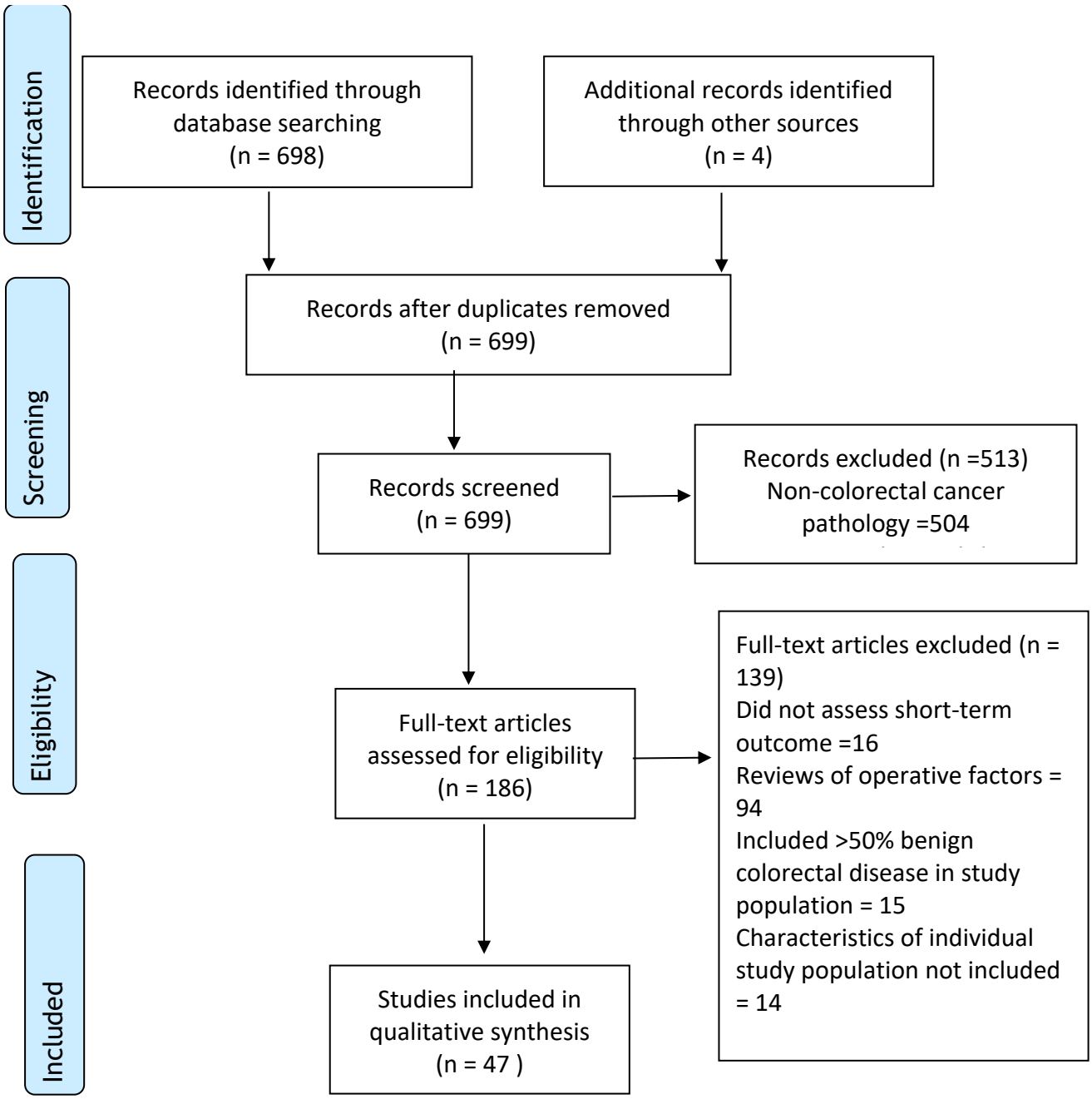
The present umbrella review synthesised the available evidence on factors associated with postoperative complications and allows for the application in the era of precision medicine. We have identified from the body of literature available that most validated factors have varying effects on short-term postoperative complications which we have broadly classified by type; infective, non-infective and 30-day mortality. The present review has identified those factors which have good evidence in terms of postoperative complications enabling careful patient selection using a minimum set of validated risk factors. We have chosen to focus on the preoperative risk factors and on this basis, offer surgeons the preoperative knowledge to decide on the potential impact of operative and treatment strategies.

There are several limitations in the current overview. Inevitably, a degree of heterogeneity exists between systematic reviews which limits qualitative comparison of the outcomes. A meta-analysis of systematic reviews was not performed due to significant heterogeneity of the study methodology and variation in outcomes of systematic reviews. We found multiple reviews assessing similar prognostic variables; however, differences in reported outcomes have been detected across reviews. These differences are reflected by the interpretation of inclusion criteria and analysis. Synthesis of multiple reviews that include overlapping studies conversely contribute to potential overestimation of the strength of the findings therefore it is crucial to be mindful of the extent of evidence available on which the conclusion is based for a specific factor. All available systematic reviews were included in this overview irrespective of the

quality, but most systematic reviews have performed either a risk of bias assessment or reported on the quality of studies included; therefore, the effect of this is expected to be minimal.

The present study included only systematic reviews; therefore, it is likely that there are other modifiable factors not included, as these have yet to be summarised in a systematic review. An area of interest with paucity of data relating to short-term outcomes is cancer-associated systemic inflammatory response. It has been well recognised that inflammation-related biomarkers play a prognostic role in predicting long-term survival; however, the effect on short-term outcomes have yet to be quantified (238-242). Despite these limitations, the present overview has not imposed a restriction on the period of included studies which allows for a stronger body of evidence on certain prognostic variables such as diabetes and body composition which have reported consistent association with short-term outcomes over a wide timeline. Importantly, it forms a consistent basis for the introduction of minimum and supplementary baseline variables to be collected prior to surgery for colorectal cancer (Table 2-11). This creates an opportunity for future work to improve on short-term outcomes following colorectal cancer surgery by modifying the variables in the three main prognostic areas identified: host, nutritional and functional aspects. It will also provide an opportunity for individualised, tailored therapy by taking the patients' specific prognostic factors into consideration. Finally, it might prove beneficial to evaluate the interaction between those individual prognostic variables, such as the influence of diabetes on body composition. The possibility of a similar inflammatory process driving both factors may have causative or synergistic roles in affecting short-term outcomes in colorectal resection.

Figure 2-1 PRISMA Flowchart demonstrating study selection



2.5 Tables

Table 2-1 Characteristics for systematic reviews on age

Review Year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias assessment
Hoshino 2019 (169)	Lap for elderly versus non-elderly	PubMed, Scopus, Cochrane. (-14 October 2017) [Observational studies]	22 studies (5466) [Colorectal]	30-day mortality	No significant difference (RD 0.00, 95% CI 0.01, 0.01)(p = 0.89)	Risk of Bias in Non-Randomised Study- High risk of bias from confounding and lack of blinding of outcome assessments
				Overall morbidity	Assoc between > morbidity with elderly (RR 1.20, 95% CI 1.08, 1.34)(p < 0.01)	
				Wound infection	No significant difference (RR 1.29, 95% CI 0.97, 1.71)(p = 0.08)	
				Anastomotic leak	No significant difference (RR 1.24, 95% CI 0.86, 1.80)(p= 0.25)	
				Pulmonary complication	No significant difference (RR 1.41, 95% CI 0.71, 2.82)(p = 0.33)	
				Postoperative Ileus	No significant difference (RR 1.47, 95% CI 0.83, 2.62)(p=0.19)	
				Cardiac complication	No significant difference (RR 1.68, 95% CI 0.79, 3.54)(p=0.18)	
Moug 2015 (170)	Lap versus open in elderly	Medline, Cochrane, Embase. (-December 2014) [RCT]	2 studies (1386) [Colorectal]	30-day mortality	No significant difference. (Narrative)	Jadad score -moderate quality
				Overall morbidity	Assoc between > morbidity and elderly (Narrative)	

Pommegaard 2014 (171)	Risk factors for anastomotic leak and colorectal cancer surgery	Medline, CINAHL, Embase (-27 September 2012) [Observational studies]	23 studies (110272) [Colorectal]	Anastomotic leak	No significant difference (OR 0.99, 95% CI 0.89, 1.10) (p=0.87)	Newcastle-Ottawa Scale- high quality
Simmonds 2000 (168)	Elderly vs non elderly	Medline, Embase, CancerLit, Cochrane, CINAHL, Healthstar, Science citation index, Edina Biosis, NHS Economic Evaluation database, Index to scientific and technical proceeding and Pascal. (-July 1998) [Observational studies]	28 studies (34194) [Colorectal]	30-day mortality	Assoc between > mortality and elderly. (Narrative review)	Downs and Black checklist- not reported
				Anastomotic leak	No significant difference (p = 0.2607)	
				Pulmonary complication	Assoc between > pulmonary complication and elderly (p < 0.0001)	
				Cardiac complication	Assoc between > cardiac complication and elderly (p <0.001)	
				Stroke	Assoc between > stroke and elderly (p < 0.0001)	
				DVT/PE	No significant difference (p = 0.0004)	

Assoc = association; CI = confidence interval; CINAHL=Cumulative Index to Nursing and Allied Health Literature; DVT=deep vein thrombosis; Lap=laparoscopic; MD= mean difference; OR= odds ratio; PE= pulmonary embolism; RCT = randomised controlled trial; RD = risk difference; RR= relative risk; VS= versus; WOS =Web of Science.

Table 2-2 Characteristics for systematic reviews on sex

Review Year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias assessment
Xu 2020 (172)	Surgical site infection in colorectal cancer surgery	PubMed, Cochrane, Embase (-18 March 2020) [Comparative studies]	15 studies (60229) [Colorectal]	Surgical site infections	Assoc between >SSI and male (OR 1.24, 95% CI 1.14, 1.34) (p < 0.0001)	Newcastle Ottawa Scale-moderate to high quality
Pommegaard 2014 (171)	Risk factors for anastomotic leak and colorectal cancer surgery	Medline, CINAHL, Embase (-27 September 2012) [Observational studies]	23 studies (110272) [Colorectal]	Anastomotic leak	Assoc between > anastomotic leak and male gender (OR 1.48, 95% CI 1.37, 1.60) (p < 0.00001)	Newcastle-Ottawa Scale-high quality

Assoc= association; CI= confidence interval; CINAHL=Cumulative Index to Nursing and Allied Health Literature; OR = odds ratio; WOS = Web of Science; SSI = surgical site infection.

Table 2-3 Characteristics of systematic reviews on diabetes

Review Year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias
Xu 2020 (172)	Surgical site infection in colorectal surgery	PubMed, Cochrane, Embase (-18 March 2020) [Observational studies]	15 studies (60229) [Colorectal]	Surgical site infections	Association between > SSI and diabetes (OR 1.34, 95% CI 1.1,1.64) (p = 0.004)	Newcastle Ottawa Scale- moderate to high quality
Stein 2010 (173)	Diabetes and colorectal cancer	Medline, Embase (- October 2008) [Observational studies]	4 studies (33518) [Colorectal]	30-day mortality	Association between > mortality and diabetes (Narrative)	Not assessed
				Anastomotic leak	Association with > anastomotic leak and diabetes (Narrative)	
				Cardiovascular complication	Association with > cardiovascular complication (Narrative)	

CI= confidence interval; OR = odds ratio; SSI= surgical site infection.

Table 2-4 Characteristics for systematic reviews on body composition

Review Year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias
Xu 2020 (172)	Surgical site infection in colorectal surgery	PubMed, Cochrane, Embase (-18 March 2020) [Comparative studies]	15 studies (60229) [Colorectal]	Surgical site infection	Assoc between > SSI and obesity (BMI) (OR 1.59, 95% CI 1.4,1.81) (p < 0.00001)	Newcastle Ottawa Scale- moderate to high quality
Almasaudi 2018 (174)	BMI and Postoperative surgical site infection	Medline, PubMed, Embase, Web of Science (- August 2016) [All studies]	16 observational (9535) [Colorectal]	Wound infection	Assoc between > wound infection with >BMI (BMI >25 OR 1.63, 95% CI 1.29, 2.06) (p < 0.001) (BMI >30 OR 2.13, 95% CI 1.66, 2.72) (p < 0.001)	Not assessed
				Intraabdominal collection	Assoc between > intraabdominal collection with > BMI (OR 1.5, 95% CI 1.08, 2.07) (p=0.01)	
Fung 2017 (175)	BMI and lap surgery	Embase, CINAHL, Global Health, BIOSIS, Web of Science, Scopus, Cochrane, DARE (- Oct 2014) [All studies]	13 observational studies (4550) [Colorectal]	Overall morbidity	Assoc between > morbidity and > BMI (OR 1.54, 95% CI 1.21, 1.97) (p = 0.0005)	MINORS criteria- moderate to high quality
				Wound infection	Assoc between > infection and > BMI (OR 2.43, 95% CI 1.46, 4.03) (p=0.0006)	
				Anastomotic leak	Assoc between > anastomotic leak and > BMI (OR 1.65, 95% CI 1.01, 2.71) (p=0.05)	

Pommegaard 2014 (171)	Risk factors for anastomotic leak (BMI) and colorectal surgery	Medline, CINAHL, Embase (-27 September 2012) [Observational studies]	23 studies (110272) [Colorectal]	Anastomotic leak	No significant difference (OR 1, 95% CI 0.93, 1.07) (p=0.95)	Newcastle-Ottawa Scale - high quality
Malietzis 2014 (179)	Computed tomography body composition (sarcopenia or visceral obesity) and colorectal surgery	Medline, Embase, Google scholar, Cochrane database (Jan 1990-March 2014) [All studies]	16 observational studies (2672) [Colorectal]	30-day mortality	Assoc between > 30-day mortality and sarcopenia (Narrative)	Modified SIGN guideline-moderate quality
				Overall morbidity	Assoc between > overall morbidity and sarcopenia. Assoc between > overall morbidity and visceral obesity in colon cancer (Narrative)	
				Wound infection	3 studies association between > wound infection and visceral obesity.2 studies reported no difference (Narrative)	
				Anastomotic leak	3 out of 4 studies reported no difference between anastomotic leak and visceral obesity (Narrative)	
Cakir 2015 (176)	Visceral obesity and colorectal surgery	Medline, Embase, Cochrane (- 4 April 2014) [All studies]	7 studies (1230) [Colorectal]	Overall morbidity	Assoc between < morbidity and non-viscerally obese (RD 0.15, 95%CI 0.1, 0.21) (p<0.00001)	Cochrane Collaboration tool-low quality

Yang 2015 (177)	Visceral obesity and lap surgery	PubMed, EMBASE, Cochrane Library (2000-2014) [All Studies]	4 Observational studies (659) [Colorectal]	Overall morbidity	Assoc between > morbidity and visceral obesity (OR 2.33, 95% CI 1.56, 3.48) (p< 0.0001)	Not assessed
				Wound infection	Assoc between > infection and visceral obesity (OR 3.22, 95% CI 1.95,5.32) (p<0.00001)	
				Anastomotic leak	No significant difference (OR 2.4 ,95% CI 1.06,5.44) (p=0.04)	
Sun 2018 (178)	Sarcopenia and colorectal cancer	PubMed, Embase, Web of Science (- 4 April 2018) [All studies]	12 observational studies (5337) [Colorectal]	30-day mortality	Assoc between > mortality and sarcopenia (OR 3.45, 95%CI 1.96.7.02) (P< 0.01)	Newcastle Ottawa Scale – moderate quality
				Overall morbidity	Assoc between> morbidity with sarcopenia (OR 1.7, 95% CI 1.07, 2.7) (p<0.01)	
				Wound infection	No significant difference (OR 2.21, 95% CI 1.5, 3.25) (p=0.9444)	
				Anastomotic leak	No significant difference (OR 0.73 ,95% CI 0.51,1.05) (p=0.417)	
Sun 2019 (180)	Preoperative prognostic nutritional index and colorectal surgery	PubMed, Embase, WOS (- Oct 2018) [Comparative studies]	10 studies (6372) [Colorectal]	Overall morbidity	Assoc between > morbidity and low prognostic nutritional index	Newcastle Ottawa Scale –high quality
				Severe complications	Assoc between > serious complication and low prognostic nutritional index	

Assoc =association; BMI = Body mass index; CINAHL=Cumulative Index to Nursing and Allied Health Literature; CI = confidence interval; Lap = laparoscopic; OR = odds ratio; RD = risk difference; SSI =

surgical site infection; WMD =weighted mean difference; UTI = urinary tract infection.

Table 2-5 Characteristics for systematic reviews on functional status

Review Year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias
Xu 2020 (172)	Surgical site infection in colorectal surgery	PubMed, Cochrane, Embase (-18 March 2020) [Comparative studies]	15 studies (60229) [Colorectal]	Surgical site infection	Assoc between > SSI and > ASA (OR 1.22, 95% CI 1.12, 1.43) (p<0.00001)	Newcastle Ottawa Scale- moderate to high quality
Lee 2018 (182)	Functional capacity testing and colorectal cancer surgery	Medline, PubMed, Embase, CINAHL, and PEDro (-November 2017) [Cohort studies]	7 studies (1418) [Colorectal]	30-day mortality	No significant difference. (Narrative)	Newcastle-Ottawa scale and Jadad score- good quality
				Overall morbidity	Assoc between < morbidity and good functional capacity (OR 0.76, 95% CI 0.66, 0.85) (p<0.0001)	
				Infective complicatio n	Assoc between < infective complication and good functional capacity (p <0.01)	
				Wound dehiscence	Assoc between < wound dehiscence and good functional capacity (p<0.01)	
				Pulmonary complicatio n	Assoc between < pulmonary complication and good functional capacity (p<0.01)	
Fagard 2016 (181)	Frailty and colorectal cancer surgery	Medline (2000-29 October 2015) [Cohort studies]	4 studies (486) [Colorectal]	30-day mortality	No significant difference (Narrative)	MINORS- good quality
				Overall morbidity	Assoc between > overall morbidity and frailty (Narrative)	

				Postoperative sepsis	Assoc between > postoperative sepsis and frailty (Narrative)	
				Readmission	Assoc between > readmission and frailty (Narrative)	
Pommegaard 2014 (171)	Risk factors for anastomotic leak and colorectal surgery	Medline, CINAHL, Embase (-27 September 2012) [Observational studies]	23 studies (110272) [Colorectal]	Anastomotic leak	Association between < anastomotic leak and low ASA (OR 1.71, 95% CI 1.09, 2.67) (p=0.02)	Newcastle-Ottawa Scale- high quality

ASA = American Society of Anesthesiologist; CINAHL= Cumulative Index to Nursing and Allied Health Literature; CI = confidence interval; OR =odds ratio; SSI= surgical site infection.

Table 2-6 Characteristics for systematic reviews on mechanical bowel preparation (MBP)

Review Year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias
Leenen 2019 (183)	MBP vs no preparation	PubMed, Medline, Embase, Central, CINAHL (2010-March 2017) [RCT]	8 studies (1065) [Colorectal]	Anastomotic leak	No significant difference (OR 1.15, 95% CI 0.638,1.94) (p=0.6)	Cochrane risk of bias tool- low quality
Guenaga 2011 (184)	MBP vs no preparation	Embase, CINAHL, Lilacs, Cochrane, Medline, SCI Search, Ibecs (- 1 December 2010) [RCT]	18 studies (5805) [Colorectal]	30-day mortality	No significant difference (OR 0.93,95% CI 0.58,1.47) (p=0.75)	Cochrane risk of bias tool-high quality
				Wound infection	No significant difference (OR 1.16, 95% CI 0.95,1.42) (p=0.15)	
				Anastomotic leakage	No significant difference (OR 0.99,95% CI 0.74,1.31) (p=0.93)	
				Reoperation	No significant difference (OR 1.4, 95%CI 0.81,1.34) (p=0.56)	
				Intraabdominal collection	No significant difference (OR 0.74, 95% CI 0.5,1.08) (p=0.12)	
Cao 2011 (185)	MBP vs no preparation	Cochrane, Embase, Medline (-May 2011) [RCT]	14 studies (5373) [Colorectal]	30-day mortality	No significant difference (OR 0.97, 95% CI 0.63,1.48) (p= 0.88)	Assessed - high quality
				Wound infection	No significant difference (OR 1.21,95% CI 1.0-1.46) (p=0.05)	
				Anastomotic leak	No significant difference (OR 1.08(0.82,1.43) (p=0.56)	
				Reoperation	No significant difference (OR 1.11 95% CI 0.86–1.45) (p= 0.42)	
Zhu 2010 (186)		Medline, Embase, Cochrane	8 studies (1147)	30-day mortality	No significant difference (OR 1.24,95% CI 0.37,4.14) (p=0.73)	

	MBP vs no preparation	(Not reported) [RCT]	[Colorectal]	Wound infection	No significant difference (OR 1.44, 95% CI 0.88,2.33) (p=0.15)	Jadad score- High quality
				Anastomotic leak	No significant difference (OR 1.78,95% CI 0.95,3.33) (p=0.07)	
				Intraabdominal collection	No significant difference (OR 1.1,95% CI 0.43,2.78) (p=0.49)	
Slim 2009 (188)	MBP vs no preparation	Cochrane, Medline, Scopus (-Jan 2008) [RCT]	14 studies (4859) [Colorectal]	30-day mortality	No significant difference (OR 0.91,95% CI 0.57,1.45) (p=0.7)	Validated scale- moderate to high quality
				Wound infections	No significant difference (OR 1.17, 95% CI 0.96, 1.44) (p=0.11)	
				Anastomotic leak	No significant difference (OR 1.12,95% CI 0.82,1.53) (p=0.492)	
				Intraabdominal collection	No significant difference (OR 0 .9, 95% CI 0.47,1.72) (p=0.75)	
				Reoperation	No significant difference (OR 1.07, 95% CI 0.81,1.42) (p=0.7)	
McCoubrey 2007(187)	MBP vs no preparation	PubMed, Medline, Embase (10 years) [RCT]	5 RCTs, 6 systematic reviews [Colorectal]	Wound infection	No significant difference (Narrative)	Not assessed
				Anastomotic leak	No significant difference (Narrative)	
				Intrabdominal abscess	No significant difference (Narrative)	
Bucher 2004 (189)	MBP vs no preparation	Medline (No restrictions) [RCT]	7 studies (1297) [Colorectal]	30-day mortality	No significant difference (OR 1.42,95%CI 0.37,5.45) (p=0.6)	Assessed – moderate quality
				Overall morbidity	No significant difference (OR 1.15, 95%CI 0.79,1.7) (p=0.45)	

				Anastomotic leak	Assoc between > anastomotic leak and bowel preparation (OR 1.85,95% CI 1.06-3.22) (p=0.03)	
				Wound infection	No significant difference (OR 1.38, 95% CI 0.89,2.15) (p=0.15)	
				Intraabdominal collection	No significant difference (OR 1.69,95% CI 0.76,3.75) (p=0.18)	
Platell 1998 (190)	MBP vs no preparation	Not reported (Not reported) [RCT]	3 RCT (903) [Colorectal]	Wound infection	Assoc between > wound infection and bowel preparation (p=0.002)	Assessed - poor quality
				Anastomotic leak	No significant difference (p=0.114)	

CI= confidence interval; CINAHL= Cumulative Index to Nursing and Allied Health Literature; MBP = mechanical bowel preparation; OAB =oral antibiotics; OR = odds ratio; RCT = randomised controlled trial.

