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An investigation of the relationship between perioperative characteristics and perioperative anaesthesia on the postoperative systemic inflammatory response and clinical outcome in patients undergoing surgery for colorectal cancer.

By

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PH D) to the University of Glasgow

From research conducted in the Academic Unit of Surgery, School of Medicine, University of Glasgow

Abstract

In UK, colorectal cancer (CRC) is the fourth most common cancer and the second most common cause of cancer death. Until now, surgical resection remains the cornerstone for the management of CRC in all stages, however, stress response elicit from surgery may cause different changes through multiple systems in human body including neural, endocrine, metabolic, inflammatory, and immunological changes. In addition, other perioperative factors such as volatile anaesthetic and opioids may induce the immuno-suppression. There is a proportional correlation between the stress response and the magnitude of the inflammatory immune response, invasiveness, and duration of surgery.

The pre-operative and post-operative status of patients are important when considering the prognosis. The systemic inflammatory response (SIR) has been recognised to correlate with tumour progression and the prognosis of CRC. An exaggerated postoperative SIR is associated with postoperative infective complications and poor survival. Several predictive markers of the SIR have been used, such as the neutrophil to lymphocyte ratio (NLR), serum C-reactive protein (CRP) level, and Glasgow prognostic score (GPS).

Some evidence reported that general anaesthesia (GA) combined with regional anaesthesia (RA) are better than the single use of general anaesthesia in reducing the post-operative immuno-suppression in some degrees. Furthermore, the peri-operative inflammatory process may be affected by the choice of anaesthetic technique, with propofol reported to have anti-inflammatory effect by targeting neutrophil activity. Up to now, there is insufficient evidence to recommend any specific anaesthetic or analgesic technique for patients undergoing surgery for tumour resection based on inflammatory response, recurrence, and metastasis.

The work presented in this thesis further examines the relationship between the perioperative characteristics, perioperative anaesthesia, and the postoperative systemic inflammatory response following surgery for colorectal cancer. Several preoperative medications along with anaesthesia might influence the postoperative systemic inflammatory response but the question is whether the post-operative systemic inflammatory response affected by the administration of different types of anaesthesia or not following surgery for colorectal cancer.

Chapter 1 discusses the epidemiology, aetiology, carcinogenesis, risk factors of colorectal cancer, pro-carcinogenic factors, anti-carcinogenic agents, inflammation and cancer, the post-operative systemic inflammatory response, tumour staging, screening, and diagnosis of colorectal cancer.

Chapter 2 discusses the treatment of colorectal cancer.

Chapter 3 discusses different anaesthetic techniques and agents.

Chapter 4 provides summary and aims of the thesis.

Chapter 5 represents findings from a systematic review and meta-analysis about the effect of anaesthesia on the postoperative systemic inflammatory response in patients undergoing surgery. The results conclude that there was some evidence that anaesthetic regimens may reduce the magnitude of the post-operative SIR. However, the studies identified in this systematic review were heterogeneous and generally of low quality.

Chapter 6 represents a retrospective cohort study about the relationship between anaesthetic technique, clinicopathological characteristics and the magnitude of the postoperative systemic inflammatory response in patients undergoing elective surgery for colon cancer. The results show that the type of anaesthesia varied over time and appears to

influence the magnitude of the postoperative SIR on post-operative day 2 for those patients who underwent for open surgery but not laparoscopic surgery.

Chapter 7 represents a prospective cohort study about the effect of anaesthesia on the magnitude of the postoperative systemic inflammatory response in patients undergoing elective surgery for colorectal cancer in the context of an enhanced recovery pathway. The results show that there was a modest but an independent association between regional anaesthesia (RA) and a lower magnitude of the postoperative SIR.

Chapter 8 represents the relationship between pre-operative medications, the type of anaesthesia and post-operative sequelae in patients undergoing surgery for colorectal cancer. The results show that there was no association between the preoperative administration of aspirin, statins and ACE inhibitors and anaesthesia.

Chapter 9 represents the relationship between nutritional status, anaesthetic approach, and peri-operative characteristics of patients undergoing surgery for colorectal cancer. The results show that there was no significant association between measures of nutritional status and anaesthetic approach.

Chapter 10 represents the relationship between opioid administration, type of anaesthesia and clinicopathological characteristics in patients undergoing surgery for colorectal cancer. The results show that opioid administration was independently associated with both anaesthetic and operative factors.

Chapter 11 represents the main findings of the thesis and some recommendation for a future work.

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Author's Declaration

- The work presented in this thesis was undertaken between 2017 and 2021 in the Academic Unit of Colorectal Surgery at Glasgow Royal Infirmary. I declare that the work presented in this thesis was undertaken by me, except where indicated below:

- Assistance with the systematic reviews and meta-analysis was provided by Dr Stephen McSorley and Dr Rachel Kearns (Chapter 5).

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Publications

The work presented in this thesis has resulted in the following publications:

1. **The effect of anaesthesia on the postoperative systemic inflammatory response in patients undergoing surgery: A systematic review and meta-analysis.**
   Aliah M. Alhayyan, Stephen T. McSorley, Campbell S. D. Roxburgh, Rachel J. Kearns, Paul G. Horgan, and Donald C. McMillan Surgery Open Science. 2020 Jan, Volume 2, Issue 1, Pages 1-2, doi.org/10.1016/j.sopen.2019.06.001
2. **The relationship between anaesthetic technique, clinicopathological characteristics and the magnitude of the postoperative systemic inflammatory response in patients undergoing elective surgery for colon cancer.**
   Aliah M. Alhayyan, Stephen T. McSorley, Rachel J. Kearns, Paul G. Horgan, Campbell S. D. Roxburgh, and Donald C. McMillan. PLOS One. 2020 April 29, Volume 15, Issue 4, Pages 1-9, doi.org/10.1371/journal.pone.0228580
3. **The effect of anaesthesia on the magnitude of the postoperative systemic inflammatory response in patients undergoing elective surgery for colorectal cancer in the context of an enhanced recovery pathway. A prospective cohort study.**
   Aliah M. Alhayyan, Stephen T. McSorley, Rachel J. Kearns, Paul G. Horgan, Campbell S.D. Roxburgh, and Donald C. McMillan. Medicine. 2021, Volume 100, Issue 2, Pages 1-7, (e23997).
4. **The relationship between opioid administration, type of anaesthesia and clinicopathological characteristics in patients undergoing surgery for colorectal cancer.**

   The article in press in PLOS ONE journal.

Presentations

The work presented in this thesis has resulted in the following presentation:

The effect of anaesthesia on the postoperative systemic inflammatory response in patients undergoing surgery: A systematic review and meta-analysis (poster), GRI St Mungo Research Prize Afternoon 2019.

Definitions/Abbreviation

ACCP	American College of Chest Physicians
ACE	Angiotensin converting enzyme inhibitors
ACTH	Adrenocorticotropic hormone
ACEIs	Angiotensin-Converting Enzyme Inhibitors
AFAP	Attenuated familial adenomatous polyposis
AJCC	American Joint Committee on cancer
APC	Adenomatous polyposis coli
ARBs	Angiotensin receptor blockers
ASA	American Society of Anesthesiologists physical status classification
ATP	Adenosine triphosphate
BIA	Balanced inhalational anaesthesia
BRRS	Bannayan-Riley-Ruvalcaba Syndrome
BMI	Body mass index
CDSR	Cochrane Database of Systematic Reviews
CNS	Central nervous system
CRC	Colorectal cancer
CS	Cowden Syndrome
CT	Computed tomography
CRP	C-reactive protein
CRT	Chemo-radiotherapy
CIMP	CpG island methylator phenotype
CIN	Chromosomal instability
CIMP	CpG Island Methylator Phenotype
CD	Crohn's disease
CI	confidence interval
COX	Cyclooxygenase
DNA	Deoxyribonucleic acid
DOR	Delta opioid receptor
EA	Epidural anaesthesia
EMBASE	Excerpta Medica Database
EMT	Epithelial mesenchymal transition

ERAS	Enhanced recovery after surgery
ERP	Enhanced recovery protocol
FAP	Familial adenomatous polyposis
FIT	Faecal immunochemical tests
gFOBT	Guaiac-based faecal occult blood testing
GA	General anaesthesia
GIT	Gastrointestinal tract
GPS	Glasgow prognostic score
HCT116	Human colon cancer cell line
HDI	Human development index
HIF	Hypoxia-inducible factor
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme
HNPCC	Hereditary non-polyposis colorectal cancer
HMPS	Hereditary Mixed Polyposis Syndrome
HPA	Hypothalamic–pituitary–adrenal axis
HPS	Hamartomatous polyposis syndrome
IA	Inhalational anaesthesia
IBD	Inflammatory bowel disease
ICCCs	Inter-class correlation coefficients
IFN-γ	Interferon gamma
IGH	Insulin like growth factor
IV	Intravenous
IL	Interleukin
JPS	Juvenile Polyposis Syndrome
KOP	Kappa opioid receptor
KRAS	Kirsten rat sarcoma viral oncogene homolog
LDH	Lactate dehydrogenase
LI	Local infiltration
MAPK	Mitogen-activated protein kinase
MMP	Matrix Metalloproteinase
MOR	Mu opioid receptor
MSI	Microsatellite instability
MUST	Malnutrition Universal Screening Tool
NCI	National Cancer Institute