Table 2-7 Characteristics for systematic reviews on antibiotic prophylaxis

Review Year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias
Nelson 2014 (191)	Antibiotics prophylaxis and colorectal surgery	Cochrane, Medline, Embase (1954-January 2013) [RCT]	260 studies (43451) [Colorectal]	Wound infection	Assoc between < wound infection and antimicrobial prophylaxis (RR 0.34, 95% CI 0.28,0.41)	GRADE- high quality
Chen 2016 (192)	MBP + OAB + systemic antibiotics (Combination regime) vs MBP + systemic antibiotics	Embase, PubMed, Cochrane (1971-October 2014) [RCT]	7 RCT (1769) [Colorectal]	SSI	Assoc between < SSI and combination regime (RR 0.47, 95% CI 0.26, 0.86) (p=0.01)	Cochrane risk of bias tool- Moderate - high quality
				Wound infection	Assoc between < wound infection and combination regime (RR 0.38, 95% CI 0.26,0.56) (p<0.00001)	
				Intraabdominal collection	No significant difference (RR 0.85, 95% CI 0.51,1.44)(p = 0.56)	

Assoc = association, CI= confidence interval, MBP=mechanical bowel preparation, OAB =oral antibiotics, RCT= randomised controlled trial, RR=relative risk, SSI=surgical site infection

Table 2-8 Characteristics of systematic reviews on anaemia

Review Year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias
Pang 2019 (193)	Peri-operative transfusion	PubMed, Cochrane, Embase (Jan 1990-June 2018) [All studies]	36 Cohort (174036) [Colorectal]	Overall morbidity	Association between > morbidity and transfusion (RR 1.86, 95% CI 1.66, 2.07) (p =0.000)	Newcastle Ottawa Scale – high quality
				Infective complications	Association between > infective complications and transfusion (RR 1.89, 95% CI 1.56, 2.28) (p<0.0001)	
				Anastomotic leak	Association between > anastomotic leak and transfusion (RR 1.51, 95% CI 1.29, 1.79) (p <0.0001)	
				Reoperation	Association between > reoperation and transfusion (RR 2.88, 95% CI 2.05, 4.05) (p<0.0001)	
				Pulmonary complication	Association between > pulmonary complication and transfusion (RR 2.01, 95% CI 1.54, 2.63) (p< 0.0001)	
				Cardiac complication	Association between > cardiac complication and transfusion (RR 2.2 ,95% CI 1.75, 2.76) (p<0.0001)	

Borstlap 2015 (195)	Iron therapy and colorectal surgery	Medline, Embase, Cochrane (Oct 2014) [RCT and non-RCT]	3 RCT 4 Cohort (470) [Colorectal]	Blood transfusion requirement	Association between < blood transfusion requirement and iron therapy (Narrative)	Downs-Black criteria – Moderate to good
Hallet 2014 (196)	Iron therapy and blood transfusion requirement	Medline, Embase, Web of Science, Cochrane (-May 2013) [RCT and non-RCT]	2 RCT 2 non-randomised studies (325) [Colorectal]	Blood transfusion requirement	No significant difference (RR 0.66 95% CI 0.42, 1.02) (p =0.06)	Cochrane risk of bias-high risk of bias and Newcastle Ottawa Scale-high quality
Acheson 2012 (194)	Allogenic blood transfusion and clinical outcomes	Medline (Dec 2004- Oct 2010) [All studies]	55 studies (20795) [Colorectal]	Infective complication	Association with > infective complication with allogenic blood transfusion (OR 3.27, 95% CI 2.05,5.20) (p < 0.001)	Newcastle-Ottawa Score: moderate-to-high quality
				Reoperation	Association with > reoperation with allogenic blood transfusion (OR 4.08, 95% CI 2.18, 7.62) (p < 0.001)	
Devon 2009 (197)	Erythropoietin and blood transfusion requirement	Medline, Embase (-May 2008) [RCT]	4 studies (436) [Colorectal]	30-day mortality	No significant difference (RR 2.12,95% CI 0.59,7.65)	Cochrane risk of bias tool-unclear risk of bias
				Blood transfusion requirement	No significant difference (RR 0.92,95% CI 0.65,1.31)	
				Thrombotic complication	No significant difference (RR 1.71,95% CI 0.41,7.08)	

CI= confidence interval; RCT = randomised controlled trial; RR= relative risk.

Table 2-9 Characteristics for systematic reviews on Enhanced Recovery Programmes

Review Year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias
Li 2013 (201)	ERAS and colorectal surgery	PubMed, Cochrane, Embase (-10 May 2013) [RCT]	6 studies (665) [Colorectal]	Overall morbidity	Association between < morbidity and ERAS (WMD 0.6, 95% CI 0.46, 0.79) (p<0.05)	Not performed
				Anastomotic leak	No significant difference (WMD 1.07,95% CI .5,2.32)(p> 0.55)	
				Wound infection	No significant difference (WMD 0.66 ,95% CI 0.33,1.32) (p>0.05)	
				Readmission	No significant difference (WMD 0.69,95% CI 0.34,1.4)(p=0.85)	
He 2013 (207)	Probiotics and colorectal cancer	PubMed, Medline, Embase, Cochrane, Academic Search Premier, China National Knowledge Infrastructure (- Feb 2012) [RCT]	6 studies (361) [Colorectal]	Infective complication	Association between < infective complication and probiotic use (OR 0.39, 95% CI 0.22, 0.68) (p=0.001)	Jadad score -moderate quality
				Wound infection	No significant difference (OR 0.66, 95% CI 0.3,1.49) (p=0.32)	
				Anastomotic leak	No significant difference (OR 0.71, 95% CI 0.14, 3.68) (p=0.68)	
				Pulmonary complication	Association between < pulmonary complication and probiotic use (OR 0.32, 95% CI 0.11, 0.93) (p=0.04)	
Ho 2014 (209)	Chewing gum and colorectal	Cochrane, Medline, Embase,	10 studies (612)	Overall morbidity	No association (RR 0.72, 95% CI 0.46,1.15)(p=0.17)	Cochrane Risk of Bias

	surgery (postoperatively)	Scopus and PubMed (-April 2013) [RCT]	[Colorectal]	Readmission	No significant difference (RR=0.805,95% CI 0.32-2.022)(p=0.7)	Tool-low risk of bias
				Reoperation	No significant difference (RR=0.851,95% CI 0.28-2.587)(p=0.44)	
Zhao 2014 (202)	Fast track surgery vs traditional perioperative care in laparoscopic colorectal surgery	PubMed, Embase, Cochrane, OVID (- 1 April 2014) (Comparative studies)	5 RCT 5 CCT (1317) [Colorectal]	30-day mortality	No significant difference (RR 1.55 , 95% CI 0.42.5.71) (p=0.51)	Jadad score- High quality
				Overall morbidity	Association between < overall morbidity and ERAS (RR0.67,95% CI 0.56-0.8) (p<0.001)	
				Readmission	No significant difference (RR 0.64, 95% CI 0.41,1.01)(p=0.06)	
Bagnall 2014 (200)	ERAS and colorectal surgery in elderly patients	Medline, Embase, Cochrane (1 Jan 1974-1 February 2014) [Comparative studies]	2 RCT 11Cohort 3 case series (5396) [Colorectal]	30-day mortality	No significant difference (Narrative)	Black and Downs Quality Index-Fair to good quality
				Overall morbidity	No significant difference (Narrative)	
				Readmission	No significant difference (Narrative)	
Boereboom 2016 (203)	Preoperative exercise and colorectal surgery	Medline, Embase, CINAHL, AMED, BNI (-12 November 2014) [RCT, Cohort]	5 RCT 3 Cohort (918) [Colorectal]	Overall morbidity	No significant difference	Newcastle Ottawa Score - moderate quality

Bruns 2016 (204)	Prehabilitation(physical) and colorectal surgery in elderly patients (>60)	Medline, Embase, CINAHL, Cochrane library (- January 2016) [RCT, case-control]	5 studies (353) [Colorectal]	Overall morbidity	No significant difference (Narrative)	Cochrane collaboration tool and Newcastle Ottawa score-Moderate quality
Wanden-Berghe 2016 (210)	Nutritional intervention and colorectal surgery	Medline, PubMed, Scopus, Embase, WOS, Cochrane, LILACS, CINAHL, IPA (-1 May 2014) [Clinical trials]	27 studies (2962) [Colorectal]	30-day mortality	No significant difference (Narrative)	CACEC-EC questionnaire-good to excellent quality
				Overall morbidity	Assoc between < complication and ERAS (Narrative)	
				Readmission	No significant difference (Narrative)	
De Andrade 2017 (205)	Probiotic and colorectal surgery	PubMed, Science Direct, LILACS, Scielo, Scopus (2005-2016) [All studies]	7 RCT (826) [Colorectal]	Infective complication	Association between < infective complication and probiotic (OR 0.5388,95% CI 0.4058,0.7154) (p<0.0001)	Not assessed
				Wound infection	No significant difference (OR 0.6538,95% CI 0.3951,1.0817) (p=0.1493)	
Mei 2017 (208)	Chewing gum and colorectal surgery	PubMed, Embase, Science Direct, Cochrane library (-April 2017) [RCT]	17 studies (1845) [Colorectal]	30-day mortality	No significant difference (RR 2.57,95% CI 0.81,8.15)(p=0.7)	Cochrane risk of bias-low risk of bias
				Postoperative ileus	No signficant difference (RR 0.29,95%CI 0.08, 0.11)(p=0.97)	
Bruns 2018 (211)	Prehabilitation (nutrition)and	Medline, Embase (-30 August 2016)	5 RCT 1 Cohort	Overall morbidity	No significant difference (OR 0.81, 95% CI 0.52,1.25) (p=0.34)	Cochrane risk of bias-

	colorectal surgery	[RCT, prospective cohort]	(583) [Colorectal]	Wound infection	No significant difference (OR 0.57,95%CI 0.3, 1.09) (p=0.09)	moderate risk of bias
				Anastomotic leak	No significant difference (narrative)	
Gillis 2018 (212)	Prehabilitation (nutritional or nutritional+ exercise) vs conventional care	Medline, Embase, CINAHL, CENTRAL, ProQuest (-7 March 2017) [RCT, Cohort]	5 RCT 4 Cohort (914) [Colorectal]	Overall morbidity	Association between prehabilitation and < overall morbidity (RR 0.79, 95% CI 0.64,0.98)	Study quality RCT -moderate to high quality Study quality observational trial-low quality
Looijaard 2018 (213)	Prehabilitation (Physical and nutritional) in elderly patients and colorectal cancer	PubMed, Embase, Cochrane, CINAHL (-16 July 2015) [RCT and Cohort]	6 studies (518) [Colorectal]	Overall morbidity	No significant difference (Narrative)	High risk of bias
Ouyang 2018 (206)	Probiotics and colorectal cancer	PubMed, Embase, Cochrane, China National Knowledge Infrastructure (-Sept 2017) [RCT]	13 studies (1186) [Colorectal]	Infective complication	Association between < complication and probiotics (OR 0.51, 95% CI 0.38,0.68) (p=0.6)	Cochrane risk of bias-low - moderate risk
				Wound infection	Association between < complication and probiotics (OR 0.59, 95% CI 0.39,0.88) (p=0.01)	
				Anastomotic leak	No significant difference (OR 0.72,95% CI 0.35,1.47) (p=0.787)	
				Urinary tract infection	No significant difference (OR 0.61, 95% CI 0.32,1.19) (p=0.15)	

				Pulmonary complication	Association between < pulmonary complication and probiotics (OR 0.56, 95% CI 0.32,0.98) (p=0.04)	
Xu 2018 (214)	Immunonutrition and colorectal surgery	Medline, Embase Cochrane (-April 2017) [RCT]	9 studies (1004) [Colorectal]	Infective complications	Association between < infectious complication and immunonutrition (OR 0.33,95% CI 0.21,0.53) (p<0.00001)	Cochrane Handbook- moderate to low risk of bias
				Surgical site infection	Association between < surgical site infection and immunonutrition (OR 0.25,95% CI 0.11, 0.58) (p=0.001)	
				Wound infection	Association between < wound infection and immunonutrition (OR 0.27,95% CI 0.12,0.64) (p=0.003)	
Ni 2019 (199)	ERAS vs conventional care	PubMed, Embase, Web of Science, Cochrane, ClinicalTrials.gov (- October 2018) [RCT]	13 RCT (1298) [Colorectal]	30-day Mortality	No significant difference (RR0.89,95%CI 0.34,2.38)(p=0.61)	Cochrane risk of bias - mod- to low risk
				Overall morbidity	Association between < morbidity and ERAS (RR 0.59,95% CI 0.4,0.86) (p <0.01)	
				Readmission	No significant difference (RR 0.65,95% CI 0.35,1.2)(p=0.77)	
Lohsiriwat 2020 (198)	ERAS vs conventional care for emergency resection	Embase, Medline (1981 -December 2019) [All studies]	3 cohort (818) [Colorectal]	30-day mortality	No significant difference (RR 0.79, 95% CI 0.11-5.38)	Newcastle Ottawa score - High quality
				Overall morbidity	Association between < morbidity and ERAS (RR 0.78, 95%CI 0.63,0.97)	
				Wound infection	No sgnificant differerence (RR 0.78 ,95% CI 0.47,12.8)(P=0.32)	

				Anastomotic leak	No significant difference (RR 0.96,95% CI 0.25,3.65)	
				Reoperation	No significant difference (RR 0.78, 95% CI 0.32,1.92)	
				Ileus	Association between < ileus and ERAS (RR 0.55, 95% CI 0.33,0.91)	
				Readmission	No significant difference (RR 0.91,95% CI 0.54,1.51)	

AMED= Allied and complementary medicine database; BNI=British Nursing Index; CCT= controlled clinical trial; CI = confidence interval; CINAHL= Cumulative Index to Nursing and Allied Health Literature; ERAS= enhanced recovery after surgery; OR = odds ratio; IPA = International Pharmaceutical Abstracts; RCT = randomised controlled trial; RR= relative risk; WMD = weighted mean difference.

Table 2-10 Characteristics for systematic reviews on steroid use

Review Year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Factors	Results (Meta-analysis) (P value)	Risk of bias
Pommergaard 2014 (171)	Risk factors for anastomotic leak and colorectal surgery	Medline, CINAHL, Embase (-27 September 2012) [Observational studies]	23 studies (110272) [Colorectal]	Steroid use	Association between > anastomotic leak and steroid use (Narrative)	Newcastle-Ottawa Score- high quality

CINAHL= Cumulative Index to Nursing and Allied Health Literature.

Table 2-11 Minimum, recommended, and potential preoperative baseline variables for collection in patients undergoing colorectal resection

Minimum preoperative variables

- Age
- Sex
- Diabetes status
- Body mass index
- Body composition (sarcopenia/ visceral obesity)
- Functional status (ASA/ Frailty)

Recommended preoperative variables

- Antibiotic prophylaxis
- Iron therapy
- Blood transfusion
- Erythropoietin
- Steroid use
- Enhanced recovery programme

Potential preoperative variables

- Systemic inflammatory response

Chapter 3 Effect of preoperative carbohydrate loading on surgical site infection in curative colon cancer

3.1 Introduction

Surgery evokes a cascade of hormonal, metabolic and immune changes commonly referred to as the stress response. The degree of stress response evoked is proportional to the magnitude of surgery. Despite advances in oncological therapies, surgical resection remains the primary treatment modality in patients with potentially curative colon cancer (241). A predominant state of elevated blood glucose becomes a major feature during the stress response as the body promotes glycogenolysis and gluconeogenesis to mobilise substrates as an energy source, along with the relative hypoinsulinaemia and transient peripheral insulin resistance (242).

Hyperglycaemia in the postoperative period may be associated with the activation of the stress response as a result of the surgical trauma or undiagnosed diabetes in patients at risk. Nevertheless, postoperative hyperglycaemia has been associated with an increased risk of morbidity and mortality, in particular surgical site infections (243, 244). This is evident even in patients deemed non-diabetic prior to surgery based on blood glucose testing (228). A large randomised controlled trial by Van den Berghe et al. showed that tight glucose control postoperatively reduced mortality by one third in critically ill surgical patients. On the contrary, findings from the NICE-SUGAR trials highlighted the detrimental effect of hypoglycaemia as a result of tight glucose control (245, 246). Optimal glucose management in the postoperative period remains an area widely debated due to the contradictory findings and therefore now focuses on individualised targets along with minimising the incidence of hyperglycaemia.

The development of enhanced recovery after surgery (ERAS) programmes was targeted at attenuating the stress response by maintaining postoperative physiological functioning and mitigating adverse short-term outcomes. Among the components widely practised within the enhanced recovery approach is preoperative oral carbohydrate loading. Advocates of preoperative carbohydrate loading suggest that it reduces the catabolic response induced by overnight fasting

and surgery. Studies have linked preoperative carbohydrate loading with reduced insulin resistance as the body's metabolism alters from a catabolic to anabolic state prior to surgery (247). Therefore, theoretically reducing the risk of postoperative hyperglycaemia and complications as a result of the attenuation of insulin resistance. However, a Cochrane review examined the role of preoperative carbohydrate loading for enhanced recovery in elective surgery reported that preoperative carbohydrate loading had little to no effect on overall complication rates, length of stay or postoperative wellbeing (248).

A previous study examined the effect of individual components of enhanced recovery on the systemic inflammatory response and found that the attenuation of the degree of injury due to the adoption of minimally invasive surgery was the only objective intervention that reduced the stress response (249). Therefore, it is unclear whether the degree of reduction in insulin resistance by preoperative carbohydrate loading would impact major postoperative outcomes, taking into consideration individuals undergoing elective colon cancer surgery. The aim of this study was to determine the effect of preoperative carbohydrate loading on the magnitude of the postoperative systemic inflammatory response and incidence of surgical site infection in colon cancer patients.

3.2 Patients and Methods

This was a retrospective analysis of patients identified from a prospectively maintained database of colorectal cancer resections at the Glasgow Royal Infirmary between January 2014 and March 2018. Patients who had undergone potentially curative colon cancer resection for diagnosis of TNM Stage I-III were included. Patients with Stage IV disease, rectal cancer, diabetics, those who underwent emergency surgery, those who did not have surgical resection or those who underwent palliative procedures were excluded.

Patients who had an unplanned admission and underwent surgery within 48 hours of admission were classified as having an emergency admission. All elective patients were routinely enrolled into the Enhanced Recovery After Surgery programme during the study period and were offered preoperative carbohydrate loading in the form of four bottles of Nutricia preOp (200ml) containing 12.6g carbohydrate/100ml over the course of the evening before surgery and two bottles of Nutricia preOp (200ml) on the day of surgery up to 2 hours before anaesthesia unless a prior diagnosis of diabetes was known. Adherence to the consumption of the preoperative carbohydrate loading drinks was documented in the admission medical records.

Comorbidities were classified using the American Society of Anesthesiologists (ASA) Physical Status Classification System (250). The malnutrition universal screening tool (MUST) was used to calculate the risk of malnutrition from admission records and categorised according to thresholds as follows: low risk (Score 0), medium risk (Score 1) and high risk (Score ≥ 2) (251).

Body mass index (BMI) was calculated from height and weight measured prior to surgery, and the BMI was categorised according to thresholds as follows: BMI<30 and BMI ≥30. Tumours were staged using the TNM classification system (8^{th} edition) (114). The postoperative systemic inflammatory response was calculated using the postoperative Glasgow Prognostic Score (poGPS) previously described by Watt et al. as follows: postoperative CRP concentration <150mg/L, regardless of albumin concentration, scored 0; CRP concentration ≥150mg/L and albumin >25g/L, scored 1; and CRP concentration ≥150mg/L and albumin <25g/L, scored 2 (252). The day 3 threshold was chosen as a previous study has demonstrated that postoperative

systemic inflammatory response evidenced by increased day 3 poGPS resulted in an increase in infective complication rates (252).

Patients were assessed for surgical site infections for up to 30 days. Surgical site infections were defined as the presence of superficial skin infection, deep organ or space infections including anastomotic leaks and abdominal collections. Superficial surgical site infection was defined by the presence of pus drained either from the wound or discharging spontaneously. Deep surgical site infection was diagnosed either on imaging, radiological drainage, or surgical drainage of intra-abdominal pus while anastomotic leak was diagnosed at laparotomy or on cross-sectional imaging. The data were collected using all available electronic patient medical records, including inpatient medical notes, discharge letters, clinic letters, radiology reports, blood test results and microbiology test results.

Ethical approval was granted for this project by the West of Scotland Research Ethics Committee, Glasgow.

3.3 Statistical Analysis

The relationship between the clinicopathological characteristics and consumption of preoperative carbohydrate loading drinks was compared using the Chi-square test for significance where appropriate. P values <0.05 were considered statistically significant. The relationship between clinicopathological factors and surgical site infection was analysed using a univariate regression model. Statistical analysis was performed using IBM SPSS Statistics for Windows Version 28 (IBM Corporation, Armonk, New York, USA).

3.4 Results

Overall, 218 patients had undergone elective resection for potentially curative colon cancer between January 2014 and March 2018 (Table 3-1). A majority of the patients were over 65 years of age (n=153, 70%), female (n=111, 51%), had a low-risk MUST (n=183, 84%), BMI <30 (n =184, 71%), and were non-smokers (n=117, 54%).

Chi-square analysis did not show an association between clinicopathological factors and preoperative carbohydrate loading (Table 3-1).

Binary logistic regression of factors associated with surgical site infections is shown in Table 3-2. On univariate analysis, surgical site infection was independently associated with open surgical approach ($p<0.026$).

3.5 Discussion

The results of the present study showed no objective evidence that preoperative carbohydrate loading was associated with a reduction in the magnitude of the postoperative systemic inflammatory response or the risk of surgical site infection in patients undergoing elective surgery for colon cancer.

In the present study, it was interesting that the surgical approach, specifically laparoscopic approach, was the only factor significantly associated with a reduction in surgical site infection. The basis of the profound effect of laparoscopic surgery on reducing the magnitude of the postoperative systemic inflammatory response and the rate of infective complications is not obvious. However, it would be reasonable to conclude that they are closely linked and that surgical approaches that minimise the magnitude of the systemic inflammatory response will also minimise infective complications (249, 253).

The traditional practice of preoperative fasting resulted in depletion of glycogen storage, increased lipolysis, enhanced gluconeogenesis, and promoted insulin resistance. This is further compounded by the insulin resistance from surgical trauma. It is now widely recognised that prolonged fasting for elective surgery serves no particular purpose, as fluids can be safely given up to 2 hours before surgery and light meals up to 6 hours preoperatively for patients requiring general anaesthesia (254). Nevertheless, there is a paucity in the literature on the additional benefits of preoperative nutrition in the form of preoperative carbohydrate loading.

The ERAS® Society currently recommends the use of preoperative oral carbohydrate loading in patients undergoing elective colorectal surgery, excluding patients with known delayed gastric emptying and diabetics (255). However, the recommendations are widely based on modest reductions in hospital stay, reduced postoperative insulin resistance and maintenance of lean body mass generalised from multiple specialities and procedures. A previous compliance study reported that the length of hospital stay can vary widely dependent on the number of bundle elements received in the enhanced recovery protocol (256). Furthermore, in the UK, approximately 17% of the obese population have a diagnosis of diabetes (257). Unsurprisingly, the proportion of obese patients in the present elective

study cohort was, at least, similar to the national population at 30%. It is of interest that 90% of these obese patients received preoperative carbohydrate loading in a population at risk for undiagnosed diabetes despite concerns of hyperglycaemia. Therefore, there may be a good argument to omit the practice of oral carbohydrate loading in particular for patients undergoing minimally invasive surgery, especially in the context of undiagnosed diabetes in a prevalent obese population. Indeed, minimally invasive surgery is likely to reduce the need for other Enhanced Recovery interventions.