NK	Natural killer
NSAIDS	Non-steroidal anti-inflammatory drugs
NF- κB	Nuclear factor kappa B
NLR	Neutrophil to lymphocyte ratio
OR	Odds ratio
PCA	Patient controlled analgesia
PG	Prostaglandin
PJS	Peutz-Jeghers Syndrome
POD	Postoperative day
POI	Post-operative ileus
PSC	Primary sclerosing cholangitis
RA	Regional anaesthesia
RCT	Randomized clinical trial
RNA	Ribonucleic acid
RON	Recepteur d' origine nantais
SA	Spinal anaesthesia
SCCM	Society of critical care medicine
SIRS	Systemic inflammatory response syndrome
SFA	Subcutaneous fat area
SFI	Subcutaneous fat index
SIR	Systemic inflammatory response
SMA	Skeletal muscle area
SMD	Skeletal muscle radiodensity
SMI	Skeletal muscle index
SNS	Sympathetic nervous system
SW620	Cellosaurus SW620 cell line
TAP	Transversus Abdominis Plane Block
TEA	Thoracic epidural anaesthesia
TFI	Total fat index
TGF	Transforming growth factor
TIVA	Total intravenous anaesthesia
TNM	Tumour node and metastasis
TNF- α	Tumour necrosis factor-alpha
TP53	Tumour suppressor gene

UC	Ulcerative colitis
UICC	Union for International Cancer Control
UK	United Kingdom
US	United States
VEGF	Vascular endothelial growth factor
VFA	Visceral fat area
VFI	Visceral fat index
VO	Visceral obesity

Dedication

Every challenging work needs self-efforts as well as guidance and support from elders especially those who were very close to my heart. My humble efforts I dedicate this thesis to my loving mother Fawziah and father Mohammad who have been a source of inspiration and who gave me strength when I thought to give up, who continually provide their moral, spiritual, emotional, and financial support. To all my sisters Shatha, Hajar, Latifah, Tamadher and Rawan. To all my mentors and friends especially Fakriah. Their love, affections, encouragement, and prays of day and night, make me able to get such success.

1 Introduction

1.1 Epidemiology of Colorectal Cancer (CRC)

In 2018, colorectal cancer (CRC) was the third commonest cancer in men and the second in women with almost newly diagnosed cases of more than 1.8 million worldwide. Approximately 881,000 deaths were observed worldwide and CRC ranks as the second most common cause of cancer death. The highest incidence rate of CRC is found in Europe, New Zealand, Australia and North America and the lowest incidence rate in Africa and South-Central Asia (Bray et al., 2018). In males, Hungary has the highest incidence of CRC followed by South Korea. Among women Norway has the highest incidence of CRC followed by Hungary. However, the lowest rates are found in most parts of African and Southern Asia. The incidence rate is three times higher in transitioned countries such as Central and Eastern Europe in comparison with countries outside Europe. However, high, or extremely high human development index (HDI) countries are associated with higher mortality rate compared with low or medium HDI regions (Bray et al., 2018). The incidence rate varies according to ethnic, racial and geographic areas (Center et al., 2009). Overall survival is poor; even in those patients who undergo potentially curative resection, more than one-third die within 5 years. By 2030, more than 2.2 million of new cases are expected with 1.1 million cancer deaths around the world (Arnold et al., 2017).

In the United Kingdom (UK), CRC is the fourth common malignancy and the most common cause of cancer death after breast, prostate, and lung cancer (**Figure 1.1**). In 2015, approximately 41,700 new cases were diagnosed with 23,100 cases in men and 18,700 in women and 16,000 deaths in 2016. The cancer is more common in white population than in black or Asian people. Older people aged 75 or above are at higher risk for developing bowel cancer. It has been predicted that the number of deaths may drop by

23% between the periods from 2014 up to 2035 (CRUK., 2015). The researchers gave several reasons to support their prediction. For instance, there were some factors that make it possible for doctors to detect colorectal polyps (pre-malignant lesions) through screening tests and public knowledge. It has been shown that screening participation rates increased by the population awareness of CRC and screening tests. Therefore, a knowledge about the disease and its prevention has been used as a measurement of public awareness (Gimeno Garcia et al., 2014).

In Scotland, CRC was the third most common cancer diagnosed in 2016 with approximately 1,949 and 1,751 cases diagnosed in men and women, respectively. This incidence rate is higher than in England with a lifetime risk of about (1 in 16) for men and (1 in 20) for the women counterparts (SPHO., 2016).

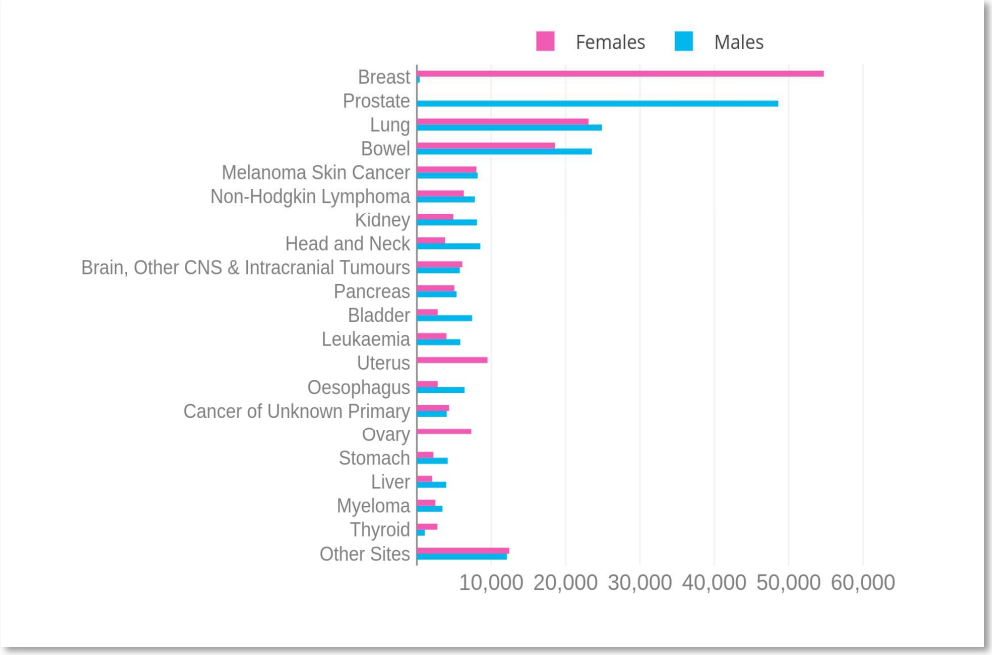


Figure 1.1: The 20 most common cancers in 2017, UK, **(**Reproduced from Cancer Research UK)

1.2 Aetiology of Colorectal Cancer

The aetiology and pathogenetic mechanisms of CRC remains complex and poorly understood. Mutations occur in specific genes causing the onset of cancer. Depending on the aetiology and genetic factors of the disease, CRC can be classified into hereditary/ inherited type, familial and sporadic (Sameer, 2013).

1.2.1 Inherited or Hereditary Colorectal Cancer

Genetic syndromes are the cause for about 3% of all CRC cases such as hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome) and 1% of people are associated with familial adenomatous polyposis (FAP) and Gardner syndrome (Bardhan and Liu, 2013). The inherited colorectal carcinoma includes those with or without adenomatous polyps as a main manifestation of cancer (Arvelo et al., 2015). These are known as polyposis and non-polyposis forms (Marmol et al., 2017). The inherited forms of CRC syndrome with polyposis variant such as familiar adenomatous polyposis (FAP) which associated with inherited adenomatous polyposis coli (APC) mutation, a tumour suppressor gene while the hereditary non-polyposis CRC or Lynch syndrome is associated with inherited mutation among one of the mismatch repair genes (Arends, 2013).