The findings of the present study are consistent with a randomised controlled trial by Gianotti and coworkers in patients undergoing major abdominal surgery (258). They reported that oral preoperative carbohydrate loading was effective at avoiding hyperglycaemia but not a reduction of postoperative infective complications (compared with placebo, water) and similarly, laparoscopic surgery was a significant protective factor for risk of infections. The Cochrane review and a recent network meta-analysis also reported no evidence of the effect of preoperative carbohydrate treatment on complication rate in major abdominal surgery (259, 260).

The hypothesis for the introduction of preoperative carbohydrate loading in surgery was based on the premise that it prevented insulin resistance, attenuated the catabolic state, and prevented postoperative hyperglycaemia. However, surgical site infection is a multifactorial phenomenon and there remains the possibility that the metabolic changes attributed with the use of preoperative carbohydrate loading play only a minimal role in major colonic cancer surgery. In view of the present results, the potential clinical benefit conferred by preoperative carbohydrate loading needs to be considered against the cost and inconvenience of the intervention in patient care.

In the preoperative period, the goals in nutrition are primarily to prevent malnutrition, minimising starvation, prevention of the catabolic state and fuel for anabolic recovery. Nevertheless, the majority of the patients in the present elective study cohort of patients had a low risk of malnutrition based on the MUST score. The main confounders that were adjusted for in the study were emergency surgery and diabetic patients, perhaps the differences in the physiology in these patients may benefit from preoperative carbohydrate loading. Most studies on

preoperative carbohydrate have excluded diabetic patients for valid concerns with regards to delayed gastric emptying times and risk of hyperglycaemia. However, Robinson and coworkers examined the limited evidence available in diabetic patients and suggest that preoperative carbohydrate loading in well controlled diabetics is feasible without increased risk of hyperglycaemia (260)(240). Nevertheless, there is a void in the evidence for the application of preoperative carbohydrate loading in diabetic and emergency patients that is yet to be studied. Further well-designed studies are also required to delineate the actual benefit of preoperative carbohydrate loading in terms of length of stay in view of variations in enhanced recovery programmes in current practice.

The main limitation of this study was the small sample size and the difference in the proportion of patients in the intervention versus non-intervention group. Propensity score matching could potentially balance the two groups, but with only 10% of the sample population not receiving preoperative carbohydrate loading after excluding diabetic patients, this would not be feasible due to the extremely small sample size. Similarly, inverse probability of treatment weighting would run the risk of overfitting due to only 20 outcome events recorded in the sample population. The retrospective nature of the study and its single centre design also increase the risk of selection bias. Another potential limitation was the confounding effect of the variations in anaesthetic technique that have been shown to have an effect on the postoperative systemic inflammatory response that can also contribute to the surgical stress response (261). Indeed, within an enhanced recovery programme, it is difficult to ascertain if certain measures are more impactful than others thereby reducing the direct correlation between preoperative carbohydrate loading and surgical site infections.

Owing to the study's principal limitations, definitive conclusions regarding the effect of preoperative oral carbohydrate loading in patients undergoing elective colon cancer surgery could not be drawn. Nevertheless, no significant differences were observed in the magnitude of postoperative systemic inflammatory response or the risk of surgical site infection between patients who received preoperative carbohydrate loading and those who did not. These findings highlight the inconsistency in the reported benefits of preoperative carbohydrate loading in the literature, with its effects potentially dependent on the magnitude and invasiveness of surgery. The introduction of minimally invasive surgery such as

laparoscopic and robotic surgery are likely to result in less insulin resistance and therefore reducing the need for and efficacy of preoperative oral carbohydrate loading (262, 263).

3.6 Tables

Table 3-1 Clinicopathological characteristics for non-diabetic patients undergoing elective colon cancer surgery

Characteristics	Total	No preoperative carbohydrate drink	Preoperative carbohydrate drink	P-value
Age <65 65-74 >74	218 65(30) 76(35) 77(35)	24 (11) 6(25) 10(42) 8(33)	194(89) 59(30) 66(34) 69(36)	0.742
Sex Female Male	218 111(51) 107(49)	24(11) 10(42) 14(58)	194(89) 101(52) 93(48)	0.337
ASA 1 2 3 4	218 45(21) 106(49) 62(28) 5(2)	24(11) 2(9) 14(58) 7(29) 1(4)	194(89) 43(22) 92(47) 55(25) 4(2)	0.404
MUST Low risk Medium risk High risk	218 183(84) 20(9) 15(7)	24(11) 18(75) 3(13) 3(12)	194(89) 165(85) 17(9) 12(6)	0.403
BMI (kg/m^2) < 30 ≥ 30	218 184(71) 64(29)	24(11) 18(75) 6(25)	194(89) 136(70) 58(30)	0.619
Smoking status Non-smoker Ex-smoker Smoker	218 117(54) 84(38) 17(8)	24(11) 14(59) 8(33) 2(8)	194(89) 103(53) 76(39) 15(8)	0.857
TNM Staging I II III	218 48(22) 92(42) 78(36)	24(11) 4(17) 10(42) 10(42)	194(89) 44(23) 82(42) 68(35)	0.736
Surgical Approach Open or converted Laparoscopic	218 116(53) 102(47)	24(11) 15(63) 9(37)	194(89) 101(52) 93(48)	0.334
Day 3 poGPS 0 1 2	198 119(60) 44(22) 35(18	21(11) 12(57) 2(10) 7(33)	177(89) 107(60) 42(24) 28(16)	0.082

Surgical site infection No Yes	218 199(91) 19(9)	24(11) 23(96) 1(4)	194(89) 176(91) 19(9)	0.402

ASA = American Society of Anesthesiologists physical status classification system; MUST = malnutrition universal screening tool; BMI = body mass index; poGPS = postoperative Glasgow prognostic score; TNM=tumour, node, metastasis.
P-values calculated using Chi square analysis.

Table 3-2 Association between clinicopathological factors and surgical site infection in non-diabetic patients undergoing elective colon cancer surgery

Characteristics	Surgical site infection	
	Univariate analysis	
	OR (95% CI)	P-value
Age (<65/65-74/>74)		0.232
Sex (Female/Male)		0.746
ASA (1/2/3/4)		0.837
MUST (Low/Medium/High risk)		0.784
BMI (kg/m^2) (<30 /≥ 30)		0.207
Smoking status (non-smoker/ex-smoker/Smoker)		0.165
TNM Staging (I/II/III)		0.403
Surgical approach (Open or converted/Lap)	0.28(0.09-0.86)	0.026*
Day 3 poGPS (0/1/2)		0.402
Preoperative carbohydrate loading (No/Yes)		0.416

ASA = American Society of Anesthesiologists physical status classification system; MUST = malnutrition universal screening tool; BMI = body mass index; poGPS = postoperative Glasgow prognostic score; TNM = tumour, node, metastasis; OR=odds ratio; CI =confidence interval.
*Statistically significant p-value.

Chapter 4 The relationship between routine preoperative clinicopathological factors and postoperative infective complications in patients undergoing elective potentially curative colon cancer resection

4.1 Introduction

Colorectal cancer remains a common cancer in the United Kingdom and the second leading cause of cancer-related death (264). Surgical resection is the primary modality of treatment for patients with non-metastatic colon cancer but is often associated with postoperative complications. Postoperative complications are defined as a deviation from the normal postoperative course, with rates ranging from 10 to 35% depending on the complexity of the colorectal resection (146, 150). Postoperative complications can be stratified by types such as superficial wound infection, deep and organ space infections or severity (Clavien-Dindo classification) and are associated with prolonged hospital stays, additional procedures and adverse short-term and long-term patient outcomes (150, 165, 265).

Diverse protocols and preventive measures have been implemented for perioperative management of surgical patients, with prevention of postoperative complications as a primary aim. Resection surgery for colon cancer is no exception, and indeed improving short-term outcomes facilitates adjuvant treatment and improvement of long-term oncological outcomes (266, 267). Despite efforts to improve surgical practices such as the World Health Organisation global guideline for prevention of surgical site infection, colorectal surgery still carries the highest risk of surgical site infection among all types of surgery in the most recent summary collected by the National Health Service in England (149, 268).

It is imperative to recognise routine preoperative clinicopathological prognostic factors for postoperative complications to concentrate efforts on improving outcomes. To date, there has been a significant body of literature that reports the impact of prognostic factors on long-term survival in patients undergoing surgery for colorectal cancer (143, 144, 269-275). Nonetheless, overall survival is

significantly influenced by the efficacy of the surgical resection and short-term outcomes. A meta-analysis by Mualla et al. reported worse overall survival rates, disease-free survival and overall recurrence in the presence of postoperative complications after curative resection for colorectal cancer (267). While McSorley et al. also reported poorer overall survival and disease-free survival with infective complications (154).

Several clinicopathological factors have been widely examined to determine the effect on postoperative complications for colorectal cancer. Chapter 2 identified that certain factors have a consistent effect on short-term outcomes and a mandatory preoperative variable set should be collected to allow comparison of outcomes (276). Simmonds et al. reported the progressively increasing incidence of postoperative complications with advancing age but commented that the relationship between age and outcomes is complex, hypothesising an indirect attribution (168). Indeed, more recent studies have focused on the role of frailty and management of pre-existing comorbidities to improve outcomes in the elderly population undergoing surgical resection (277-281). Body mass index is widely used as a crude marker of tissue adiposity and has previously been reported as a prognostic indicator for short-term outcomes in colorectal cancer surgery along with other host factors such as sex and socioeconomic deprivation in large population studies (16, 18, 171, 174, 282-286). More recently, the systemic inflammatory response measured preoperatively and postoperatively has been reported to have a prognostic value for postoperative infective complications independent of the tumour stage (164, 252). The aim of the present study was to examine the association between the routinely reported preoperative clinicopathological factors and postoperative complications in a large regional cohort of patients undergoing elective potentially curative colon cancer surgery.

4.2 Patients and Methods

A prospective dataset is maintained by the West of Scotland Colorectal Cancer Managed Clinical Network (MCN) for all patients diagnosed with colorectal cancer in the West of Scotland. This covers four health boards (Ayrshire and Arran, Forth Valley, Lanarkshire and Greater Glasgow and Clyde) and serves approximately 50% of the Scottish population (287). These patients are usually followed up for a period of 3-5 years and receive treatment in line with national guidelines. Data extracted from the MCN database for this study included patient names, date of birth, hospital numbers, type of cancer and list of comorbidities. Patient-identifiable information was excluded from the research dataset, and each patient was assigned a unique study identifier to maintain confidentiality.

Patients diagnosed with colon cancer between January 2011 and December 2014 within the West of Scotland were identified from the MCN database. Patients undergoing curative surgery for diagnosis of TNM Stage I-III colon cancer were included. Patients with emergency presentation, Stage IV disease, rectal cancer, macroscopically involved margins (R2 resections), those who did not have surgical resection or those who underwent palliative procedures were excluded.

Comorbidities were classified using the American Society of Anesthesiologists (ASA) Physical Status Classification System (250). Socioeconomic deprivation has been stratified using the Scottish Index of Multiple Deprivation (SIMD). Body mass index (BMI) was calculated from height and weight measured within 6 months prior to surgery and the BMI was categorised according to thresholds as follows: normal range <25 kg/m^2, overweight 25-29.9 kg/m^2, obese 30-34.9 kg/m^2 and morbidly obese ≥35 kg/m^2. Tumours were staged using the TNM classification system. The preoperative systemic inflammatory response was categorised by Systemic Inflammatory Grade (SIG) as previously described (144).

Patients were assessed for any postoperative complications, infective complications, and surgical site infections up to 30 days from the date of surgery. Infective complications included respiratory tract infections, urinary tract infections or any surgical site infections. Surgical site infections were defined as the presence of superficial skin infection, deep organ or space infections including anastomotic leaks and abdominal collections.

The data were collected retrospectively by a single investigator utilising all available electronic patient medical records, including inpatient medical notes, discharge letters, clinic letters, radiology reports, blood test results and microbiology test results up to 30 days following surgery. Using a single investigator and a standardised review of the available medical records helped ensure consistency in the identification and assessment of postoperative complications.

In 2010, regional healthcare infrastructure changes led to the migration of physical patient medical records to an electronic record system. However, complete electronic records for entire hospital episodes were unavailable for some patients identified through the MCN database. Consequently, postoperative outcome data were entirely unavailable for these patients, rather than being missing for individual variables. Patients with unavailable outcome data were excluded from analysis.

Ethical approval was granted for this project from the Public Benefit and Privacy Panel (NHS Scotland) for Health and Social Care (PBPP) and Caldicott Guardian Approval.

4.3 Statistical analysis

The relationship between the clinicopathological characteristics and complications was compared using the Chi-square test for significance where appropriate. P values <0.05 were considered statistically significant. All complications, infective complications and surgical site complications were analysed using univariate and multivariate binary logistic regression models. Those variables associated with a p <0.10 on univariate analysis were entered into a backward conditional multivariate model where variables with a p value <0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows Version 27 (IBM Corporation, Armonk, New York, USA).

4.4 Results

A total of 6547 patients were diagnosed with colorectal cancer in the West of Scotland from January 2011 to December 2014, 2261 of whom had undergone elective curative resection for TNM Stage I-III colon cancer. After exclusion of patients who had missing complication data, 1887 patients remained and were included in this study.

4.4.1 All postoperative complications

As shown in Table 4-1, in patients undergoing elective surgery for colon cancer (n =1887), 763 of the patients (40%) developed postoperative complications. Factors associated with development of postoperative complications were male sex (p=0.002), higher ASA grade (p=0.003), higher BMI (p=0.001), diabetes (p<0.001), smoking (p<0.001) and open or laparoscopic converted to open surgical approach (p<0.001). On multivariate analysis (Table 4-2), there was a significant independent association between sex (OR 0.79, 95% CI 0.64-0.99, P<0.05), ASA grade (OR 1.22, 95% CI 1.03-1.45, P<0.05), BMI (OR 1.20, 95% CI 1.07-1.35, p≤0.001), diabetes (OR 1.49, 95% CI 1.1-2.02, p<0.05), smoking (OR1.32, 95% CI 1.12-1.54, p<0.001) and open or laparoscopic converted to open surgical approach (OR 0.71, 95% CI 0.57-0.89, P<0.01) with the development of postoperative complications.

4.4.2 Infective complications

As shown in Table 4-3, in patients undergoing elective surgery for colon cancer, 554 of the patients (29%) developed infective complications. Factors associated with development of infective complications were higher ASA grade (p=0.014), higher BMI (p<0.001), diabetes (p<0.001), smoking (p<0.001) and an open or laparoscopic converted to open surgical approach (p <0.001). On multivariate analysis (Table 4-3), there was a significant independent association between BMI (OR 1.29, 95% CI 1.15-1.46, p<0.001), diabetes (OR 1.45, 95% CI 1.06-1.99, p<0.05), smoking (OR 1.26, 95% CI 1.07-1.49, p<0.01) and open or laparoscopic converted to open surgical approach (OR 0.66, 95% CI 0.52-0.84, P<0.01) with the development of postoperative infective complications.

4.4.3 Surgical site infections

As shown in Table 4-5, in patients undergoing elective surgery for colon cancer, 368 of the patients (19%) developed surgical site infections. Factors associated with the development of surgical site infections were older age (p=0.005), higher BMI (p<0.001), diabetes (p<0.001) and open or laparoscopic converted to open surgical approach (p=0.004). On multivariate analysis (Table 4-6), there was a significant independent association between BMI (OR 1.40, 95% CI 1.23-1.60, p≤0.001), diabetes (OR 1.57, 95% CI 1.12-2.22, p<0.01) and open or laparoscopic converted to open surgical approach (OR 0.70, 95% CI 0.53-0.93, P<0.05) with the development of postoperative surgical site infections.

4.4.4 30-day Mortality

As shown in Table 4-7, in patients undergoing elective surgery for colon cancer, 43 of the patients (2%) died within 30 days. Factors associated with 30-day mortality were older age (p<0.001), higher ASA grade (p<0.001), higher TNM stage (p=0.006), higher preoperative SIG score (p=0.004) and open or laparoscopic converted to open surgical approach (p=0.031). On multivariate analysis (Table 4-8), there was a significant independent association between Age (OR 2.5, 95% CI 1.28-4.89, p=0.007), ASA (OR 2.3, 95% CI 1.28-4.13, p=0.006) and Preop SIG (OR 1.36, 95% CI 1.02-1.81, p=0.035).

4.4.5 Association between BMI and diabetes

The relationship between BMI and diabetes is shown in Table 4-9. The proportion of patients with a known diagnosis of diabetes increased from 7% in those with BMI < 25 to 30% in those with BMI ≥ 35.

4.4.6 Association between BMI, diabetes, and surgical site infection rate

As shown in Table 4-10, the rate of surgical site infections increased from 3% in patients with a BMI of < 25 kg/m² to 47% in patients with BMI ≥35 kg/m² in the diabetic cohort. The overall rate of surgical site infection was also higher in those with diabetes than those without.

4.4.7 Association between infective complications, BMI, diabetes, and day 4 CRP ≥150

As shown in Table 4-11, there was no clear additive effect on the rate of infective complications when the day 4 CRP threshold is breached.

4.5 Discussion

The present results show that postoperative complications remain common after curative surgery for colon cancer even after adjustment for mode of presentation. In particular, an elevated BMI and diabetes status were consistently associated with infective complications and surgical site infective complications, ranging between 3% and 47% dependent on these factors. Also, that BMI is associated with the proportion of patients with a known diagnosis of diabetes varying from 7% in those with BMI < 25 kg/m^2 to 30% in those with BMI ≥ 35 kg/m^2. Therefore, BMI and diabetes status should be determined in patients undergoing elective surgery for colon cancer.

Infective complications have been reported as the most common type of postoperative complication after colorectal surgery, and the findings in the present study were consistent with approximately 70% of the overall complications attributed to infective complications and specifically surgical site infections (269). In the present study, the results were consistent with previous work reporting the association between obesity and increased risk of infective complications (174, 282, 283, 288). A large panniculus of fat not only makes surgery technically challenging, but hypovascularisation in adipose tissue predisposes wounds to poor tissue oxygenation and prolonged healing (289). The presence of excess adipose tissue also upsets the balance of cytokines and immune cell regulation, resulting in a proinflammatory state and altered immunity, leading to a poor response in the presence of infection (290). In the context of the present study, it is of interest that the Global Burden of Disease, Injuries, and Risk Factors (GBD) study has listed high body mass index as part of the five leading risk factors contributing to deaths and disability-adjusted life years, with an increase in exposure to high body mass index (approximately 70%) between 1990 and 2017 (291). Obesity is not only recognised to be a risk factor for cancer but also other chronic diseases such as cardiovascular disease, diabetes mellitus, hypertension, and chronic kidney disease.

Body mass index in the present study had a strong association with diabetes. The exact mechanism that links the two conditions is unclear, but several proposed mechanisms include metabolic dysfunction with insulin resistance, deranged fatty acid metabolism and mitochondrial dysfunction (292). The pathogenesis of Type 2

diabetes mellitus relies on the presence of both: pancreatic islet cell dysfunction and peripheral insulin resistance. Adipose tissue has been proposed to produce hormonal and proinflammatory cytokines that affect insulin sensitivity, and this is increased in obese individuals (293). The influence of obesity on diabetes is determined not only by the degree of adipose tissue but also by the distribution and differences in metabolic effects that may relate to the fact that not all patients who are obese are diabetic (294). BMI is broadly used as a parameter to measure the effect of body fat. However, not all patients with the same BMI have similar body composition. BMI is typically a better indicator of subcutaneous and total fat rather than visceral fat. Therefore, it would be of interest to study the differences in body composition on the effect of postoperative complications in patients undergoing curative surgery for colon cancer.

Although BMI and diabetes are associated, multivariate analysis demonstrated that both remained independent predictors of postoperative infective complications and surgical site infections. Increasing BMI was associated with 40% higher odds of surgical site infections with each increase in BMI category (adjusted OR 1.4, 95%CI 1.23-1.60, $p<0.001$), while diabetes was associated with 58% higher odds of surgical site infections (adjusted OR 1.58, 95% CI 1.12-2.22, $p=0.009$) after adjusting for other variables included in the model. This suggests that the association between BMI and postoperative complication cannot be explained solely by the presence of diabetes and vice versa. The findings may reflect the distinct but potentially overlapping mechanisms through which obesity and diabetes influence postoperative complications. Obesity may contribute to impaired wound healing through altered tissue perfusion, increased tissue depth and technical challenges during surgery, whereas diabetes may increase susceptibility to infection through hyperglycaemia and impaired immune function (220, 295). The persistence of both variables in the multivariable model suggests that each provides additional prognostic information regarding postoperative infective risk. These findings highlight the importance of considering both BMI and diabetes when assessing preoperative risk in patients undergoing colorectal cancer surgery.

In the present study, although both an elevated BMI and diabetes were independently associated with infective complications, they were not independently associated with 30-day mortality. In contrast, the association

between ASA and SIG with postoperative 30-day mortality represents a noteworthy finding. This finding suggests that increased systemic inflammation may reflect underlying physiological susceptibility and reduced resilience to surgical stress. However, only 2% of deaths occurred in the cohort; the small number of mortality events limits the estimate's reliability, particularly after multivariable adjustment. Therefore, although the finding is statistically significant, it should be interpreted with caution. Further studies with larger cohorts and sufficient mortality events are required to determine whether preoperative SIG provides reproducible prognostic information on short-term postoperative outcomes.

The present study has several limitations, as with any study based on a database there lies the potential for inadequacies such as completeness of data that may introduce a selection bias. There may also be some intrinsic and extrinsic factors that have not been taken into account for analysis that could alter the relationship between the prognostic factors and risk of postoperative infective complications. However, the present data were taken from a large database which is maintained by the West of Scotland Colorectal Cancer Managed Clinical Network (MCN) for all patients diagnosed with colorectal cancer in the West of Scotland, and this should mitigate such limitations.

In conclusion, the present results show that an elevated BMI and diabetes status were consistently associated with infective complications and the surgical site infective complication varied from 3% to 47% depending on these factors. Therefore, BMI and diabetes status should be determined in patients undergoing elective surgery for colon cancer.