1.2.1.1 Familial Adenomatous Polyposis (FAP)

Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary disease presented with people having multiple polyps throughout the full colon in early age and this may predispose the individual to high risk of developing colorectal carcinoma if not recognized or left untreated. The mean age of colon cancer diagnosed in untreated individuals is 39. This is caused by germline mutation in APC gene leading to dysfunction of the APC tumour suppressor gene and accumulation of β-catenin, which has a major role in cell communication (Nojadeh et al., 2018). At teen age, it can be diagnosed by using flexible sigmoidoscopy and a prophylactic colectomy has been performed as a preventive

treatment. Despite of that, patients are still at risk of developing other type of cancer such as hepatopancreatic, hepatoblastoma and thyroid carcinoma (Burt, 2016). Other subtypes of FAP that are caused by different germline mutations in *APC* gene including attenuated FAP (AFAP), Gardner syndrome, gastric adenocarcinoma, proximal polyposis of the stomach and Turcot syndrome (Nojadeh et al., 2018).

1.2.1.2 Hereditary Non-polyposis Colorectal Cancer (HNPCC)

The most common hereditary form of hereditary CRC is Lynch syndrome, also known as hereditary non-polyposis colorectal cancer syndrome (HNPCC). It is an autosomal dominant hereditary disease caused by a germline mutation among one of the four DNA mismatch repair (MMR) genes including *MLH1, MSH2, MSH6, and PMS2*. Another cause of Lynch syndrome is the large removal in a non-mismatch repair gene, called epithelial cellular adhesion molecule (EPCAM) which silences *MSH2* expression. During DNA replication, the mismatch repair genes are necessary for repairing incorrect pairing of nucleotide bases. If these mismatches are not corrected, then the resulting copy may not work properly leading to an increased risk of developing cancer. Individuals with Lynch syndrome may have less than ten adenomatous polyps in their life. Adenomas are mainly observed in patients younger than 40 years of age and having a villous growth pattern with dysplasia of moderate to high grade. Adenomas tend to transform more rapidly into cancers in individuals who have adenomas with Lynch syndrome than those with adenomas in the general population. The right side of the colon or the cecum is the most frequent affected lesion with colon tumours associated with Lynch syndrome (Lynch et al., 2009).

It is well known that the risk of developing endometrial cancer may be increased in women who carry a mutation in an HNPCC gene. Lynch syndrome accounts for approximately 3% of all CRC cases and around 2.5% of endometrial cancer cases. About one in 35 CRC

and one in total of 50 endometrial cancers are linked to Lynch syndrome. The affected patients diagnosed with CRC with an average age of 44 to 61, whilst for endometrial cancer, the mean age at diagnosis is 48 to 62 years.

Patients identified by this syndrome if they have family history of malignancy with specific clinical testing criteria such as Amsterdam criteria II or Revised Bethesda guidelines. These should be followed by tumour testing for Lynch syndrome, for example microsatellite instability test. The vast majority of this syndrome follow the high level microsatellite instability (MSI-H), however, the germline screening test is needed for high tumours microsatellite instability since this pattern can be observed in sporadic colorectal cancer (Lynch and Shaw, 2013).

1.2.1.3 Hamartomatous Polyposis Syndromes

The hamartomatous polyposis syndromes (HPS) comprise a group of hereditary autosomal dominant disorders, account for less than 1% of all hereditary CRC. In comparison with neoplastic and hyperplastic polyps, it is rare to find a hamartomatous polyp in gastrointestinal tract, however, it is the most common type of polyp in children (Jelsig et al., 2014). These conditions include Juvenile Polyposis Syndrome (JPS), Peutz-Jeghers Syndrome (PJS), PTEN-Hamartoma Tumour Syndrome including either Bannayan-Riley-Ruvalcaba Syndrome (BRRS) or Cowden Syndrome (CS) and Hereditary Mixed Polyposis Syndrome (HMPS). The progression of these polyps to cancer is not fully understood, and represents a different mechanism than that seen in adenomatous polyposis (Calva and Howe, 2008, Manfredi, 2010).

1.2.2 Familial Colorectal Cancer

Only 25% of all cases are of familial syndromes caused by inherited mutations but not classified among the inherited type. This type of cancer is shown in patients with a family history of cancer or colorectal adenomas (Stoffel and Kastrinos, 2014).

1.2.3 Sporadic Colorectal Cancer

The spontaneous, non-inherited or sporadic CRC accounts for the vast majority of cases, starting as adenomatous polyp in the large intestine and rectum, representing 60-80% of all cases and described by the fact that not showing any kind of inherited or family link (Arvelo et al., 2015, Watson and Collins, 2011). Environmental factors such as age, diet, physical activity and obesity play an important role in the formation of CRC. Age is being the main risk factor for this type of cancer and common in elderly people specifically those over 50 years old (Sameer, 2013). Also, the genetic factors are the main cause in the carcinogenesis of sporadic CRC (Fernandes et al., 2014).