4.6 Tables

Table 4-1 Clinical characteristics and systemic inflammatory response according to presence of complications for patients undergoing elective resection for colon cancer

Characteristics	Total n (%)	Postoperative No complication n (%)	Postoperative All complications n (%)	P-value
Age	1887	1124(60)	763(40)	0.066
<65	577(31)	363 (32)	214 (28)	
65-74	694(37)	392(35)	302(40)	
>74	616(33)	369(33)	247(32)	
Sex	1887	1124(60)	763(40)	0.002*
Male	995(53)	560(50)	435(57)	
Female	892(47)	564(50)	328(43)	
ASA	1830	1090(60)	740(40)	0.003*
1	189(10)	129(12)	60(8)	
2	1049(57)	640(59)	409(55)	
3	544(30)	295(27)	249(34)	
4	48(3)	26(2)	22(3)	
SIMD	1887	1124(60)	763(40)	0.22*
Most deprived	511(27)	274(24)	237(31)	
2	407(22)	243(22)	164(22)	
3	325(17)	203(18)	122(16)	
4	298(16)	189(17)	109(14)	
Least deprived	348(18)	215(19)	131(17)	
BMI (kg/m^2)	1486	886(60)	600(40)	0.001*
<25	498(33)	323(37)	175(29)	
25- <30	519(35)	312(35)	207(35)	
30- <35	307(21)	175(20)	132(22)	
35+	162(11)	86(8)	76(14)	
Diabetes	1877	1118(60)	759(40)	<0.001*
Yes	288(15)	134(12)	154(20)	
No	1589(85)	984(88)	605(80)	
Smoking status	1819	1088(60)	731(40)	<0.001*
Non-smoker	871(48)	569(52)	302(41)	
Ex-smoker	732(40)	409(38)	323(44)	
Smoker	216(12)	110(10)	106(15)	
Tumour location	1873	1118(60)	755(40)	0.591
Right	1003(54)	593(53)	410(54)	
Left	870(46)	525(47)	345(46)	
TNM Stage	1887	1124(60)	763(40)	0.949

I	449(24)	269(24)	180(24)	
II	783(42)	463(41)	320(42)	
III	655(35)	392(35)	263(34)	
Preoperative SIG	1054	622(59)	432(41)	0.126
0	442(42)	277(45)	165(38)	
1	280(27)	164(26)	116(27)	
2	190(18)	106(17)	84(19)	
3	80(8)	46(7)	34(8)	
4	62(6)	33(8)	29(5)	
Surgical Approach	1873	1113(69)	760(41)	<0.001*
Open or converted	1144(61)	57(56)	506(67)	
Laparoscopic	729(39)	475(43)	254(33)	

ASA=American Society Anesthesiologist; SIMD=Scottish Index of Multiple Deprivation; BMI=body mass index; TNM=Tumour, node, metastasis; SIG= systemic inflammatory grade.

*Statistically significant p-value, P-value calculated with Chi square analysis.

Table 4-2 Association between clinicopathological factors and all complications in patients undergoing elective resection for colon cancer

Clinicopathological characteristics	Postoperative All Complications	
	Multivariate analysis OR (95% CI)	P-value
Age, years (<65/65-74/>74)		0.21
Sex (male/ female)	0.79 (0.64-0.99)	0.037*
ASA (1/2/3/4/5)	1.22 (1.03-1.45)	0.021*
BMI (kg/m^2) (<25/25- <30/30-<35/+35)	1.20 (1.07-1.35)	0.001*
Diabetes (Yes/No)	1.49 (1.1-2.02)	0.011*
Smoking status (non-smoker/ex-smoker/smoker)	1.32(1.12-1.54)	0.001*
Surgical approach (Open or converted/Laparoscopic)	0.71(0.57-0.89)	0.002*

ASA=American Society Anesthesiologist; BMI=body mass index; OR=odds ratio; CI=confidence interval.

* Statistically significant p-value.

Table 4-3 Clinical characteristics and systemic inflammatory response according to infective complications for patients undergoing elective resection for colon cancer

Characteristics	Total	No infective complication	Infective complications	P-value
Age	1887	1333(71)	554(29)	0.078
<65	577(30)	407(31)	170(31)	
65-74	694(37)	472(35)	222(40)	
>74	616(33)	454(34)	162(29)	
Sex	1887	1333(71)	554(29)	0.07
Male	995(53)	685(51)	310(56)	
Female	892(47)	648(49)	244(44)	
ASA	1830	1294(71)	536(29)	0.014*
1	189(10)	144(11)	45(8)	
2	1049(57)	758(59)	291(54)	
3	544(30)	363(28)	181(34)	
4	48(3)	19(4)	29(2)	
SIMD	1887	1333(71)	554(29)	0.305
Most deprived	511(27)	343(26)	168(30)	
2	407(22)	298(22)	109(20)	
3	325(17)	235(18)	90(16)	
4	298(16)	212(16)	86(16)	
Least deprived	346(18)	245(18)	101(18)	
BMI (kg/m^2)	1486	1058(71)	428(29)	<0.001*
<25	498(34)	383(36)	115(27)	
25- <30	519(35)	378(36)	141(33)	
30- <35	307(20)	205(19)	102(24)	
35+	162(11)	92(9)	70(16)	
Diabetes	1877	1327(71)	550(29)	<0.001*
Yes	288 (15)	171(13)	117(21)	
No	1589(85)	1156(87)	433(79)	
Smoking status	1819	1289(71)	530(29)	<0.001*
Non-smoker	871(48)	651(51)	220(42)	
Ex- smoker	732(40)	503(39)	229(43)	
Smoker	216(12)	135(10)	81(15)	
Tumour location	1873	1326(71)	547(29)	0.41
Right	1003(54)	702(53)	301(55)	
Left	870(46)	624(47)	246(45)	
TNM Stage	1887	1333(71)	554(29)	0.625
I	449(24)	319(24)	130(24)	
II	783(41)	544(41)	239(43)	

III	655(35)	470(35)	185(33)	
Preop SIG	1054	745(71)	309(29)	0.75
0	442(42)	328(44)	114(37)	
1	280(27)	195(26)	85(28)	
2	190(18)	122(16)	68(22)	
3	80(8)	60(8)	20(6)	
4	62(6)	40(6)	22(7)	
Surgical Approach	1873	1322(71)	551(29)	<0.001*
Laparoscopic	729(39)	558(42)	171(31)	
Open or converted	1144(61)	764(58)	380(69)	

ASA=American Society Anesthesiologist; SIMD=Scottish Index of Multiple Deprivation; BMI=body mass index; TNM =Tumour, node, metastasis; SIG=systemic inflammatory grade.

* Statistically significant p-value. P-value calculated with Chi-square analysis.

Table 4-4 Association between clinicopathological factors and infective complications in patients undergoing elective resection for colon cancer

Clinicopathological characteristics	Infective Complication	
	Multivariate analysis OR (95%CI)	P-value
Age, years (<65/ 65-74/ >74)		0.496
Sex (male/ female)		0.833
ASA (1/ 2 / 2 / 3/ 4/ 5)		0.068
BMI (kg/m^2) (<18.5/ 18.5- <25/ 25- <30/ 30- <35/ +35)	1.29 (1.15-1.46)	<0.001*
Diabetes (Yes/ No)	1.45(1.06-1.99)	0.022*
Smoking status (non-smoker/ ex-smoker/ smoker)	1.26 (1.07-1.49)	0.007*
Surgical approach (Laparoscopic/ Open or converted)	0.66(0.52-0.84)	0.001*

ASA=American Society Anesthesiologist; BMI=body mass index; OR=odds ratio; CI=confidence interval.

* Statistically significant p-value.

Table 4-5 Clinical characteristics and systemic inflammation according to surgical site infection for patients undergoing elective resection for colon cancer

Characteristics	Total	No surgical site infection	Surgical site infection	P-value
Age	1887	1519(81)	368(19)	0.005*
<65	577(31)	453(30)	124(33)	
65-74	693(37)	544(36)	150(41)	
>74	616(33)	422(34)	94(26)	
Sex	1887	1519(81)	368(19)	0.132
Male	995(53)	788(52)	207(56)	
Female	892(47)	731(48)	161(44)	
ASA	1830	1474(81)	356(19)	0.429
1	189(10)	158(11)	31(9)	
2	1049(57)	849(58)	200(56)	
3	544(30)	431(29)	113(32)	
4	48(3)	36(2)	12(3)	
SIMD	1887	1519(81)	368(19)	0.42
Most deprived	511(27)	402(27)	109(30)	
2	407(22)	340(22)	67(18)	
3	325(17)	263(17)	62(17)	
4	298(16)	240(16)	58(16)	
Least deprived	346(18)	274(18)	72(20)	
BMI (kg/m^2)	1486	1206(81)	280(19)	<0.001*
18.5- <25	498(34)	432(36)	66(24)	
25- <30	519(35)	432(36)	87(31)	
30- <35	307(20)	234(19)	73(26)	
35+	162(11)	108(9)	54(19)	
Diabetes	1887	1512(81)	365(19)	<0.001*
Yes	288(15)	202(13)	86(24)	
No	1589(85)	1310(87)	279(76)	
Smoking status	1819	1467(81)	352(19)	0.392
Non-smoker	871(48)	713(49)	158(45)	
Ex-smoker	732(40)	585(40)	147(42)	
Smoker	216(12)	169(11)	47(13)	
Tumour location	1873	1510(81)	363(19)	0.182
Right	1003(54)	820(54)	183(50)	
Left	870(46)	690(46)	180(50)	
TNM Stage	1887	1519(81)	368(19)	0.276
I	449(24)	362(24)	87(24)	
II	783(42)	618(41)	165(45)	
III	655(35)	539(36)	116(32)	

Preop SIG	1054	858(81)	196(19)	0.604
0	442(42)	369(43)	73(37)	
1	280(27)	221(26)	59(30)	
2	190(18)	152(18)	38(19)	
3	80(7)	66(8)	14(7)	
4	62(6)	50(6)	12(6)	
Procedure	1873	1506(80)	367(20)	0.004*
Open or converted	1144(61)	896(60)	248(68)	
Laparoscopic	729(39)	610(40)	119(32)	

ASA=American Society Anesthesiologist; SIMD=Scottish Index of Multiple Deprivation; BMI= body mass index; TNM= Tumour, node, metastasis; SIG: systemic inflammatory grade.

* Statistically significant p-value. P-values calculated using Chi square analysis.

Table 4-6 Association between clinicopathological factors and surgical site infection in patients undergoing elective resection for colon cancer

Clinicopathological characteristics	Surgical site infection	
	Multivariate OR (95% CI)	P-value
Age, years (<65/65-74/>74)		0.096
BMI (kg/m^2) (<25/25- <30/30-<35/+35)	1.40(1.23-1.60)	<0.001*
Diabetes (Yes/ No)	1.58(1.12-2.22)	0.009*
Surgical approach (Open or converted/Laparoscopic)	0.70(0.53-0.93)	0.012*

BMI=body mass index; OR=odds ratio; CI=confidence interval.

* Statistically significant p-value.

Table 4-7 Clinical characteristics and systemic inflammation according to 30-day mortality for patients undergoing elective resection for colon cancer

Characteristics	Total	Alive at 30-Days	30-Day mortality	P-Value
Age	2261	2218(98)	43(2)	<0.001*
<65	667(30)	666(30)	1(2)	
65-74	841(37)	831(38)	10(23)	
>74	753(33)	721(32)	32(75)	
Sex	2261	2218 (98)	43(2)	0.058
Male	1202(53)	1173(53)	29(67)	
Female	1059(47)	1045(47)	14(33)	
ASA	2178	2137(98)	41(2)	<0.001*
1	223(10)	223(10)	0	
2	1246(57)	1230(58)	16(39)	
3	646(30)	625(29)	21(51)	
4	63(3)	59(3)	4(10)	
Diabetes	2234	2193(98)	41(2)	0.058
Yes	359(16)	348(16)	11(27)	
No	1875(84)	1845(84)	30(73)	
BMI ($kg/m^{2)}$	1631	1612(99)	19(1)	0.851
<25	543(33)	536(33)	7(37)	
25- <30	575(35)	569(35)	6(32)	
30- <35	336(21)	333(21)	3(16)	
35+	177(11)	174(11)	3(16)	
Smoking status	2149	2115(98)	34(2)	0.303
Non-smoker	1024(48)	1012(48)	12(35)	
Ex-smoker	874(41)	856(40)	18(53)	
Smoker	251(11)	247(12)	4(12)	
Tumour location	2243	2200(98)	43(2)	0.059
Right	1194(53)	1165 (53)	29(67)	
Left	1049(47)	1035(47)	14(33)	
TNM Stage	2261	2218(98)	43(2)	0.006*
I	539(24)	536(24)	2(5)	
II	935(41)	916(41)	19(44)	
III	788(35)	766(35)	34(51)	
Preop SIG	1297	1267(98)	30(2)	0.004*
0	531(41)	525(41)	6(20)	

1 2	345(27) 237(18)	339(27) 228(18)	6(20) 9(30)	
3 4	101(8) 83(6)	98(8) 77(6)	3(10) 6(20)	
Procedure	2242	2199(98)	43(2)	0.031*
Open or converted Laparoscopic	1420(63) 822(37)	1386(63) 813(37)	34(79) 9(21)	

ASA=American Society Anesthesiologist; SIMD=Scottish Index of Multiple Deprivation; BMI=Body mass index; TNM= Tumour, node, metastasis; SIG=systemic inflammatory grade.

* Statistically significant p-value. P-values calculated using Chi square analysis.

Table 4-8 Association between clinicopathological factors and 30-day mortality in patients undergoing elective resection for colon cancer

Clinicopathological characteristics	30-day Mortality	
	Multivariate OR (95% CI)	P-Value
Age, years (<65/65-74/>74)	2.50(1.28-4.89)	0.007*
Sex (Male/female)		0.173
ASA (1/2/3/4)	2.30(1.28-4.13)	0.006*
Diabetes (Yes/No)		0.092
Tumour location (Right/Left)		0.28
TNM Stage (I/II/III)		0.073
Preop SIG (0/1/2/3/4)	1.36(1.02-1.81)	0.035*
Procedure (Open or converted/Laparoscopic)		0.155

ASA=American Society Anesthesiologist; TNM=Tumour, node, metastasis; SIG= systemic inflammatory grade; OR=odds ratio; CI=confidence interval.

* Statistically significant p-value.

Table 4-9 Association between diabetes and BMI

Diabetes	BMI (kg/²)				Total	P-value
	<25	25- < 30	30- <35	≥35		
	n (%)	n (%)	n (%)	n (%)	n (%)	
No	500(3)	491(86)	261(78)	124(70)	1376(85)	<0.001
Yes	40(7)	82(14)	75(22)	53(30)	250(15)	
Total	540(33)	573(35)	336(21)	177(11)	1626	

BMI=body mass index; p-value calculated using Chi-square analysis.

Table 4-10 Association between BMI, diabetes and surgical site infection rate

Diabetes	BMI (kg/m²)										P-Value[a]
	<25		25-<30		30-<35		35+		Total		
	n	%	n	%	n	%	n	%	n	%	
No	461	14	447	15	238	22	113	27	1203	17	0.001
Yes	35	3	70	26	69	30	49	47	279	28	<0.001
Total	496	13	517	17	307	24	162	33	1482	19	<0.001[c]
P Value[b]	0.059		0.028		0.14		0.016		<0.001[d]		

BMI=body mass index; [a]Chi-square test was used to analyse P-value for SSI with and without diabetes against all BMI categories aside from total; [b]Chi-square exact test was used to analyse P-value for SSI in individual BMI category against those with and without diabetes aside from total; [c]Chi-square exact test was used to analyse the P-value between SSI and body mass index for all patients; [d]Chi-square exact test was used to analyse the P-value between SSI and diabetes for all BMI.

Table 4-11 Association between BMI, diabetes and Day 4 CRP ≥150 mg/L

	BMI (kg/m²)										P-value[a]
	<25		25-<30		30-<35		35+		Total		
Diabetes	n	%	n	%	n	%	n	%	n	%	
No	110	58%	110	59	80	58	39	64	339	59	0.913
Yes	8	-	23	78	24	58	19	79	74	70	0.354
Total	118	59	133	62	104	58	58	69	413	61	0.484[c]
P-value[b]	0.811		0.084		0.942		0.251		0.072		

BMI=body mass index; CRP=C-reactive protein; [a]Chi square test was used to analyse P-value for Day4 CRP with against presence or absence of diabetes aside from total; [b]Chi square exact test was used to analyse P-value for Day4 CRP with in individual BMI category against those with and without diabetes aside from total; [c]Chi square exact test was used to analyse the P-value between Day 4 CRP and body mass index for all patient; [d]Chi square exact test was used to analyse the P-value between SSI and diabetes for all BMI.

Chapter 5 The relationship between computed tomography-derived body composition, body mass index, diabetes, and surgical site infection in patients undergoing curative colon cancer resection

5.1 Introduction

Colorectal cancer remains among the most diagnosed cancers worldwide (155). As surgical resection is the primary treatment modality, there is a risk of postoperative complications. Surgical site infection (SSI) is the most frequently encountered infective complication and is reported to have the highest incidence in colorectal resection (268). This is of particular concern in colorectal cancer surgery as it increases the risk of recurrence and negatively impacts overall survival (154, 165). Despite quality improvement initiatives such as the World Health Organisation global guideline for prevention of surgical site infection, SSI continues to contribute to the healthcare burden, costing an average £3500 per SSI (296, 297).

The rate of SSI is dependent on a complex interaction between host and surgical factors, nevertheless potentially preventable in most occurrences. Chapter 4 demonstrated that obesity and diabetes have a strong association with surgical site infections, with rates ranging from 3% to 47% dependent on the presence of these factors. In the United Kingdom, approximately 30% of those above the age of 15 have been reported to have a BMI>30 kg/m^2 (298). Obesity is a well-established risk factor for developing colorectal cancer but is increasingly recognised to confer adverse short-term outcomes following colorectal cancer surgery (174, 299, 300). A recent study reported that obesity affects postoperative outcomes in colorectal cancer mainly by triggering infective complications (288).

Similar to obesity, diabetes poses an increasing health risk, with its prevalence tripled over the last 20 years (301). Approximately 15% of surgical patients have diabetes, and it carries a significant risk for developing surgical site infection (226). Obesity and diabetes are likely to share similar underlying mechanisms, but the characterisation of the relationship is unclear. Approximately 30% of patients who are morbidly obese are likely to be diagnosed as diabetic.

Both visceral and subcutaneous adipose tissue contribute to obesity in BMI calculations. However, fat tissue distribution is an important determinant of metabolic risk, with visceral fat being particularly associated with markers of insulin resistance leading to diabetes (302). The use of CT-derived body composition has garnered interest due to the precision in measuring adiposity compared to BMI. As fat is principally deposited in two compartments, the subcutaneous and visceral compartments, it is of interest to determine if either of these components or both can function as a surrogate for the relationship between BMI, diabetes, and surgical site infection.

Thus far, no study has examined in detail the relationship between computer tomography-derived body composition, body mass index, diabetes, and surgical site infection. Therefore, the aim of the present study is to examine the relationship in a large regional cohort of patients undergoing elective potentially curative colon cancer surgery.

5.2 Patients and Methods

A prospective dataset is maintained by the West of Scotland Colorectal Cancer Managed Clinical Network (MCN) for all patients diagnosed with colorectal cancer in the West of Scotland. This covers four health boards (Ayrshire and Arran, Forth Valley, Lanarkshire and Greater Glasgow and Clyde and serves approximately 50% of the Scottish population (287). These patients are usually followed up for a period of 3-5 years and receive treatment in line with national guidelines.

Patients diagnosed with colon cancer between January 2011 and December 2014 within the West of Scotland were identified from the MCN database. Patients undergoing curative surgery for a diagnosis of TNM Stage I-III colon cancer were included. Patients with emergency presentation, Stage IV disease, rectal cancer, macroscopically involved margins (R2 resections), those who did not have surgical resection, or those who underwent palliative procedures were excluded.

BMI was calculated from height and weight measured within 6 months prior to surgery, and the BMI was categorised according to thresholds as follows: normal range < 25 kg/m^2, overweight 25-29.9 kg/m^2, obese 30-34.9 kg/m^{2}and morbidly obese ≥ 35 kg/m^2. The diabetes status at the time of diagnosis was determined from medical records. The preoperative computed tomography images of eligible patients were identified and required cross-sectional scanning at the level of the third lumbar vertebra. Furthermore, scans with significant movement artefact or missing region of interest were not considered for inclusion.

Each CT image was individually analysed using ImageJ—a freely available Java-based program, developed by NIH (NIH ImageJ version 1.47; http://rsbweb.nih.gov/ij/), shown to provide reliable measurements (303). Body composition was assessed using a single axial CT image at the third lumbar vertebral level (L3). Each axial CT image was selected by identifying the L3 vertebra on sagittal and coronal views prior to selecting an axial view image including both transverse processes in the image. The analysis was performed manually by tracing the anatomical boundaries of the relevant tissue compartments using ImageJ's region-of-interest selection tool. Following delineation of each region, the software calculated the corresponding cross-sectional area based on selected pixels and the image scale. Predefined

attenuation thresholds were from −190 to +30 Hounsfield units (HU) for fat and −29 to +150 HU for muscle.

The total fat area (TFA) was quantified by depicting the outer contours of the abdominal wall, compared with the inner contour of the psoas and abdominal wall muscles for visceral fat area (VFA). Similarly, skeletal muscle area (SMA) was measured by manually delineating muscle areas including the quadratus lumborum, psoas, rectus abdominis, and erector spinae muscles, and the internal transverse and external oblique muscle groups. Skeletal muscle density (SMD) was calculated (in Hounsfield units) as the mean of the measured muscle area used to calculate SMI. Subcutaneous fat area (SFA) was calculated by subtraction of the VFA from TFA. SFA and SMA measurements were then normalised by division by the patient's height in meters squared to generate a subcutaneous fat index (SFI: centimetres squared/metres squared) and skeletal muscle index (SMI: centimetres squared/metres squared). These indices were then compared with established thresholds for body composition status (Table 5-1).

Eligible patients were assessed for presence of surgical site infections. Surgical site infections were defined as the presence of superficial skin infection, deep organ or space infections including anastomotic leaks and abdominal collections. The data were collected utilising all available electronic patient medical records, including inpatient medical notes, discharge letters, clinic letters, radiology reports, blood test results and microbiology test results.

Ethical approval was granted for this project from the Public Benefit and Privacy Panel (NHS Scotland) for Health and Social Care (PBPP) and Caldicott Guardian Approval.

5.3 Statistical analysis

Categorical variables were compared using the Chi-square test for significance. Two-tailed P values <0.05 were considered statistically significant. A multivariate binary logistic regression model was used to determine the relationship to determine the relationship between clinical characteristics and surgical site infections. Statistical analysis was performed using IBM SPSS Statistics for Windows Version 28 (IBM Corporation, Armonk, New York, USA).

5.4 Results

A total of 6547 patients were diagnosed with colorectal cancer in the West of Scotland from January 2011 to December 2014, 2261 of whom had undergone elective curative resection for TNM Stage I-III colon cancer. Following the exclusion of patients with missing data, 1409 patients were eligible for analysis, as shown in Figure 5-1. Approximately 30% of the patient population had a BMI ≥30 kg/m^2, and a large proportion was found to have a high SFI (81%) and high VFA (78%).

5.4.1 Association between BMI, diabetes, and surgical site infection rate

As shown in Table 5-2, the surgical site infection rate increased steadily with an increasing BMI and the presence of diabetes, ranging from 3% in those with BMI < 25 kg/m^2 to 48% in those with BMI ≥ 35 kg/m^2 ($p<0.001$).

5.4.2 Association between BMI and body composition

As shown in Table 5-3, there was a positive association between BMI and high SFI ($p < 0.001$), high VFA ($p<0.001$) and high SMI ($p<0.001$). There was an inverse association between BMI and low SMD ($p<0.001$).

5.4.3 Association between diabetes and body composition

As shown in Table 5-4, there was a positive association between diabetes and high SFI ($p<0.05$) and high VFA ($p<0.001$). There was an inverse association between diabetes and low SMD ($p<0.05$).

5.4.4 Binary logistic regression of BMI, diabetes, and body composition versus surgical site infection

In separate multivariable logistic regression model adjusted for diabetes and surgical approach, BMI, SFI and VFA were each associated with surgical site infection. The largest observed odds ratio was for VFA (OR 1.66, 95% CI 1.25-2.21), followed by SFI (OR 1.54, 95% CI 1.13-2.09) and BMI (OR 1.35, 95% CI 1.19-1.53) (Table 5-5) (Table 5-6) (Table 5-7).