1.3 Colorectal Cancer Carcinogenesis

The disease is heterogeneous because a mutation may target different genes with differences between the prognosis, clinical presentation, and treatment response. The fundamental features of CRC carcinogenesis are the gene mutations, epigenomic instability and local inflammatory changes that allow the differentiation between the neoplastic from the normal colonic epithelium (Grady and Markowitz, 2015). The cancer may arise from either one pathway or a combination of multiple pathways. The three common molecular pathways that are responsible for genetic instability including the "classical" or chromosomal instability (CIN) also known as the adenoma-carcinoma sequence resulting in sporadic CRC, microsatellite instability (MSI) and epigenetic changes such as CpG Island Methylator Phenotype (CIMP) pathway. Genomic instability is the main part in the transformation of normal mucosa of colonic or rectal type to adenoma then to malignant cancer (Al-Sohaily et al., 2012, de Wit et al., 2013). Mutation of adenomatous polyposis coli oncogene (APC), Kirsten rat sarcoma viral oncogene homolog (KRAS) and tumour suppressor gene (TP53) is associated with CIN and the frequent mutation of DNA mismatch repair genes is associated with MSI. The CIMP pathway involves hypermethylation of the gene promoter due to transcriptionally inactivated genes (Arends, 2013). Recently, other pathways have been established which include non-coding microRNA (miRNA) (Tariq and Ghias, 2016). The molecular pathogenesis of classical CIN pathway including series of events proposed by Fearon and Vogelstein in 1990 which leads to colonic mucosal change (Fearon and Vogelstein, 1990).

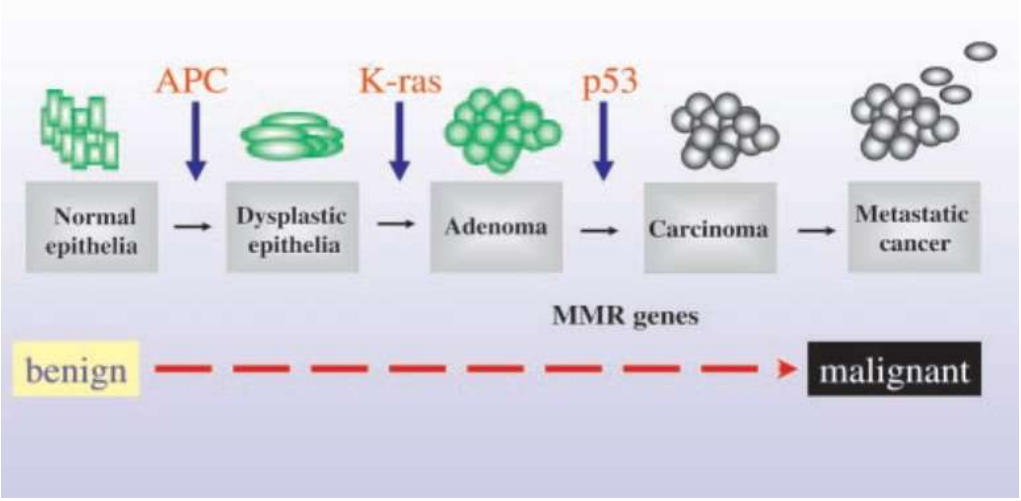


Figure 1.1: Genetic changes required for the progression from adenoma to carcinoma in the development of CRC showing the order of mutations in APC, K-ras, p53, and the DNA MMR genes adopted from (Fearon and Vogelstein, 1990).

1.3.1 Adenoma Carcinoma Sequence

Adenoma carcinoma sequence is a term used to describe the progression from normal to dysplastic adenomas (precursor adenomatous polyps) to carcinoma. This sequence accounts for most of the sporadic colorectal cancer that is associated with chromosomal instability (Hagland et al., 2013). The process begins with genetic alterations and accrual mutations of somatic origin occurred in oncogenes or tumour suppressor genes which are responsible for the progression of the epithelial to cancerous cells including APC followed by mutational activation of KRAS oncogene and eventually the inactivation of TP53. The initial step is the inactivated mutation of APC gene, in which their role to prevent the tumorigenesis and this found in 80% of colorectal adenoma and carcinoma cells. This causes an increase and accumulation of β-catenin levels as a result of activation of the Wnt signalling pathway (Grady and Markowitz, 2015). The second step is a mutational activation of KRAS oncogene, which found in 40-45% of colorectal adenoma and carcinoma cells particularly at codons 12, 13 and 61. The last stage of the transition of adenoma to carcinoma involve the inactivated mutation of TP53 which also known as the guardian of the genome and found in more than 60% of CRC (Arends, 2013). These gene

mutations are often accompanied by chromosomal instability, which accounts for 70% of all sporadic type of CRC. This comprises the structural changes of chromosomes, aneuploidy which defined as imbalance in the chromosome number and a loss of heterozygosity (Tariq and Ghias, 2016).