In contrast, BMI demonstrated the highest observed discriminatory performance with an area under the curve (AUC) of 0.61 (95% CI 0.57-0.65), compared with 0.591 (95% CI 0.56-0.63) for VFA and 0.580 (95%CI 0.55-0.62) for SFI.

5.5 Discussion

In the present study, an elevated BMI was significantly associated with body composition components including greater SFI, greater VFA, normal SMI and lower SMD. In contrast, the diagnosis of diabetes was associated with greater SFI, greater VFA, lower SMD, but not SMI. All three measures of adiposity (BMI, SFI and VFA) were associated with surgical site infection in separate multivariable logistic regression models adjusted for diabetes and surgical approach, with the largest observed odds ratio for VFA. Nevertheless, BMI demonstrated the highest observed discriminatory performance.

Previous studies have explored the relationship of CT measurements of body composition and outcomes following colorectal cancer resection (160). Studies have linked high visceral adipose tissue (VFA) and reduced muscle mass (SMI) to poorer outcomes (304). However, there are no studies directly comparing the efficacy of CT measurements of body composition in the presence of BMI and diabetes in predicting the risk of surgical site infections.

The relationship between obesity and postoperative outcomes is complex. The concept of the 'obesity paradox' has been proposed to explain observations in which patients with higher BMI experience comparable or better outcomes than patients with lower BMI in certain clinical settings (305). In the present cohort, a substantial proportion of patients classified as obese (BMI>30 kg/m^2) had normal skeletal muscle mass according to SMI calculations. Preserved muscle mass may represent an important physiological reserve during the catabolic stress of surgery. BMI may also reflect aspects of body size and adiposity that are not fully captured by individual CT-derived body composition measurements. However, the higher observed AUC for BMI does not establish the mechanism underlying its discriminatory performance or demonstrate that it captures the metabolic and inflammatory consequences of obesity more effectively than SFI and VFA.

In the present study, it was of interest that, in contrast to BMI, diabetes was only associated with high VFA, high SFI, low SMD and was independently associated with postoperative infective complications. Low muscle densities are associated with reduced muscle strength and physical function and therefore the quality of muscle tissue (306). It may be that the skeletal muscle structure changes due to

infiltration by fat influence the ability of skeletal muscle to buffer the variation in glucose concentrations and impair insulin pathways (307). Against this background the surgical stress response results in increased catecholamines, cortisol and inflammatory cytokines which in turn increase secretion of glucagon, growth hormone as well as a state of decreased insulin sensitivity that is magnified in diabetic patients (242). The induced hyperglycaemia from the catabolic state and diabetes consequently elevates the risk of infective complications in patients undergoing colorectal cancer resection (172). The importance of the metabolic and/or the systemic inflammatory response as the primary mechanism for surgical site infection is yet to be determined.

To compare the discriminatory performance of the three adiposity measures, receiver operating characteristic (ROC) analysis was performed using predicted probabilities from the respective adjusted models. Although VFA had the largest adjusted odds ratio, BMI had the highest observed AUC (0.610, 95% CI 0.57–0.65), compared with VFA (0.591, 95% CI 0.56–0.63) and SFI (0.580, 95% CI 0.55–0.62). This apparent difference illustrates that the magnitude of association between a variable and SSI does not necessarily correspond to its ability to discriminate between patients who develop SSI and those who do not. However, discrimination was limited for all three models, and the differences in AUC do not establish that BMI performs statistically better than the CT-derived measures. Furthermore, because the analysis was conducted in the study cohort without independent validation, the findings should be considered exploratory. External validation is required to establish whether the observed differences translate into more reliable prognostic performance in other patient populations.

The strength of the present study lies in the relatively large cohort of patients undergoing elective curative colon cancer resection. Limitations of the present study include the retrospective analysis of the data and exclusion of patients with missing data that may lead to selection bias. In addition, the discriminatory performance of the models was assessed in the same cohort used to estimate the model parameters, potentially resulting in optimistic estimates of performance.

In conclusion, BMI, SFI and VFA were each associated with the risk of surgical site infection in separate multivariable models adjusted for diabetes and surgical approach. BMI demonstrated the highest observed discriminatory performance,

although discrimination was limited across all three models. These findings suggest that CT-derived measures of body composition did not demonstrate an apparent advantage over BMI in this cohort. Further validation is required to determine whether CT-derived body composition measurements provide additional prognostic value beyond routinely available clinical variables, including BMI in predicting risk of surgical site infection.

5.6 Tables

Table 5-1 Computer tomography-derived body composition and thresholds

Body composition measurements
Subcutaneous fat index (SFI): High (308) (Male > 50cm²m² and Female > 42cm²m²)
Visceral fat area (VFA): High (231, 309) (Males > 160cm² and Female > 80cm²)
Skeletal Muscle Index (SMI- Martin) Low (231) (Male: BMI ≤25 kg²m² SMI <43 cm²m² and BMI >25 kg²m² SMI <53 cm²m²) (Female: BMI ≤ 25 kg²m² SMI <41 cm²m² and BMI >25 kg²m² SM<41 cm²m²)
Skeletal Muscle Density (SMD-Martin) Low (231) (BMI < 25 kg/m² and SMD < 41 HU or BMI ≥ 25 kg/m² and SMD < 33 HU)

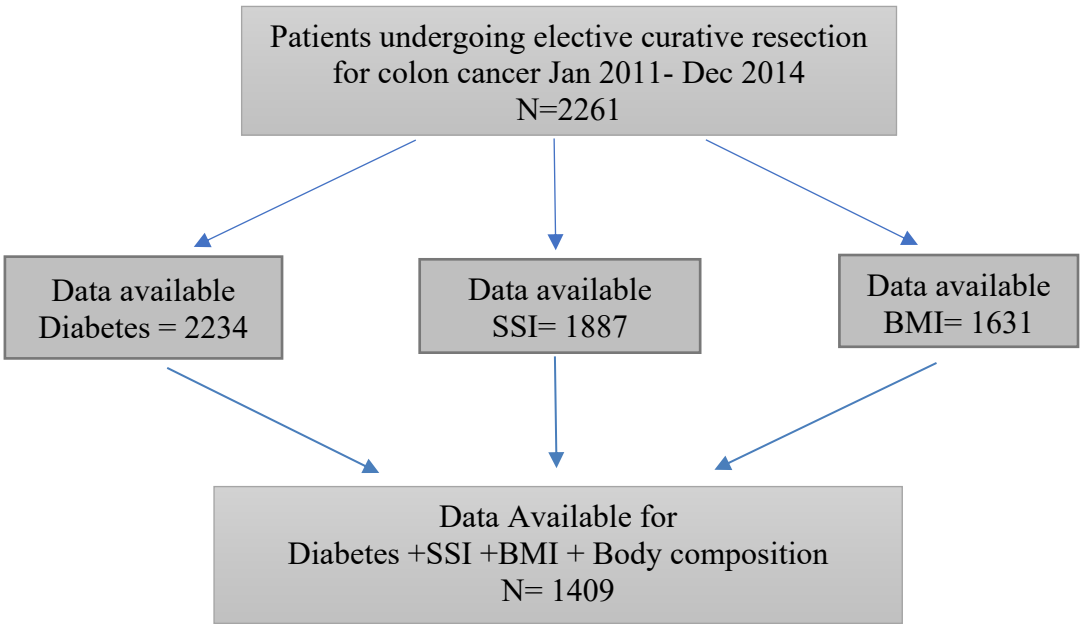


Figure 5-1 Flow diagram for analysis of BMI, diabetes, body composition and surgical site infection

Table 5-2 Association between BMI, diabetes and surgical site infection rate

Diabetes	BMI (kg/m²)										P-Value[a]
	<25		25-<30		30-<35		35+		Total		
	n	%	n	%	n	%	n	%	n	%	
No	429	14	425	14	231	22	110	27	1195	17	0.001
Yes	35	3	66	23	65	31	48	48	214	28	<0.001
Total	464	13	491	16	296	24	158	34	1409	19	<0.001c
P Value[b]	0.057		0.08		0.147		0.011		<0.001d		

BMI, body mass index; [a]Chi-square test was used to analyse P-value for SSI with and without diabetes against all BMI categories aside from total; [b]Chi-square exact test was used to analyse P-value for SSI in individual BMI category against those with and without diabetes aside from total; [c]Chi-square exact test was used to analyse the P-value between SSI and body mass index for all patient; [d]Chi-square exact test was used to analyse the P-value between SSI and diabetes for all BMI.

Table 5-3 Association between BMI, SFI, VFA, SMI and SMD

Body composition		Total (N)	BMI (kg/m²)										P-value
			<25		25- < 30		30- <35		35+		Total		
			n	%	n	%	n	%	n	%	n	%	
SFI	Normal	1409	195	42	66	13	5	2	3	2	269	19	**<0.001***
	High		269	58	425	87	291	98	155	98	1140	81	
VFA	Normal	1409	254	55	46	9	4	1	2	1	306	22	**<0.001***
	High		210	45	445	91	292	99	156	99	1103	78	
SMI	Normal	1409	185	40	176	36	181	61	130	82	672	48	**<0.001***
	Low		279	60	315	64	115	39	28	18	737	52	
SMD	Normal	1409	107	23	237	48	97	33	49	31	490	35	**<0.001***
	Low		357	77	254	52	199	67	109	69	919	66	

BMI=body mass index; SFI=subcutaneous fat index; VFI=Visceral fat index; SMI=skeletal muscle index; SMD=skeletal. muscle density.

*Statistically significant P-value.

Table 5-4 Association between diabetes, SFI, VFA, SMI and SMD

Body composition		Total N	Diabetes						P- value
			No		Yes		Total		
			n	%	N	%	N	%	
SFI	Normal	1409	241	20	28	13	269	19	**0.015***
	High		954	80	186	87	1140	81	
VFA	Normal	1409	295	25	11	5	306	22	**<0.001***
	High		900	75	203	95	1103	78	
SMI	Normal	1409	562	47	110	51	672	48	0.238
	Low		633	53	104	49	737	52	
SMD	Normal	1409	431	36	59	28	490	35	**0.016***
	Low		764	64	155	72	919	65	

SFI=subcutaneous fat index; VFI=Visceral fat index; SMI=skeletal muscle index; SMD=skeletal muscle density.
*Statistically significant P-value.

Table 5-5 Binary logistic regression of BMI, diabetes and surgical approach versus surgical site infection

Clinical characteristics	Surgical site infections	
	Multivariate OR (95% CI)	P-value
Diabetes (No/Yes)	1.49 (1.08-2.05)	0.015*
BMI kg/m² (25/25-<30/30-<35/>35)	1.35 (1.19-1.53)	<0.001*
Surgical Approach (Open /Laparoscopic)	0.66 (0.51-0.86)	0.002*

BMI=body mass index; OR=odds ratio; CI=confidence interval. *Statistically significant P-value.

Table 5-6 Binary logistic regression of SFI, diabetes and surgical approach versus surgical site infection

Clinical characteristics	Surgical site infections	
	Univariate OR (95% CI)	P-value
Diabetes (No/Yes)	1.62 (1.21-2.17)	0.001*
SFI (Normal /High)	1.54 (1.13-2.09)	0.006*
Surgical Approach (Open /Laparoscopic	0.63 (0.49-0.81)	<0.001*

BMI=body mass index; SFI=subcutaneous fat index; OR=odds ratio; CI=confidence interval. *Statistically significant P-value.

Table 5-7 Binary logistic regression of VFA, diabetes and surgical approach versus surgical site infection

Clinical characteristics	Surgical site infections	
	Univariate OR (95% CI)	P-value
Diabetes (No/Yes)	1.58 (1.19-2.09)	0.001
VFA(Normal/High)	1.66 (1.25-2.21)	<0.001
Surgical approach (Open/Laparoscopic)	0.66 (0.51-0.83)	<0.001

BMI=body mass index; VFA=visceral fat index; OR=odds ratio; CI=confidence interval. *Statistically significant P-value.

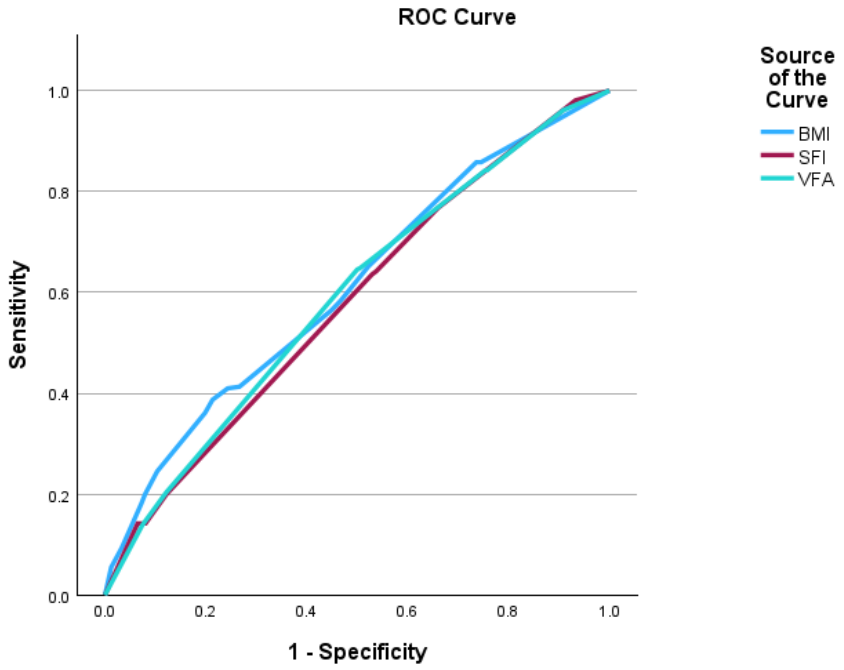


Figure 5-2 Receiver operating characteristic curve comparing the discriminatory performance of BMI, SFI and VFA for surgical site infection following colon cancer surgery, adjusted for diabetes status and surgical approach.

Chapter 6 Relationship between preoperative glycated haemoglobin and surgical site infection in patients undergoing elective colon cancer surgery

6.1 Introduction

Surgical resection remains the primary management for Stage I-III colon cancer but not for Stage IV colon cancer (241, 310). Surgical site infection remains an important postoperative complication following elective colon cancer resection. Postoperative complications not only intensify the burden on the healthcare system but are increasingly recognised to influence long-term oncological outcomes (154).

Previous chapters of this thesis have examined the association between established clinicopathological factors, including diabetes mellitus and body mass index and surgical site infection. Although a diagnosis of diabetes is recognised as a risk factor for surgical site infection, this diagnosis may not identify all patients with abnormal glycaemic status before surgery. There are no national screening programmes for diabetes, and tests are usually performed for diagnostic purposes in symptomatic patients. A study extrapolated that patients are likely to have the onset of diabetes at least 4-7 years prior to diagnosis, long after dysglycaemia has taken effect (311).

Glycated haemoglobin represents the average plasma glucose over three months, and tests can be performed at any time and therefore eliminate the effect of day-to-day variability and the need for preceding dietary restrictions while creating the opportunity for identification of patients with asymptomatic diabetes in the preoperative setting (312). Unlike a single blood glucose measurement, glycated haemoglobin is less affected by short-term fluctuations in glucose concentration. The International Federation of Diabetes estimates that almost 1 in 2 adults living with diabetes are undiagnosed in 2021 (313). This raises the question of the proportion of undiagnosed diabetics, especially in those in the higher BMI range.

Despite its potential utility, the prognostic association between preoperative glycated haemoglobin and surgical site infection in patients undergoing colon cancer surgery requires further evaluation. Furthermore, the respective availability of glycated haemoglobin measurements may provide an opportunity to examine this relationship in routine clinical practice, although the selection of patients who underwent testing must be considered when interpreting the findings.

The aim of this study was to investigate the association between preoperative haemoglobin measurements and surgical site infection in patients undergoing elective potentially curative colon cancer resection. Secondary objectives were to examine the relationship between glycated haemoglobin and clinicopathological characteristics, identify patients with elevated glycated haemoglobin without a recorded diagnosis of diabetes and explore surgical site infection rates across categories of glycated haemoglobin and body mass index.

6.2 Patients and methods

Study population. A dataset is maintained by the West of Scotland Colorectal Cancer Managed Clinical Network (MCN) for all patients diagnosed with colorectal cancer in the West of Scotland. The West of Scotland Colorectal Cancer Managed Clinical Network (MCN) is a collaborative made up of four NHS health boards (NHS Greater Glasgow and Clyde, NHS Lanarkshire, NHS Forth Valley and NHS Ayrshire and Arran**)** and serves approximately 50% of the Scottish population (287)**.** These patients are usually followed up for a period of 3-5 years and receive treatment in line with national guidelines. The analysis of the clinicopathological data from the MCN dataset and complication data was performed retrospectively.

Inclusion and exclusion criteria. Patients diagnosed with colon cancer between January 2011 and December 2014 within the West of Scotland were identified from the MCN database. Patients who underwent curative surgery for TNM Stage I-III colon cancer were included. Only patients who had preoperative glycated haemoglobin (HbA1c) levels measured in mmol/mol within 3 months prior to the date of surgery were included. Patients with emergency presentation, Stage IV disease (distant metastasis), rectal cancer, macroscopically involved resection margins (R2 resections), those who did not have surgical resection, or those who underwent palliative procedures were excluded.

Data collection. Patients were assessed for any postoperative complication, infective complication, and surgical site infections. Infective complications included respiratory tract infections, urinary tract infections or any surgical site infections. Surgical site infections were defined as the presence of superficial skin infection, deep organ or space infections including anastomotic leaks and abdominal collections. Abdominal collections are intra-abdominal collections of pus or infected material identified either by radiological or intraoperative findings. The data were collected utilising all available electronic patient medical records including referral letters, preassessment records, anaesthetic records, inpatient medical notes, discharge letters, clinic letters, radiology reports, blood test results and microbiology test results.

Comorbidities were classified using the American Society of Anesthesiologists (ASA) Physical Status Classification System (250). Socioeconomic deprivation was

stratified using the Scottish Index of Multiple Deprivation (SIMD). BMI was calculated from height and weight measured within 6 months prior to surgery and categorised according to the following thresholds: normal range <25 kg/m^2, overweight 25-29.9 kg/m^2, obese 30-34.9 kg/m^2, and morbidly obese ≥35 kg/m^2. In the present study, the majority of the BMI results were calculated from height and weight measurements taken at the preoperative admission episode for surgery (n=217, 85%). The mean time height and weight were measured before surgery was 27.6 days, with a standard deviation of 36.6 days and a range of 0-165 days. However, in order to minimise missing data, height and weight recorded in the initial referral letter from the general practitioner, with a maximum extension of up to 6 months prior to surgery, were included. Tumours were staged using the TNM classification system (114). The preoperative systemic inflammatory response was categorised by Systemic Inflammatory Grade (SIG) as previously described (144).

Body composition measurements were derived from the preoperative computed tomography (CT) image slice at the level of the third lumbar vertebra and included total fat area (TFA), visceral fat area (VFA), and skeletal muscle area (SMA). Each CT image was individually analysed using ImageJ—a freely available Java-based program, developed by NIH (NIH ImageJ version 1.47; http://rsbweb.nih.gov/ij/), shown to provide reliable measurements (303). Attenuation thresholds were from −190 to +30 Hounsfield units (HU) for fat and −29 to +150 HU for muscle. The TFA was quantified by depicting the outer contours of the abdominal wall, compared with the inner contour of the psoas and abdominal wall muscles for VFA. Similarly, SMA was measured by manually delineating muscle areas including the quadratus lumborum, psoas, rectus abdominis, and erector spinae muscles, and the internal transverse and external oblique muscle groups. Skeletal muscle density (SMD) was calculated (in Hounsfield units) as the mean of the measured muscle area used to calculate SMI. Subcutaneous fat area (SFA) was calculated by subtraction of the VFA from TFA. SFA and SMA measurements were then normalised by division of the patient's height in meters squared to generate a subcutaneous fat index (SFI: centimetres squared/meters squared) and skeletal muscle index (SMI: centimetres squared/meters squared). These indices were then compared with established thresholds for body composition status (Table 5-1).

Ethics. Ethical approval (ref. no. 1617-0079) was granted for this project by the Public Benefit and Privacy Panel (NHS Scotland) for Health and Social Care (PBPP) and Caldicott Guardian Approval.

6.3 Statistical analysis

The relationship between the clinicopathological characteristics and preoperative HbA1c was compared using the Chi-square test and Fisher's exact test for significance where appropriate. $P<0.05$ was considered statistically significant. Surgical site complications were analysed using univariate and multivariate binary logistic regression models. Variables associated with surgical site infection at $P<0.10$ on univariate analysis were entered into a backward conditional multivariate model where variables with a $P<0.05$ were considered statistically significant. Correlation between body mass index and preoperative HbA1c was performed via bivariate analysis using Pearson's correlation coefficient. The relationship between HbA1c, BMI and surgical site infection was assessed using Fisher's exact test. Statistical analysis was performed using IBM SPSS Statistics for Windows Version 28 (IBM Corporation, Armonk, New York, USA).

6.4 Results

6.4.1 Study population.

A total of 2,261 patients underwent elective curative resection for TNM Stage I-III colon cancer in the West of Scotland from January 2011 to December 2014. Following exclusion of patients with missing data, 362 patients had HbA1c levels available within 3 months preoperatively (Figure 6-1). Most of the patients who had HbA1c levels (n=315) available had a pre-existing diagnosis of diabetes, representing 87% of the eligible study population.

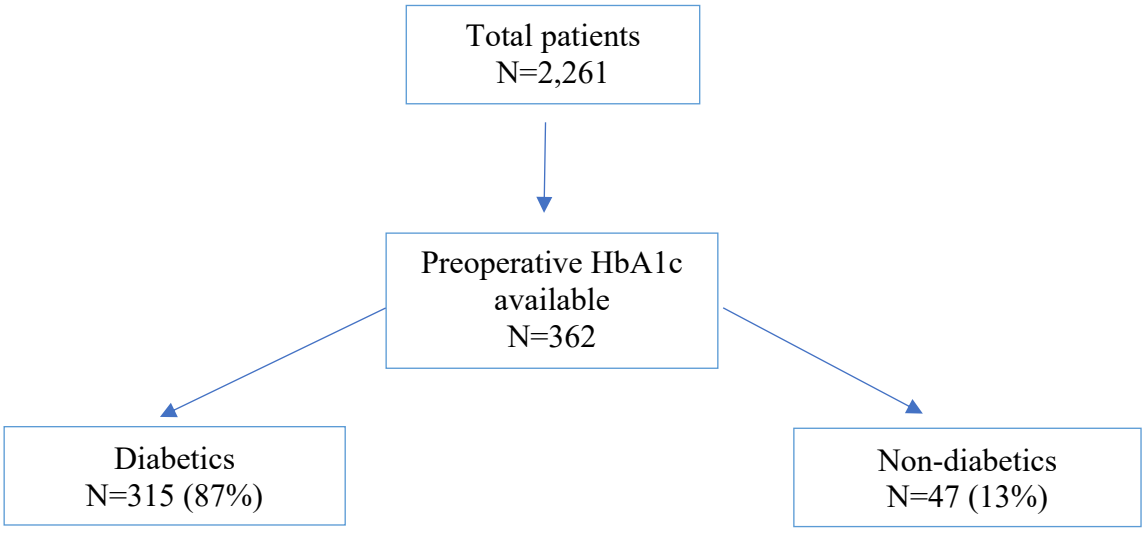


Figure 6-1 Preoperative HbA1c recorded for patients undergoing colon cancer surgery and proportion of diabetics and non-diabetics with HbA1c levels available

6.4.2 Clinicopathological characteristics.

The relationship between the clinicopathological characteristics with preoperative HbA1c is shown in Table 6-1. Approximately 57% of the patients had a HbA1c >48 mmol/mol. Preoperative HbA1c was significantly associated with body mass index (P<0.05), diabetes status (P<0.001), type of diabetic control (P<0.001), smoking status (P<0.001), visceral fat area (P<0.01), skeletal muscle index (P<0.05) and surgical site infections (P<0.05). However, when surgical site infection was subdivided into wound infection, abdominal collection, and anastomotic leak, only wound infection (P<0.05) was significantly associated with preoperative HbA1c.

6.4.3 Surgical site infection.

Binary logistic regression of factors associated with surgical site infections are shown in Table 6-2. On univariate analysis, surgical site infection was associated with age (P<0.10), BMI (P<0.001), HbA1c (P<0.05) and SMI (P<0.10). On multivariate analysis, surgical site infection was independently associated with BMI (OR 1.9, 95% CI 1.36- 2.37; P<0.001) and preoperative HbA1c (OR 1.69, 95% CI 1.05-2.7; P=0.031).

6.4.4 Rate of surgical site infection based on HbA1c and BMI.

A scatter plot of BMI versus preoperative HbA1c levels is shown in Figure 6-2. The Pearson's correlation analysis showed no statistically significant linear correlation between BMI and HbA1c for both sexes. The scatter plot of visceral fat area versus HbA1c levels is shown in Figure 6-3, subcutaneous fat index versus HbA1C levels is shown in Figure 6-4 while skeletal muscle index versus HbA1c levels is shown in Figure 6-5. The Pearson's correlation analysis showed no statically significant linear correlation between VFA and HbA1c as well as SFI and HbA1c for both sexes as well. While sex-stratified analysis demonstrated a weak negative correlation between Hba1c and SMI in males (r=-0.168, p=0.045) whereas no significant correlation was observed in females (r=-0.03, p=0.767).

The relationship between preoperative HbA1c and BMI on surgical site infection rate is shown in Table 6-3 represented in a line graph in Figure 6-6. The presence of both, high preoperative HbA1c and high BMI was associated with an increased rate of surgical site infection compared with a lower BMI and HbA1c (59% vs. 8%; P<0.001).

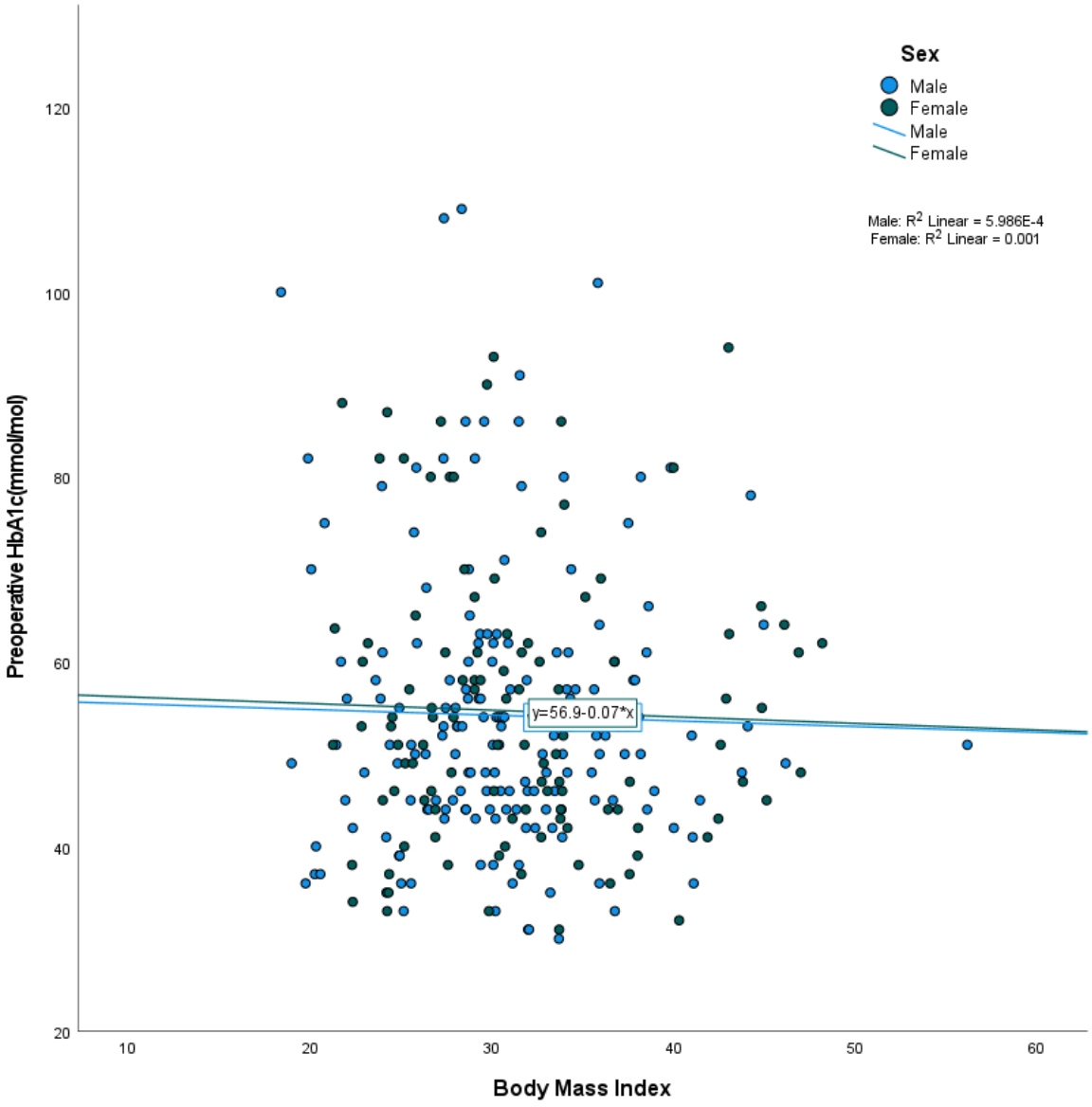


Figure 6-2 Scatter plot of body mass index (kg/m²) versus preoperative HbA1c level (mmol/mol)

The blue dots represent males, and green dots represent females with corresponding best fit line for both sexes. Pearson's correlation analysis performed using SPSS Statistics software showed r=-0.24 (P=0.751) for males and r=-0.32 (P=0.736) for females. HbA1c= glycated haemoglobin.

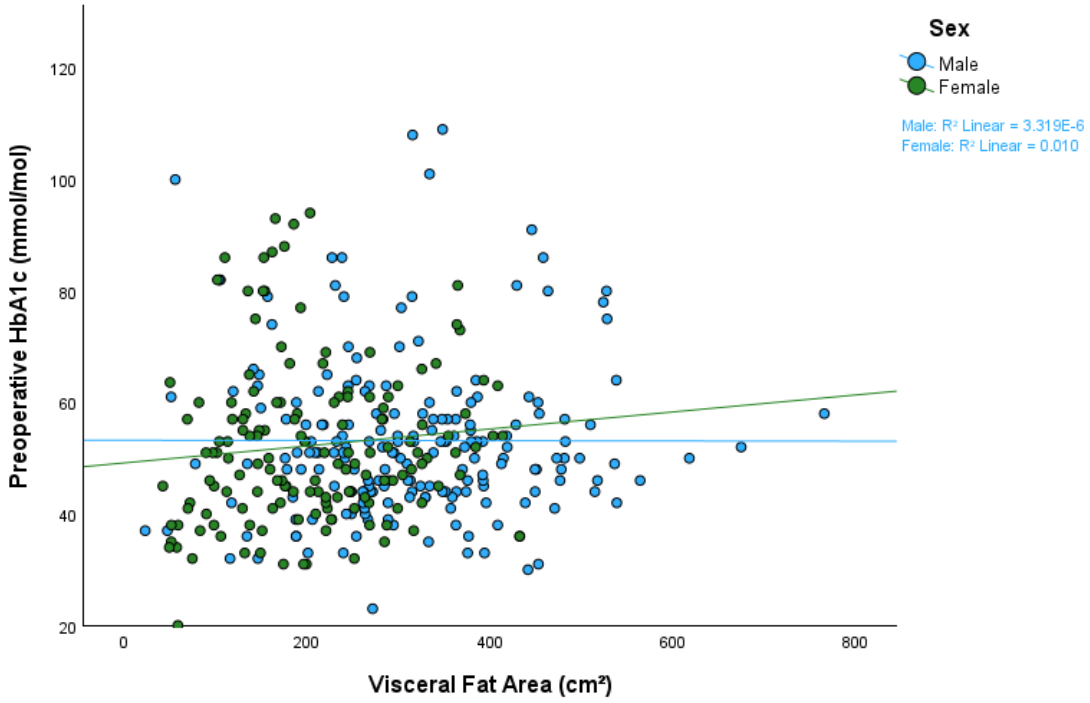


Figure 6-3 Scatter plot of visceral fat area (cm²) versus preoperative HbA1c level (mmol/mol)

The blue dots represent males, and green dots represent females with corresponding best-fit line for both sexes. Pearson's correlation analysis performed using SPSS Statistics software showed r=-0.002 (P=0.98) for males and r=0.098(P=0.24) for females. HbA1c= glycated haemoglobin.

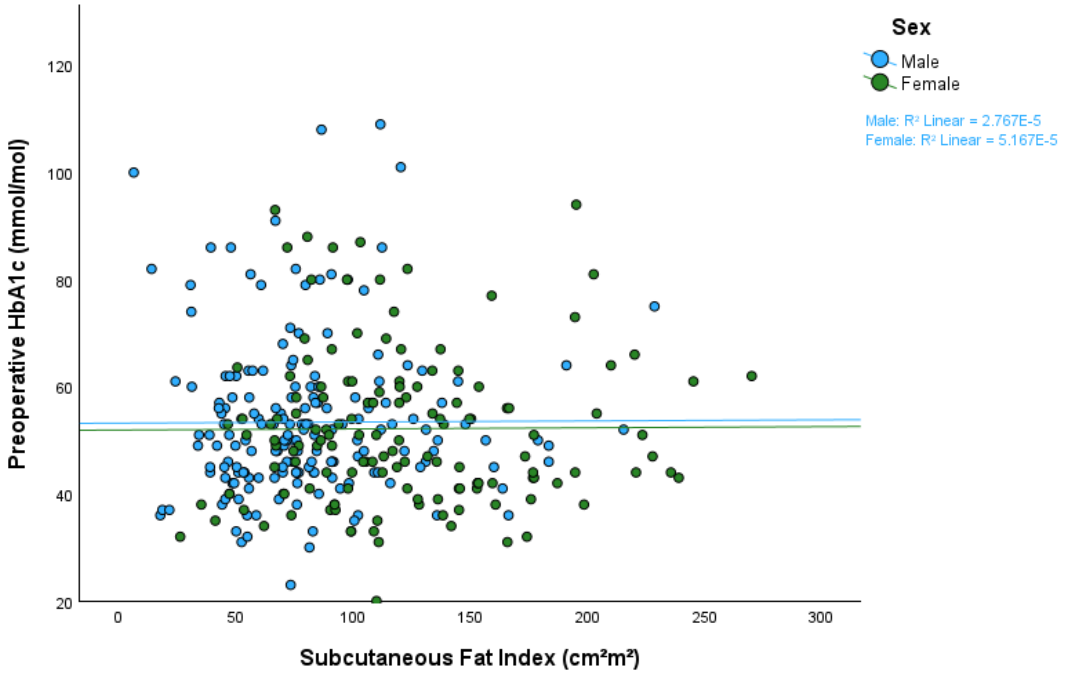


Figure 6-4 Scatter plot of subcutaneous fat index (cm²m²) versus preoperative HbA1c level (mmol/mol)

The blue dots represent males, and green dots represent females with corresponding best-fit line for both sexes. Pearson's correlation analysis performed using SPSS Statistics software showed r=0.028(P=0.685) for males and r=0.14 (P=0.08) for females. HbA1c= glycated haemoglobin

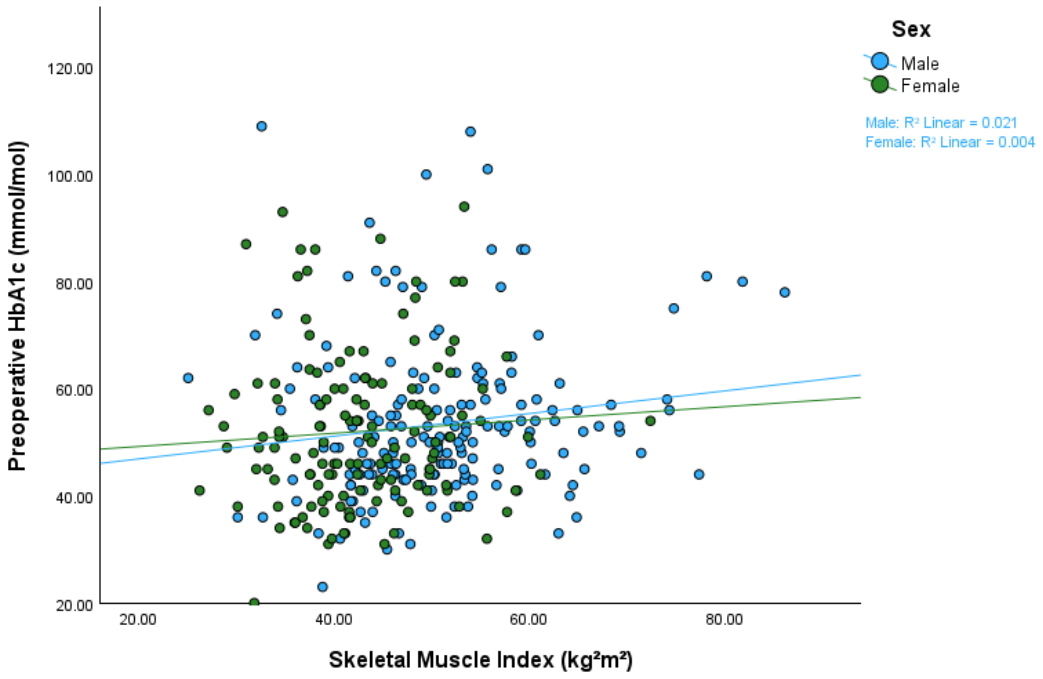


Figure 6-5 Scatter plot of skeletal muscle index (kg²m²) versus preoperative HbA1c level (mmol/mol)

The blue dots represent males, and green dots represent females with corresponding best-fit line for both sexes. Pearson's correlation analysis performed using SPSS Statistics software showed r=-0.168(P=0.045) for males and r=-0.03 (P=0.767) for females. HbA1c= glycated haemoglobin

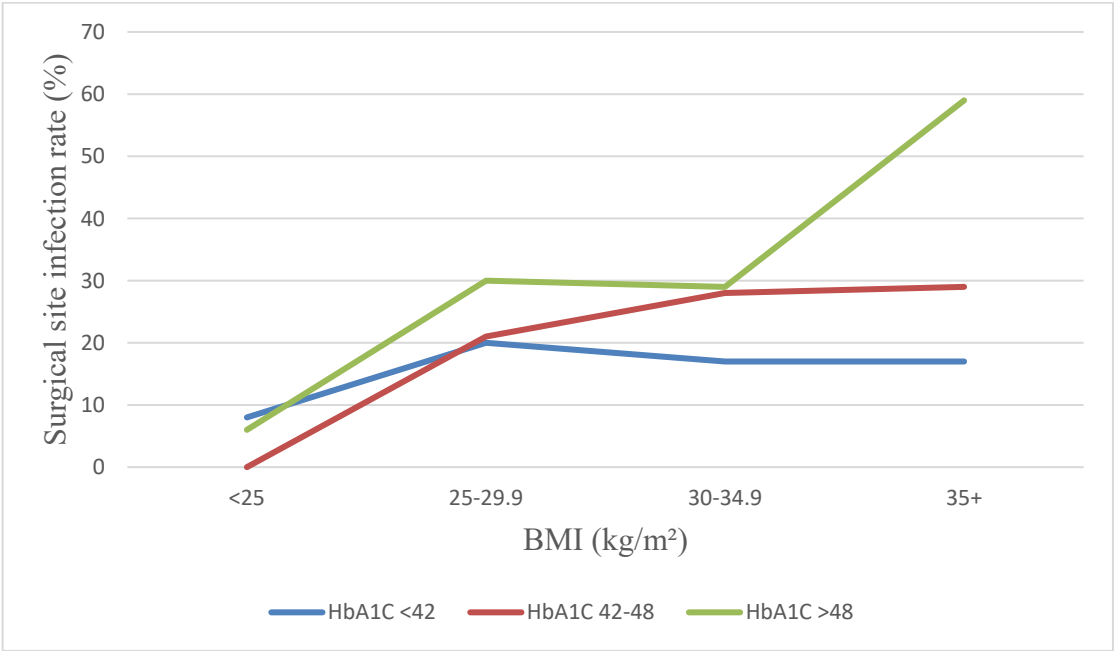


Figure 6-6 Relationship between preoperative HbA1c(mmol/mol), BMI (kg/m²) and surgical site infection

The blue line shows the rate of surgical site infection for patients with preoperative HbA1c <42 with corresponding BMI. The red line shows the rate of surgical site infection for patients with preoperative HbA1c 42-28 with corresponding BMI. The green line shows the rate of surgical site infection for patients with preoperative HbA1c >48 with corresponding BMI. BMI=body mass index; HbA1c=glycated haemoglobin.

6.5 Discussion

The present study shows the relationship between preoperative HbA1c and clinicopathological characteristics in patients who underwent potentially curative colon cancer surgery. As the preoperative level of HbA1c and BMI became greater, a greater proportion of patients developed surgical site infection. Therefore, HbA1c would appear to have clinical utility as an objective preoperative measure to evaluate the risk of a postoperative surgical site infection.

In the present study, it was of interest that there was a discrepancy between BMI, HbA1c and a diagnosis of diabetes. The basis of this discrepancy is not clear; however, currently the diagnosis of diabetes mellitus tends to present after a patient becomes symptomatic, and so it is likely that the onset of diabetes began earlier, in some cases years before. The present study identified that 5% of patients examined had HbA1c levels above the threshold for diabetes diagnosis and were not known to be diabetic prior to surgery. Given that this was in patients who were not screened using HbA1c, this is likely to be an underestimation of the discrepancy. Indeed, in the Diabetes Control and Complication Trial, 25% of patients were reported to have a high abnormal HbA1c level (>6% or >42 mmol/mol) in a screened undiagnosed population undergoing major colorectal surgery (314). Despite this, HbA1c levels are currently rarely used as a preoperative assessment tool due to the lack of evidence on the prognostic effect on postoperative outcomes in undiagnosed diabetics (225). Nevertheless, the results of the present study support the measurement of HbA1c in patients undergoing surgery for colorectal cancer, particularly in those patients defined as obese patients by BMI.

No linear correlation was observed between preoperative HbA1c and BMI, and further exploratory analysis did not demonstrate a linear relationship between HbA1c and either VFA or SFI. Although obesity is associated with insulin resistance and type 2 diabetes, these findings suggest that the linear relationship between adiposity and glycaemic status was not evident in the present cohort. Similarly, a weak negative correlation was observed between HbA1c and SMI, although this did not reach statistically significant in the overall cohort (Pearson's r=-0.109, p=0.088). Sex-stratified analysis demonstrated a negative correlation between HbA1c and SMI in males (r=-0. 168, p=0.045), whereas no significant correlation

was observed in females (r=-0.030, p=0.767). The findings in males may be consistent with the physiological role of skeletal muscle in insulin-mediated glucose uptake; however, the correlation was weak and only marginally statistically significant. Potential explanations for the observed pattern include differences in body composition and metabolic characteristic between sexes, although linear regression analysis incorporating HbA1c x sex interaction demonstrated no statistically significant interaction in this cohort (t=-0.871, p-0.384).

BMI does not distinguish between fat and lean mass, while VFA and SFI provide measures of specific aspects of adiposity and SMI reflects skeletal muscle quantity; none directly measures insulin sensitivity or glucose metabolism. Furthermore, HbA1c reflects glycaemic control over the preceding three months and may be influenced by diabetes duration, pancreatic cell function and glucose-lowering treatment. The high prevalence of diabetes in this cohort, which was restricted to patients with available HbA1c measurements, may have influenced the observed association. These findings should therefore be interpreted in the context of the selected study population.

A diagnosis of diabetes has been long recognised to be associated with poor postoperative outcomes (300). However, the mechanism by which diabetes influences postoperative complications is not particularly evident. One potential mechanism relates to hyperglycaemia, where its effect on the innate immune response leads to impairment of neutrophil and monocyte dysfunction such as adherence, chemotaxis and phagocytosis (221, 315). This in turn leads to increased inflammatory markers and oxidative stress, lowering the host immune defences against infection. Furthermore, there is good evidence that correction of hyperglycaemia reduces postoperative complications in general surgery patients (316). Taken together, there is considerable potential for HbA1c as a predictive factor, particularly in those patients who are undiagnosed diabetics undergoing colon cancer resection.

The incidence of surgical site infections varies depending on speciality. Nevertheless, diabetes has been consistently reported as an independent risk factor with an overall pooled odds ratio of 1.53 (95% CI 1.11-2.12) across multiple specialities in a previous meta-analysis (317). In oncological resections, there are

similar trends towards higher rates of surgical site infection in patients with pre-existing diabetes. In abdominal gynaecological oncology, surgical site infection rates range from 16-35%, but elevated rates of 45% have been reported in patients with a diagnosis of diabetes (318-320). While in breast cancer surgery, the incidence was reported to range from 3-15% to 20% in diabetic patients (321, 322). Whereas the incidence in the diabetic population following elective colorectal cancer resection is less well studied, reported rates of surgical site infection range between 3- 23% in colon cancer and 14-27% in rectal cancer surgery (323, 324). Despite the wide range in reported rates of surgical site infection, the expected rates are usually between 10-13% (191). Of note, in the present study, the reported rate of surgical site infection was slightly higher compared to the average. This could be explained by the patient selection for the study based on patients with available preoperative glycated haemoglobin, which included a relatively higher prevalence of diabetic patients, a majority of open or converted procedures, as well as patients with malignancy that have been shown to increase the incidence of surgical site infection in previous work (172, 253, 325)

The main limitation of the present study was the retrospective nature and relatively small sample size, which raises the risk of selection bias. However, the clinicopathological data for the patient cohort were derived from a prospective MCN dataset, and the complication data collection and analysis were performed retrospectively. Due to the inclusion criterion requiring a preoperative glycated haemoglobin measurement, the present cohort had a high prevalence of diabetes, with 87% of patients having a documented diagnosis of diabetes mellitus, as patients undergoing testing may have been more likely to have known diabetes or other metabolic factors. The Scottish Diabetes Survey reports a diabetes prevalence of 5.7% in the Scottish population, while the prevalence of diabetes in the overall surgical population is approximately 15% (226, 326). Based on NICE guidelines, HbA1c testing is only recommended in patients with known diabetes; however, several patients had HbA1c levels measured preoperatively. Another potential limitation of the present study was the potential confounding effect of immunosuppression agents that have been implicated in impaired wound healing. However, a report by the World Health Organisation suggests that there is low-quality evidence to support discontinuation of immunosuppressant agents in the preoperative period would be of benefit in reducing surgical site infection rate

(149). Nevertheless, the present study yielded new information on the relationship between BMI, body composition, HbA1c (all objective measures) and surgical site infections and future prospective studies examining these relationships are warranted.