1.3.2 Microsatellite Instability

Microsatellite instability (MSI) is a sign of inactivating mutations and impairment of the DNA mismatch repair genes (*MMR*), which are responsible for correcting the DNA replication errors. The genes mutation occurs among one of the following genes (*MLH 1, MLH 2, MLH 3, MLH 6, PMS 1 and PMS 2*). MSI with high level is responsible for the development of both sporadic CRC (12%), caused by hypermethylation of the *MLH1* gene and hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome (3%), caused by germline mutations in *MLH1, MSH2, MSH6,* and *PMS2* (Nikiforova and Nikiforov, 2011, Gatalica et al., 2016).

According to the National Cancer Institute (NCI) panel, the MSI tumours can be either high, low or stable level. The classification consists of five markers; two of them are mononucleotide repeats called BAT25 and BAT26 and three dinucleotide repeats called D5S346, D2S123 and D17S250. If the MSI tumours labile in two or more markers this is called MSI-high level (MSI-H) but if the instability shown in one marker this is called MSI-low level (MSI-L) (Boland et al., 1998).

1.3.3 Hypermethylation

Hypermethylation in a specific region of DNA is another pathway in the carcinogenesis of CRC, which silences the tumour suppressor genes. This knows as serrated pathway (Murcia et al., 2016). The serrated polyps of CRC accounts for only 20% which involve both mutation in *BRAF* oncogene and changes in DNA methylation. A CpG island

methylator phenotype with high frequency methylated gene (CIMP-H) is a particular type of epigenomic alterations in sporadic colorectal cancer which associated with hypermutated gene of *BRAF* V600E leading to the progression of malignant serrated polyps. This mutation is not observed in normal mucosa (Bond et al., 2018).

1.4 Risk factors for CRC development

The risk factors associated with the incidence of CRC including those that an individual cannot control such as age, hereditary factors, and inflammatory bowel disease. In addition, there are modifiable risk factors including environmental and lifestyle risk factors which may play an important role in the development of CRC.

1.4.1 Age

Age is a significant risk factor linked with CRC. The chance of diagnosis increases after the age of 40 and significantly rise after the age of 50. Around 90% or more of CRC cases found in people aged 50 or older. The incidence rate is more than 50 times higher in people aged 60 to 79 years than in those younger than 40 years. However, colorectal cancer appears to be increasing among younger people (Pandurangan et al., 2018).

1.4.2 Diet

Diet is a substantial factor linked to the prevention of disease and the risk of CRC. It is responsible for about 30%-50 % of CRC incidence (Ferlay et al., 2014). Prior to the hypothesis of Burkitt in 1970, who proposed that diet containing high fibres associated with a reduction in the incidence of CRC by depending on the results of observational study among African population who received high fiber diet (Burkitt, 1971). In contrast, another cohort study by the European Prospective Investigation into Cancer and Nutrition (EPIC), reported that there was no association between the intake of high fiber and the risk of CRC (Bingham et al., 2003). In 2011, a meta-analysis of prospective cohort studies conducted by Aune et al, found that a diet that contains cereal and whole grains was associated with a lower incidence of CRC (Aune et al., 2011).

Many studies have discussed the influence of a healthy diet on health. There is convincing evidence that the risk of CRC increased with high intake of red and processed meat

(Bradbury et al., 2020). For example, several studies comparing meat diets with vegetarian diets which shown a lower incidence of CRC with vegetarian dietary patterns. In 2015, a meta-analysis conducted by Alexander et al., reported that the consumption of red meat does not appear to be an independent predictor of CRC (Alexander et al., 2015). However, in recent years, a case-control study among Jewish and Arab populations was carried out to examine the relationship between red and processed meat intake. Data from this study resulted in a weak association between red or processed meat and the risk of CRC. In particular, an intake of lamb or pork may consider as relevant risk factors than beef intake even at a low level (Saliba et al., 2019).