The present results are consistent with a previous study that reported that the level of preoperative HbA1c rather than the diagnosis of diabetes was independently associated with clinical outcome following surgery (327). HbA1c has the potential to predict complications with glycaemic control in those with elevated levels preoperatively. However, to date, there are no studies examining the clinical effectiveness of optimising glycated haemoglobin preoperatively in patients undergoing colon cancer surgery. This would be of considerable interest in future studies. In conclusion, objective measurements of BMI and glycated haemoglobin effectively stratified the risk of developing surgical site infection from 8 to 59%. Of interest, approximately 8% of patients not known to have diabetes had HbA1c levels above 42 mmol/mol. Therefore, glycated haemoglobin levels should be determined in all patients regardless of diabetes status to allow for preoperative optimisation.

6.6 Tables

Table 6-1 Clinical characteristics and preoperative HbA1c for patients undergoing elective potentially curative resection for colon cancer

Characteristics	Total (%)	Preoperative HbA1c, mmol/mol			P-value[a]
		<42	42-48	>48	
Age, years	362	69 (19)	86 (24)	207 (57)	0.051
<65	80 (22)	16 (23)	12 (14)	52 (25)	
65-74	154 (43)	22 (32)	40 (47)	92 (45)	
≥75	128 (35)	31 (45)	34 (39)	63 (30)	
Sex	362	69 (19)	86 (24)	207 (57)	0.179
Male	209 (58)	33 (48)	52 (61)	124 (60)	
Female	153 (42)	36 (52)	34 (39)	83 (40)	
ASA	345	66 (19)	85 (25)	194 (56)	0.294[b]
1	2 (3)	2 (2)	2 (2)	12 (6)	
2	32 (49)	32 (38)	32 (38)	95 (49)	
3	29 (44)	48 (57)	48 (57)	79 (41)	
4	3 (4)	3 (3)	3 (3)	8 (4)	
SIMD	362	69 (19)	86 (24)	207 (57)	0.87
Most deprived	113 (31)	22 (32)	28 (32)	63 (30)	
2	82 (23)	18 (27)	16 (19)	48 (23)	
3	63 (17)	8 (11)	18 (21)	37 (18)	
4	47 (13)	8 (11)	12 (14)	27 (13)	
Least deprived	57 (18)	13 (19)	12 (14)	32 (16)	
BMI kg/m^2	255	41 (16)	57 (22)	157 (62)	0.032*
<25	41 (16)	13 (32)	4 (7)	24 (15)	
25-29.9	79 (31)	7 (17)	19 (33)	53 (34)	
30-34.9	78 (31)	14 (34)	20 (35)	44 (28)	
≥35	57 (22)	7 (17)	14 (25)	36 (23)	
Diabetes	362	69 (19)	86 (24)	207 (57)	<0.001*
No	47 (13)	19 (28)	11 (13)	17 (8)	
Yes	315 (87)	50 (72)	75 (87)	190 (92)	
Type of diabetic control	306	47 (15)	72 (24)	187 (61)	<0.001[b*]
Diet	89 (29)	28 (60)	25 (35)	36 (19)	
Oral antihyperglycaemic medication (Metformin/Sulphonylurea)	181 (59)	17 (36)	45 (63)	119 (64)	
Insulin	21 (7)	0 (0)	2 (3)	19 (10)	
Insulin + oral antihyperglycaemic medication	15 (5)	2 (4)	0 (0)	13 (7)	
Metformin	306	47 (15)	72 (24)	187 (61)	0.101
No	139 (45)	28 (60)	32 (44)	79 (42)	

Yes	167 (55)	19 (40)	40 (56)	108 (28)	
Sulphonylurea	306	47 (15)	72 (24)	187 (61)	0.055
No	218 (71)	40 (85)	52 (72)	126 (67)	
Yes	88 (29)	7 (15)	20 (28)	61 (33)	
Smoking status	346	63 (18)	83 (24)	200 (58)	0.001*
Non-smoker	155 (45)	27 (43)	36 (43)	92 (46)	
Ex-smoker	159 (46)	22 (35)	44 (53)	93 (47)	
Smoker	32 (9)	14 (22)	3 (4)	15 (7)	
Tumour location	359	68(19)	86(24)	205(57)	0.173
Right	207 (58)	45 (66)	44 (51)	118 (58)	
Left	152 (42)	23 (34)	42 (49)	87 (42)	
TNM	362	69 (19)	86 (24)	207 (57)	0.06*
I	81 (22)	17 (25)	16 (19)	48 (23)	
II	139 (38)	35 (50)	33 (38)	71 (34)	
III	142 (39)	17 (25)	37 (43)	88 (43)	
Preop SIG	226	46 (20)	62 (27)	118 (52)	0.988[b]
0	89 (39)	17 (37)	26 (42)	46 (39)	
1	59 (26)	12 (26)	16 (26)	31 (26)	
2	44 (20)	8 (17)	13 (21)	23 (20)	
3	21 (9)	6 (13)	4 (7)	11 (9)	
4	13 (6)	3 (7)	3 (5)	7 (6)	
Procedure	360	69 (19)	86 (24)	206 (57)	0.066
Laparoscopic	236 (66)	37 (54)	59 (69)	140 (68)	
Open or converted	124 (34)	32 (46)	26 (31)	66 (32)	
SFI	316	63(20)	76 (24)	177 (56)	0.637
Normal	38 (12)	9 (14)	7 (9)	22 (12)	
High	278 (88)	54 (86)	69 (91)	155 (88)	
VFA	346	68 (20)	82 (24)	196 (56)	0.002*
Normal	30 (9)	13 (19)	3 (4)	14 (7)	
High	316 (91)	55 (81)	79 (96)	182 (93)	
SMI	244	40(16)	56(23)	148(61)	0.044*
Normal	124 (51)	19 (48)	21 (37)	84 (57)	
Low	120 (49)	21 (52)	35 (64)	64 (43)	
SMD	244	40 (16)	56 (23)	148 (61)	0.397
Normal	62 (25)	9 (23)	11 (20)	42 (28)	
Low	182 (75)	31 (78)	45 (80)	106 (72)	
All complications	289	56 (19)	58 (24)	165 (57)	0.14
No	134 (46)	27 (48)	38 (56)	69 (42)	
Yes	155 (54)	29 (52)	30 (44)	96 (58)	
Infective complication	289	56 (19)	68 (24)	165 (57)	0.084
No	174 (60)	40 (71)	43 (63)	91 (55)	

Yes	115 (40)	16 (29)	25 (37)	74 (45)	
Surgical site infections	289	56 (19)	68 (24)	165 (57)	0.049*
No	205 (71)	47 (84)	48 (71)	110 (67)	
Yes	84 (29)	9 (16)	20 (29)	55 (33)	
Wound infection	289	56 (19)	68 (24)	165 (57)	0.041[b]
No	231 (80)	51 (91)	55 (81)	125 (76)	
Yes	58 (20)	5 (9)	13 (19)	40 (24)	
Abdominal collection	289	56(19)	68(24)	165(57)	0.449[b]
No	275 (95)	52 (93)	64 (94)	159 (96)	
Yes	14 (5)	4 (7)	4 (6)	6 (4)	
Anastomotic leak	289	56 (19)	68 (24)	165 (57)	0.103[b]
No	268 (93)	55 (98)	60 (88)	153 (93)	
Yes	21 (7)	1 (2)	8 (12)	12 (7)	
30-day mortality	362	69 (19)	86 (24)	207 (57)	0.447[b]
No	67(97)	81 (94)	201 (97)	349 (96)	
Yes	2 (3)	5 (6)	6 (3)	13 (4)	

ASA= American Society of Anesthesiologists; BMI=body mass index; SIMD=Scottish Index of Multiple Deprivation; TNM= tumour, nodal and metastasis; SIG=systemic inflammatory grade; SFI=subcutaneous fat index; VFA=visceral fat area; SMI =skeletal muscle index; SMD=skeletal muscle density.

[a] P-value calculated using Chi-square analysis except for b.

[b] P-value calculated using Fisher's exact test.

Table 6-2 Factors associated with surgical site infection in patients undergoing elective potentially curative resection for colon cancer

Clinical characteristics	Surgical site infection			
	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
Age, years (<65/65-74/>74)	0.74 (0.53-1.03)	0.072	1.04 (0.67-1.60)	0.848
BMI (kg/m^2) (<25/25-29.9/30-34.9/≥35)	1.80 (1.31-2.49)	<0.001	1.91 (1.36-2.67)	<0.001*
Diabetes (No/Yes)	1.32 (0.57-3.06)	0.518		
Preoperative HbA1c (<42/42-48/>48)	1.51 (1.07-2.15)	0.020	1.69 (1.05-2.70)	0.031*
Type of diabetic control (diet/oral antihyperglycaemic medication /insulin/insulin + oral antihyperglycaemic medication)	1.04 (0.73-1.48)	0.842		
Metformin (No/Yes)	1.23 (0.72-2.11)	0.446		
Sulphonylurea (No/Yes)	1.22 (0.98-2.21)	0.503		
Smoking status (Non-smoker/Ex-smoker/Smoker)	0.76 (0.50-1.15)	0.195		
Tumour location (Right /Left)	1.31 (0.78-2.20)	0.305		
TNM (I/II/III)	0.87 (0.63-1.20)	0.383		
Procedure (Laparoscopic/Open or converted)	0.89 (0.52-1.53)	0.684		
VFA (Normal/High)	1.29 (0.46-3.66)	0.627		
SMI (Normal/High)	0.60 (0.33-1.10)	0.099	0.94 (0.48-1.85)	0.881

BMI= body mass index; CI= confidence interval; HbA1c= glycated haemoglobin; OR= odds ratio; TNM= tumour, nodal and metastasis; VFA=visceral fat area; SMI=skeletal muscle index.

*Statistically significant p-value.

Table 6-3 Association between preoperative HbA1c, BMI and SSI rate

HbA1c (mmol/mol)	BMI (kg/m²)					P-value[a]
	<25	25-29.9	30-34.9	≥35	Total	
	All/SSI (%)	All/SSI (%)	All/SSI (%)	All/SSI (%)	All/SSI (%)	
<42	13/1 (8)	5/1 (20)	12/2 (17)	6/1 (17)	36/5 (14)	0.844
42-48	3/0 (-)	14/3 (21)	18/5 (28)	14/4 (29)	49/12 (25)	0.891
>48	18/1 (6)	46/14 (30)	41/13 (29)	32/19 (59)	137/47 (34)	<0.001
Total	34/2 (6)	65/18 (28)	71/20 (28)	52/24 (46)	222/64 (29)	<0.001[c]
P-value[b]	1	0.898	0.666	0.059	0.042[d]	

BMI=body mass index; HbA1c=glycated haemoglobin; SSI=surgical site infection in category.

[a]Fisher's exact test was used to analyse P-value for SSI in individual HbA1c category against all BMI categories aside from total; [b]Fisher's exact test was used to analyse P-value for SSI in individual BMI category against all HbA1c categories aside from total; [c]Fisher's exact test was used to analyse the P-value between SSI and body mass index for all patients with HbA1c available; [d]Fisher's exact test was used to analyse the P-value between SSI and HbA1c for all patients with BMI measurements available.

Chapter 7 Prospective validation of the relationship between preoperative glycated haemoglobin and surgical site infection in patients undergoing surgery for colon cancer

7.1 Introduction

Surgical site infection remains the most common postoperative complication following surgery. It accounts for up to 14.5% of hospital-associated infections in the United Kingdom (328). Surgical site infections are potentially preventable and contribute to significant postoperative morbidity and mortality. Aside from the direct impact on the patient's treatment, surgical site infections are also associated with increased length of stay, readmission rates and inflated healthcare costs. Each surgical site infection is estimated to cost £10 000 per person, ranging up to £100,000 for deep incisional surgical site infection (328). The rate of surgical site infections varies depending on the procedure. This represents an essential problem in colon cancer surgery, with significantly increased rates as high as 14-30% (329). Surgical site infection is influenced by complex and multifactorial pathology. Therefore, prevention bundles have become a target for quality improvement initiatives in an effort to reduce surgical site in colorectal surgery (330).

Type 2 diabetes is a well-recognised risk factor for surgical site infection across multiple types of surgery (317). Diabetes is a slowly progressing disease characterised by the loss of insulin secretion from pancreatic islet ß cells as a result of insulin resistance over time. The diagnosis of diabetes in accordance with the diagnostic criteria published by the World Health Organisation includes testing of symptomatic individuals either with fasting glucose testing, 2-hour oral glucose tolerance testing, random glucose testing or glycated haemoglobin (HbA1c) levels. Nevertheless, there are no dedicated screening programmes for asymptomatic individuals.

Glycated haemoglobin is often used as a measure of diabetic control, as it reflects glucose concentration over preceding months. However, HbA1c measurements are not currently part of the standard workup for non-diabetic elective surgical patients under the United Kingdom National Institute for Clinical Excellence (NICE)

preoperative care guideline (225). Nevertheless, the study from Chapter 6 has demonstrated that preoperative HbA1c levels are independently associated with increased risk of surgical site infection in colon cancer surgery and can effectively stratify the risk of developing surgical site infection along with objective body mass index measurements (331). Indeed, there has been an increasing number of studies investigating the use of HbA1c in predicting surgical outcomes (320). Kopp Lugli et al. similarly reported that most surgical site infections were found in patients undergoing visceral, vascular or trauma surgery, with HbA1c levels indicating pre/diabetic state, with the highest percentage of infection in patients with undiagnosed diabetes undergoing major surgery (332). While Kukeev et al. reported a statistically significant relationship between elevated HbA1c levels (≥8%) and an increased risk of postoperative complications, including surgical site infections, venous thromboembolism, and urinary tract infections, in patients undergoing both elective and urgent abdominal surgeries (333). A more recent systematic review across multiple surgical specialties reported that higher preoperative HbA1c levels were associated with increased odds of overall postoperative complications with each 1% increase correlating with increased odds of complications (334).

As most studies focused on retrospective capture of available HbA1c levels, the aim of our current study is to prospectively validate the relationship between preoperative glycated haemoglobin levels and postoperative complications in patients undergoing surgery for colon cancer.

7.2 Patient and Methods

Consecutive patients undergoing potentially curative colon cancer resection for the diagnosis of TNM Stage I-III at the Glasgow Royal Infirmary between May 2022 and January 2024 were included. Patients with Stage IV disease, rectal cancer, emergency admission, those who did not have surgical resection, or those who underwent palliative procedures were excluded. Patients who had an unplanned admission and underwent surgery within 48 hours of admission were classified as having an emergency admission.

All elective patients were routinely enrolled in the Enhanced Recovery After Surgery (ERAS) programme during the study period. Preoperative carbohydrate loading was offered using Nutricia preOp drinks, each containing 12.6 g carbohydrate per 100 mL. Patients received four 200 mL bottles during the evening before surgery and two 200 mL bottles on the day of surgery, up to 2 hours before anaesthesia, unless they had a pre-existing diagnosis of diabetes mellitus. Patients with diabetes were managed in accordance with the NHS Greater Glasgow and Clyde (NHSGGC) perioperative diabetes management guideline (335). Their medication regimens were reviewed during preoperative assessment, with written instructions provided regarding medications to omit or adjustments to insulin doses where appropriate. Capillary blood glucose was checked on the day of surgery.

Mechanical bowel preparation (MBP) and oral antibiotic prophylaxis were determined by the site of colonic resection. Patients undergoing left colonic resection routinely received MBP on the day before surgery, together with oral antibiotics comprising neomycin 1 g on three occasions and metronidazole 400 mg on three occasions. MBP was not routinely prescribed for patients undergoing right colonic resection.

All patients undergoing colon cancer resection received triple intravenous antibiotic prophylaxis at induction of anaesthesia, comprising gentamicin, metronidazole 500 mg and amoxicillin 1 g, in accordance with to NHSGGC guideline (336). In patients with a documented true penicillin allergy, amoxicillin was replaced with teicoplanin 400 mg. These perioperative measures formed part of the routine clinical practice during the study period.

All elective patients underwent preoperative assessment with preoperative glycated haemoglobin (HbA1c) levels measured in mmol/mol, unless results within 3 months of the planned date of surgery were available. The preoperative diabetes status and methods of glycaemia control were collected for all patients. Comorbidities were classified using the American Society of Anesthesiologists (ASA) Physical Status Classification System (250). Socioeconomic deprivation was stratified using the Scottish Index of Multiple Deprivation (SIMD). Body mass index (BMI) was calculated from height and weight measured prior to surgery, and the BMI was categorised according to thresholds as follows: normal range <25 kg/m^2, overweight 25-29.9 kg/m^2, obese 30-34.9 kg/m^{2}and morbidly obese ≥ 35 kg/m^2. Tumours were staged using the TNM classification system (8th edition) (114). The systemic inflammatory response was calculated using the modified Glasgow Prognostic Score (mGPS) as follows: preoperative CRP concentration <10mg/L, regardless of albumin concentration, scored 0; CRP concentration ≥10mg/L and albumin >35g/L, scored 1; and CRP concentration ≥10mg/L and albumin <35g/L, scored 2 (141).

Patients were prospectively followed up to assess for any postoperative complication, infective complication and surgical site infection. Infective complications included respiratory tract infection, urinary tract infection or any surgical site infection. Patients were assessed for surgical site infections for up to 30 days. Surgical site infections were defined as the presence of superficial skin infection, deep organ or space infections including anastomotic leaks and abdominal collections. Superficial surgical site infection was defined by the presence of pus drained either from the wound or discharging spontaneously. Deep surgical site infection was diagnosed either on imaging, radiological drainage, or surgical drainage of intra-abdominal pus, while anastomotic leak was diagnosed at laparotomy or on cross-sectional imaging. Complications were further categorised based on severity using the Clavien-Dindo classification of surgical complications (150). The data were collected using all available electronic patient medical records, including inpatient medical notes, discharge letters, clinic letters, radiology reports, blood test results and microbiology test results.

Body composition analysis was performed using automated segmentation of preoperative computed tomography (CT) image slices by a deep learning neural network (Mosamatic^{TM}) that has been validated on a large dataset of cancer

patients (337). A single slice from the preoperative CT at the level of the third lumbar vertebra (L3) on which both transverse processes are visible was retrieved for analysis. Body composition parameters of skeletal muscle tissue (SM), visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were measured, and cross-sectional surface areas were calculated (cm^2). The Hounsfield units (HU) threshold for adipose tissue was defined between −190 and −30 HU and for skeletal muscle between −29 and 150 HU. All body composition areas (SM, VF and SAT) were corrected for patient height and are presented as indices (cm^2/m^2). SAT and SM measurements were then normalised by division by the patient's height in metres squared to generate a subcutaneous fat index (SFI: centimetres squared/meters squared) and skeletal muscle index (SMI: centimetres squared/meters squared). These indices were then compared with established thresholds for body composition status (Table 7-1).

7.3 Statistical analysis

The relationship between the clinicopathological characteristics and preoperative HbA1c levels was compared using the Chi-square test and Fisher's exact test for significance where appropriate. $P<0.05$ was considered statistically significant. Surgical site complications were analysed using a univariate binary logistic regression model. Those variables associated with $P<0.10$ on univariate analysis were entered into a backward conditional multivariate model, where variables with $P<0.05$ were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows version 29 (IBM Corporation, Armonk, New York, USA).

7.4 Results

A total of 135 patients underwent elective curative resection for TNM Stage I-III colon cancer in Glasgow Royal Infirmary from May 2022 to January 2024, with HbA1c results available for 118 patients (Figure 7-1). Patients with a pre-existing diagnosis of diabetes made up 26% of the eligible study population.

The relationship between the clinicopathological characteristics and preoperative HbA1c is shown in Table 7-1. Approximately 20% of patients had HbA1c > 48mmol/mol. Preoperative HbA1c was significantly associated with age ($p<0.001$), body mass index ($p<0.001$), diagnosis of diabetes ($p<0.001$), type of diabetic control ($p<0.001$), surgical site infection ($p<0.05$), subcutaneous fat index ($p<0.05$) and visceral fat index ($p<0.005$).

Binary logistic regression of factors associated with surgical site infection is shown in Table 7-2. The analysis included only age, BMI and preoperative HbA1C given the limited sample size, the number of SSI and the potential for multicollinearity among the variables. BMI was selected as the principal measure in preference to SFI and VFA based on findings in Chapter 5. Preoperative HbA1c was selected as a measure of glycaemic status in preference to diabetes status and the type of diabetes treatment as it provides a continuous measure of longer-term glycaemic control. On univariate analysis, surgical site infection was only associated with preoperative HbA1c (OR 2.39, 95% CI 1.19-4.83, $p=0.014$).

The relationship between preoperative HbA1c, BMI and surgical site infection is shown in Table 7-3 and is represented in Figure 7-2. High preoperative HbA1c appears to be more strongly associated with an increase in the rate of surgical site infection compared to BMI ($P=0.024$).

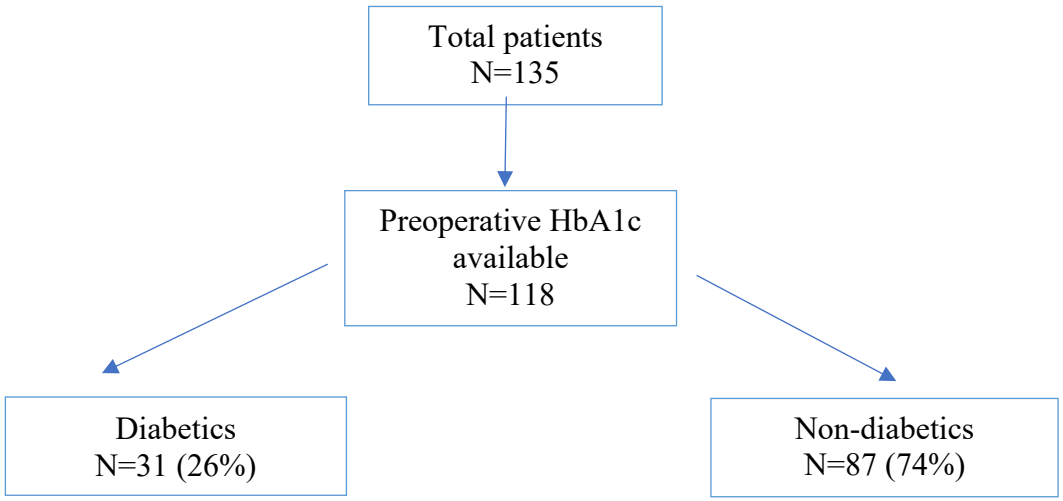


Figure 7-1 Flow chart showing preoperative HbA1c collection and the proportion of diabetic and non-diabetic patients.

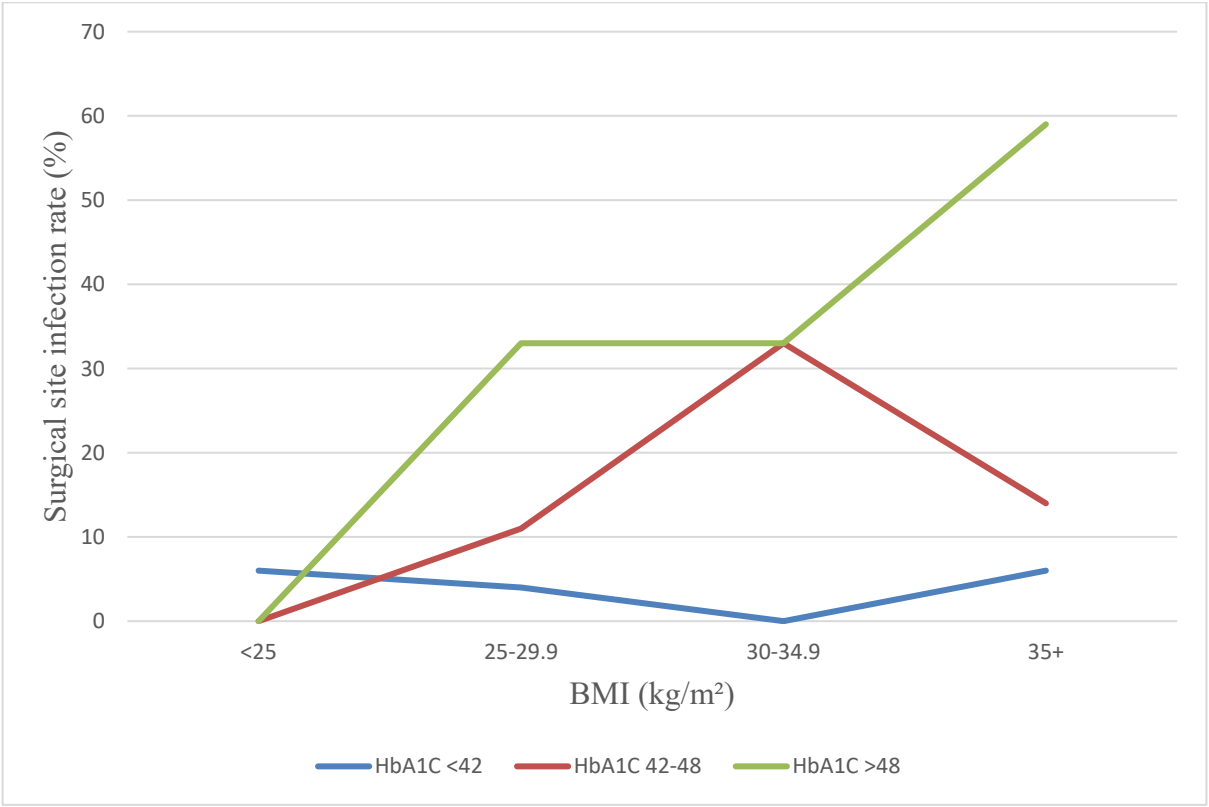


Figure 7-2 Relationship between preoperative HbA1c(mmol/mol), BMI (kg/m²) and SSI

The blue line shows the rate of surgical site infection for patients with preoperative HbA1c <42 with corresponding BMI. The red line shows the rate of surgical site infection for patients with preoperative HbA1c 42-28 with corresponding BMI. The green line shows the rate of surgical site infection for patients with preoperative HbA1c >48 with corresponding BMI. BMI, body mass index; HbA1c, glycated haemoglobin.

7.5 Discussion

The results of the present study suggest that the presence of surgical site infection was associated with preoperative glycated haemoglobin levels in patients undergoing potentially curative colon cancer surgery. This is the first prospective study utilising HbA1c in consecutive patients, regardless of the diagnosis of diabetes, undergoing curative colon cancer surgery as an objective measure to evaluate the postoperative complications.

The present study demonstrated that HbA1c levels were associated with surgical site infection independent of body mass index and diagnosis of diabetes. Interestingly, the incidence of detection of previously unknown impaired glucose tolerance or undiagnosed diabetes was 16.1% in the current study. Within colorectal oncology, the proportion of undiagnosed diabetics is unknown. In prospective studies, Iavazzo et al. reported 17.3% of patients with previously unknown impaired glucose tolerance or undiagnosed diabetes in a cohort undergoing gynaecological oncology surgery, while Gustafsson et al. reported 25% of previously unknown impaired glucose tolerance or undiagnosed diabetes in a cohort undergoing major colorectal surgery (314, 338).

Plasma glycated haemoglobin is a non-enzymatic glycation of the valine and lysine residues in the Hb molecule and reflects time-averaged blood glucose in the preceding 2-3 months (339). HbA1c is therefore an indicator of long-term glycaemic control and is considered the gold-standard outcome predictor for diabetic patients. Nevertheless, with the prevalence of patients with unknown impaired glucose tolerance/undiagnosed diabetes, HbA1c levels could potentially act as a surrogate for stratifying preoperative risk. Poor glucose control as a result of insulin resistance is the main factor in the development of postoperative complications. Hudson et al. demonstrated that in non-diabetics, an elevated preoperative HbA1c level was independently associated with early mortality risk after elective cardiac surgery (340). Okamura et al showed that higher HbA1c levels were associated with increased risk of anastomotic leak, surgical site infection and pneumonia in patients undergoing transthoracic esophagectomy (341).

Although other studies have also identified a similar association between elevated HbA1c and postoperative complications, at present there are no established national guidelines on the optimal preoperative HbA1C level. However, there are general recommendations for consideration of optimising or postponing surgery if HbA1c levels are above 69 mmol/mol, if it is felt safe to do so by individual clinicians (222). Currently, there are no randomised controlled trials to determine whether preoperative management of HbA1C level improves clinical outcomes and may be an area of further interest.

The main strength of our study is the prospective design with the implementation of a change in practice in the preoperative assessment setting prior to the start of the study. This ensured all patients undergoing potentially curative colon cancer surgery had their HbA1c levels measured preoperatively, although a small number of patients were excluded at the start of the implementation. Previous studies on preoperative glycated haemoglobin in abdominal surgery had utilised the readily available records for HbA1c, which inadvertently raises the risk of selection bias (342) . This is indeed evident from the difference in the characteristics of the cohorts with and without HbA1c measurements as reported by Goodenough et al (342). They noted that patients who had measured HbA1c levels tend to be older, obese, non-white, diagnosed with COPD, coronary artery disease and elevated ASA. These factors correlated with factors found in this study, particularly age and obesity, which influence HbA1c levels.

The present study also has several limitations. The relatively small sample size from a single centre may limit the generalisability of the findings. In particular, only 12 surgical site infections occurred among the 118 patients included in the study, representing an overall surgical site infection rate of 10.2%. The low number of outcome events limits the statistical power to detect associations and increases the risk of imprecise effect estimates. Furthermore, the small number of events restricts the number of variables that can be reliably included in multivariable regression models, raising the potential for model overfitting. Consequently, the observed association between preoperative glycated haemoglobin and surgical site infection should be interpreted cautiously and considered an exploratory study rather than definitive evidence of an independent association. In addition, the status and intensity of hyperglycaemic control of the

individual patients perioperatively and postoperatively were not examined and could potentially have had a bearing on the postoperative complication outcomes. The observational nature of the study also lends itself to performance bias. Nevertheless, none of the patients with elevated levels of glycated haemoglobin had a change in their preoperative journey as a result of their HbA1c results, either in terms of preoperative medication or postponement of surgery.

In conclusion, this prospective study identified an association between preoperative glycated haemoglobin levels and risk of surgical site infection following potentially curative colon cancer surgery. The study also identified a proportion of patients with HbA1c levels within the diagnostic range for diabetes that were undiagnosed at the time of surgery in this study, supporting the potential value of routine preoperative glycated haemoglobin assessment. However, the small numbers of surgical site infection events limit the precision of the observed association. These findings warrant validation in a larger prospective multicentre study before definitive conclusions can be drawn regarding the prognostic value of glycated haemoglobin and the potential benefits of preoperative glycaemic optimisation.

7.6 Tables

Table 7-1 Clinicopathological characteristics and preoperative HbA1c for patients undergoing elective potentially curative resection for colon cancer

Characteristics	Total	Preoperative HbA1c (mmol/mol)			P-value
		<42	42-48	>48	
Age	118	72	22	24	**0.006***
<65	37	27	4	6	
65-74	40	15	12	13	
≥75	41	30	6	5	
Sex	118	72	22	24	0.298
Male	62	35	11	16	
Female	56	37	11	8	
ASA	118	72	22	24	0.245
1	3	2	1	0	
2	55	34	12	9	
3	57	36	8	13	
4	3	0	1	1	
SIMD	118	72	22	24	0.506
Most deprived	43	27	7	9	
2	21	13	4	4	
3	19	11	3	5	
4	18	9	3	6	
Least deprived	17	12	5	0	
BMI (kg/m^2)	118	72	22	24	**0.001***
<25	35	32	1	2	
25-30	44	23	9	12	
30-34.9	26	11	9	6	
≥ 35	13	6	3	4	
Diabetes	118	72	22	24	**<0.001***
No	87	68	15	4	
Yes	31	4	7	20	
Type of diabetic control	118	72	22	24	**<0.001***
Diet	19	9	4	2	
Oral antihyperglycemic	4	1	4	14	
Insulin	1	0	0	4	
Insulin +Oral antihyperglycemic	1	0	0	1	
Non-diabetic	79	62	14	3	
Metformin	31	4	7	20	0.086
No	15	4	3	8	
Yes	16	0	4	12	

Sulphonylurea	31	4	7	20	1.000
No	28	4	6	18	
Yes	3	0	1	2	
SGLT2	31	4	7	20	1.000
No	22	3	6	13	
Yes	9	1	1	7	
Insulin	31	4	7	20	0.643
No	27	4	7	16	
Yes	4	0	0	4	
Smoking status	118	72	22	24	0.566
Non-smoker	71	44	14	13	
Ex-smoker	33	20	7	6	
Smoker	14	8	1	5	
Tumour location	118	72	22	24	0.993
Right	70	43	13	14	
Left	48	29	9	10	
TNM	118	72	22	24	0.14
I	37	17	11	9	
II	47	32	5	10	
III	34	23	6	5	
mGPS	118	72	12	24	0.704
0	93	57	19	17	
1	13	8	2	3	
2	12	7	1	4	
Procedure	118	72	22	24	0.214
Open	34	16	9	9	
Laparoscopic	35	26	5	4	
Robotic	49	30	8	11	
Approach	118	72	22	24	0.137
Open	34	16	9	9	
Minimally Invasive	84	56	13	15	
All Complications	118	72	22	24	0.36
No	70	39	15	16	
Yes	48	33	7	8	
Clavien Dindo	118	72	22	24	0.335
0	70	39	15	16	
1	14	11	2	1	
2	31	21	4	6	
3	2	1	1	0	
4	1	0	0	1	
Infective complication	118	72	22	24	0.682
No	89	54	18	17	

Yes	29	18	4	7	
Surgical site infections	118	72	22	24	**0.024***
No	106	68	20	18	
Yes	12	4	2	6	
Wound infection	118	72	22	24	0.170
No	112	70	21	21	
Yes	6	2	1	3	
Abdominal collection	118	72	22	24	0.655
No	115	70	22	23	
Yes	3	2	0	1	
Anastomotic Leak	118	72	22	24	0.202
No	116	72	21	23	
Yes	2	0	1	1	
30-Day mortality	118	72	22	24	-
No	118	72	22	24	
Yes	0	0	0	0	
SFI	118	72	22	24	**0.021***
Normal	30	24	1	5	
High	88	48	21	19	
VFA	118	72	22	24	**0.002***
Normal	34	29	1	4	
High	84	43	21	20	
SMI	118	72	22	24	0.068
Normal	54	27	12	15	
Low	64	45	10	9	
SMD	118	72	22	24	0.457
Normal	49	30	7	12	
Low	69	42	15	12	

ASA=American Society of Anesthesiologists; BMI=body mass index; HbA1c=glycated haemoglobin; SIMD=Scottish Index of Multiple Deprivation; TNM=tumour, nodal and metastasis; mGPS=modified Glasgow prognostic score; SFI=subcutaneous fat index; VFA=visceral fat area; SMI=skeletal muscle index; SMD=skeletal muscle density.

P-value calculated using Fisher's exact test. * Statistically significant P-value

Table 7-2 Factors associated with surgical site infections in patients undergoing elective potentially curative resection for colon cancer

Clinical characteristics	Surgical site infection	
	Univariate OR (95%CI)	P -Value
Age, years (<65/65-74/>74)	0.82(0.36-1.86)	0.635
BMI kg/m²(<25/25-<30/30-35/>35)	0.857(0.42-)	0.669
Preoperative HbA1c mmol/mol (<42/42-48/>48)	2.39(1.19-4.83)	0.014*

BMI=body mass index; CI=confidence interval; HbA1c= glycated haemoglobin; OR=odds ratio.
* Statistically significant P-value

Table 7-3 Association between preoperative HbA1c, BMI and SSI rate

HbA1c (mmol/mol)	BMI (kg/m²)					
	<25	25-29.9	30-34.9	≥35	Total	P-value[a]
	All/SSI (%)	All/SSI (%)	All/SSI (%)	All/SSI (%)	All/SSI (%)	
<42	32/2 (6)	23/1(4)	11/1(9)	6/0(-)	72/4(6)	0.871
42-48	1/0 (-)	9/1(11)	9/0(-)	3/1(33)	22/2(10)	0.347
>48	2/0 (-)	12/4(33)	6/2(33)	4/1(25)	24/6 (25)	0.446
Total	35/2 (6)	44/6(14)	26/3 (11)	13/1 (8)	118/12(10)	0.687[c]
P-value[b]	0.905	0.058	0.133	0.164	0.024[d]	

BMI = body mass index; HbA1c = glycated haemoglobin; SSI = surgical site infection category. [a]Fisher's exact test was used to analyse P-value for SSI in individual HbA1c category against all BMI categories aside from total; [b]Fisher's exact test was used to analyse P-value for SSI in individual BMI category against all HbA1c categories aside from total; [c]Fisher's exact test was used to analyse the P-value between SSI and body mass index for all patients with HbA1c available; [d]Fisher's exact test was used to analyse the P-value between SSI and HbA1c for all patients with BMI measurements available.

Chapter 8 Conclusion

8.1 Overview of work

During the start of the research, it was clear that there was an abundance of literature reporting that the presence of postoperative complications was associated with worse long-term outcomes in patients undergoing colorectal cancer surgery. Specific prognostic factors such as systemic inflammatory response and tumour stage were known to be related to long-term outcomes as well, but there was little literature describing the relationship between clinical prognostic factors and short-term outcomes. One of the main limitations in this area of research relates to the variety of classifications used to describe short-term outcomes and the variability of factors included.

Therefore, Chapter 2 examined systematic reviews that reported on short-term outcomes in colorectal cancer regardless of the classification system used, the number of host- or tumour- factors included. During the initial search, it became evident that several validated variables had been examined on multiple occasions and included in systematic reviews. The systematic reviews revealed that age, sex, diabetes status, body mass index, body composition and functional status were consistently associated with short-term outcomes after colorectal surgery. While antibiotic use, iron therapy, blood transfusion, erythropoietin, steroid use and ERAS programmes were inconsistently associated with short-term outcomes. This thesis presents the first umbrella review of systematic reviews to comprehensively summarise clinical predictive factors affecting short-term outcomes in colorectal surgery. Due to the heterogeneity of the data, a minimum, recommended and potential dataset of preoperative baseline variables for collection in patients undergoing colorectal resection was determined.

In Chapter 3, the effect of preoperative carbohydrate loading on surgical site infection following curative colon cancer surgery in a single tertiary unit was examined, reflecting the current practice. In this chapter, the aim was to determine the effect of carbohydrate loading within an Enhanced Recovery Pathway (ERAS) in reducing the systemic inflammatory response and ultimately postoperative complications. The results from this chapter showed that there was no objective evidence that preoperative carbohydrate loading was associated with

a reduction in surgical site infections. The theoretical benefit of preoperative carbohydrate loading is based on attenuating the magnitude of postoperative systemic inflammatory response and subsequent hyperglycaemia. In this cohort of patients, diabetic patients were removed as a confounder, as they do not routinely receive preoperative carbohydrate drinks, and the open surgical approach was the only factor associated with surgical site infection.

In Chapter 4, the dataset of preoperative baseline variables (reported in Chapter 2) was used to determine the relationship with postoperative infective complications in patients undergoing potentially curative colon cancer resection in a regional cohort. There is strong evidence to suggest the differences in the management of rectal cancer as discussed in Chapter 1. Therefore, for this thesis, the more in-depth investigation has only been carried out in patients undergoing potentially curative surgery for TNM I-III colon cancer. This chapter showed that although preoperative variables differ depending on the type of complication reported, body mass index and diabetes were consistently associated with infective complications and surgical site infections. On further analysis, the body mass index increase appears to be associated with a greater proportion of known diabetics, with almost 30% in those with BMI ≥35.

Chapter 5 aimed to examine the relationship between computed tomography-derived body composition, body mass index and surgical site infection in patients undergoing resection surgery for curative colon cancer. The study demonstrated that elevated body mass index was significantly associated with a higher subcutaneous fat index, greater visceral fat area, lower skeletal muscle density and a normal skeletal muscle index. On the other hand, diabetes was associated with a higher subcutaneous fat index, greater visceral fat area and lower skeletal muscle density only, without influencing skeletal muscle index.

Body mass index, subcutaneous fat index and visceral fat index were each associated with the risk of surgical site infection in separate multivariable models adjusted for diabetes and surgical approach. However, body mass index demonstrated the highest observed discriminatory performance, although discrimination was limited across all three models. These findings suggest that CT-derived measures of body composition did not demonstrate an apparent advantage over BMI.

In Chapter 6, the relationship between preoperative glycated haemoglobin and surgical site infection in patients undergoing elective colon cancer surgery was examined. As previously described in Chapters 2 and 4, diabetes is an independent predictive factor for surgical site infection. Nevertheless, diabetes is not readily tested for patients undergoing elective colon cancer surgery in the United Kingdom. Therefore, this chapter utilised the available preoperative glycated haemoglobin levels from a regional cohort of patients undergoing colon cancer surgery.

The study showed that 57% of the patients had preoperative glycated haemoglobin levels of >48 mmol/mol, including 5% of patients who were not known to have diabetes. The preoperative glycated haemoglobin levels were independently associated with the risk of surgical site infection. This risk could be stratified further in combination with increasing body mass index. The study demonstrated the increased risk of surgical site infection from 8% in those in the lowest category to 59% in those in the highest category for both glycated haemoglobin and body mass index.

A scatter plot of body mass index and preoperative glycated haemoglobin showed that the relationship was non-linear in both sexes. This further strengthens the findings in Chapter 4. Although both obesity and diabetes are thought to exert a chronic inflammatory response and influence the glucose utilisation pathway, there remains an unknown factor that differentiates their effect leading to surgical site infection. This would be an area for future research, particularly as the use of antidiabetics has also demonstrated an association with the preoperative glycated haemoglobin levels. The findings of this chapter support the routine measurement of glycated haemoglobin levels regardless of the diagnosis of diabetes and should represent a change in wider practice. Although this study is limited to colon cancer patients, studies including other major abdominal surgeries such as oesophageal cancer may be of interest.

In Chapter 7, the relationship between preoperative glycated haemoglobin and postoperative complications was examined prospectively. The findings from Chapter 6, although significant, arise from a selected group of patients with available preoperative glycated haemoglobin. Due to the retrospective nature of the study, it was impossible to determine the rationale for testing. In this chapter,

a group of unselected patients undergoing colon cancer surgery in a single tertiary unit was examined. Preoperative glycated haemoglobin levels were collected for all patients undergoing elective colon cancer surgery. The results validate the findings from Chapter 6, showing that preoperative glycated haemoglobin levels are associated with surgical site infection. The study has again identified the presence of impaired glucose tolerance or previously undiagnosed diabetes in up to 16% of patients. Interestingly, in this cohort, body mass index and the diagnosis of diabetes were not associated with surgical site infection. Although the small sample size may attenuate the results, this may also indicate that the presence of an elevated glycated haemoglobin level was a predictor compared to body mass index.

In summary, the clinical predictive factors affecting the short-term outcome are dependent on the type of complication of interest. Nevertheless, obesity and diabetes have consistently demonstrated a significant association with surgical site infection during this study. Therefore, diabetes should be routinely screened for in populations undergoing colon cancer surgery.

8.2 Implications and Future work

Colon cancer resection evokes a cascade of hormonal, metabolic and immune changes that result in the systemic inflammatory response. There is no doubt that the degree of stress response is proportionate to the magnitude, invasiveness and duration of surgery. Previous studies have examined surgeon factors influencing short-term postoperative outcomes, with a large paradigm shift in surgical specialisation for elective colon cancer surgery (343, 344).

Similarly, efforts have been made to standardise care via enhanced recovery after surgery (ERAS) programmes with the aim of reducing the systemic inflammatory response. Although studies have shown reduced length of stay and postoperative complications with ERAS, there is little evidence that individual components of the ERAS programme affect the systemic inflammatory response after surgery aside from minimally invasive surgery (249). Nevertheless, despite increased adoption of minimally invasive techniques in colorectal cancer resection, postoperative complications remain.

The work in this thesis has demonstrated the importance of a metabolic defect in the form of diabetes in affecting short-term postoperative outcomes after colon cancer surgery, particularly with regard to surgical site infections. Stress hormones, mainly cortisol, catecholamines, glucagon and growth hormones, promote increases in blood glucose via the breakdown of glycogen, fat and protein, which ensures energy for healing and repair. In the presence of diabetes, reduced insulin sensitivity results in increased hepatic gluconeogenesis and reduced glucose uptake by muscle and fat, causing elevated circulating glucose and free fatty acid levels and therefore inducing an exaggerated hyperglycaemia state (345). Similarly, the effects of cortisol and catecholamines are amplified, causing lipolysis and proteolysis. Therefore, diabetes chemically amplifies the surgical stress response by weakening insulin counter-regulation of stress hormones, leading to excessive glucose production, heightened inflammation, and impaired cellular recovery.

Worldwide, there are no national guidelines on routine preoperative glycated haemoglobin testing to determine the presence of diabetes in those who are not already known to be diabetic prior to elective colorectal surgery. There is variation in clinical practice, with the Australian and New Zealand guidelines recommending preoperative haemoglobin testing for those undergoing major surgery in high-risk patients (increasing age, high BMI and high AUSDRISK score) while guidelines from the United States, United Kingdom, Canada and Europe do not recommend routine testing (225, 346-349).

Nevertheless, the implication of this thesis is clear: diabetes is a much stronger predictor of postoperative complications, even in the presence of overweight/obese individuals. The present work has implications for future care, particularly in minimising postoperative complications after colon cancer surgery, as practices remain varied. Preoperative assessment is important in identifying these patients who have undiagnosed diabetes and appropriately optimised via prehabilitation. It is hypothesised that most of these patients are likely to be Type 2 Diabetics; therefore, the preoperative optimisation would be straightforward provided the diagnosis of diabetes is known. There is an already established route for the management of diabetics prior to surgery, and this would not significantly delay the usual course to surgery provided early preoperative assessment is in place (350).

Notably, there has been a rise in the use of glucagon-like peptide (GLP-1) receptor antagonists, e.g., semaglutide, for both diabetes control and weight loss. GLP-1 agonists function by mimicking the incretin hormone GLP-1, which plays a crucial role in glucose homeostasis by stimulating insulin secretion, inhibiting glucagon release, promoting weight loss and exerting anti-inflammatory effects (351). A recent large observational study has reported a significant reduction in postoperative complications in diabetic patients with active GLP-1 prescription, although the effect of GLP-1 agonists in diabetics specifically after colorectal cancer surgery has yet to be studied (352).

The findings of the current thesis would provide the basis for future work to focus on the biochemical pathways linking hyperglycaemia and surgical stress in the form of inflammation and the effect on the immune system in undiagnosed diabetics. The current work would also provide the platform to examine the long-term outcomes (recurrence and survival) in patients who had undiagnosed diabetes at the time of surgical intervention. Furthermore, to examine the relationship between preoperative optimisation of diagnosed and undiagnosed diabetes and postoperative complications.

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