Furthermore, the benefits of some nutrients have been discussed in the literature and their link with the incidence of CRC. These include high intake of dietary fibre, calcium, fish, and plasma vitamin D (Orlich et al., 2015). Elevated amount of diet rich in fibre may associated with lower incidence of colorectal cancer. This can be shown in a large prospective study by Kunzmann and co-workers, were they found that the risk of incident colorectal carcinoma and distal colon cancer reduced by consuming high intake of fibres in particular fruits and cereals (Kunzmann et al., 2015).

High intake of dietary calcium has been shown to have a benefit against CRC. In 2015, a case-control study in Korean people, whose level of dietary calcium intake is low, has been conducted to explore the dose response relationship in the associations between dietary calcium intake and the risk of CRC. The results showed that calcium consumption was correlated with CRC risk in Korean population. The risk of CRC was lower with higher calcium intake and this was observed in both sexes (Han et al., 2015).

The anticancer and protective role of vitamin D has been proven by some preclinical and epidemiological studies. However, some randomised controlled trials showed conflicting results (Dou et al., 2016).

1.4.3 Physical activity

The regular exercise and physical activity have anti-oncogenic effect which shows a significant decrease in the risk of developing CRC. These has been reported in several observational studies and meta-analysis (Wolin et al., 2009, Boyle et al., 2012). Recently, a prospective cohort study by Ratjen and colleagues who examined the relationship between physical activity, sedentary lifestyle such as hours of sleeping and hours spent to watch a TV and mortality in long-term CRC survivors. They suggested that the lifestyle recommendations with regards to physical activity may enhance the survival after treatment of CRC survivors (Ratjen et al., 2017). The mechanism of how the physical activity reduce the risk of CRC is unclear, however, some assumptions are presented. For example, changes in gastrointestinal transmit time, immune function, prostaglandin levels, insulin and hormones (Friedenreich et al., 2016).

1.4.4 Medical history of inflammatory bowel disease

Patients with inflammatory bowel disease (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) are at higher risk of developing CRC, 2-6 times more than the healthy population and having the disease at age younger than those who affected with sporadic CRC along with a 50% survival rate at 5 years. The disease associated with chronic inflammation in the gastrointestinal tract, but the pathogenesis remains unclear (Mattar et al., 2011). Genetic factors are responsible for IBD-CRC and the risk factors for the development of CRC are represented by the duration and extent of the colitis (Lukas, 2010). Geography may impact the risk of IBD-CRC development. For example, population in North American and UK are at higher risk to develop IBD-CRC than those population who lived in Scandinavia (Von Roon et al., 2007).

1.5 Pro-carcinogenic factors

1.5.1 Smoking and alcohol consumption

There is an association between a cigarette smoking and the risk of colorectal (Hannan et al., 2009). About 20% of CRCs are associated with smoking (Derry et al., 2013). Nicotine stimulates the growth of colon tumour and causes activation of survival pathways that enhance the proliferation and reduce apoptosis of colon cancer cells (Cucina et al., 2012).

Another modifiable risk factor is alcohol consumption. A dose response meta-analysis of 25g of alcohol intake daily among 30 studies was associated with a higher risk of colorectal adenoma, however the heterogeneity was wide between studies (Ben et al., 2015). In addition, clinical studies about alcohol abuse are not clear. However, different doses of alcohol per day including 25,50 and 100 mg responsible to estimate the higher risk of CRC development in about 1.14,1.21 and 1.32 respectively (López et al., 2014).

1.5.2 Obesity

Many epidemiological studies in the last 15 years, have examine the relationship between obesity and the risk of CRC. Obese people are more likely to develop colorectal cancer than normal weight people for about 30%. In both genders, a higher BMI is associated with increased risks of colon than rectal cancers, but the increases are higher in men than in women (Massat et al., 2013). Moreover, obesity is linked to cancer because it is a state of low-grade chronic inflammation. The adipose tissue is largest endocrine organ in the body, and it induces secretion the of several signalling cytokines, fatty acids, and peptide hormones. The cytokines produced by adipose tissue are IL-6, IL-8, IL-2, tumour necrosis factor alpha (TNFα), lactate dehydrogenase (LDH), as well as IL-2 receptor alpha (IL-2ra) (Gregor and Hotamisligil, 2011).

1.6 Anti-carcinogenic agents

There is a large number of published studies describing the preventive role of some medications in reducing the incidence and mortality of CRC. This medication including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) in particular, selective cyclooxygenase-2 (COX-2) inhibitors, statins and hormone replacement therapy.

1.6.1 NSAIDs, Aspirin and COX-2 inhibitors

There is previous research about the efficacy of aspirin and NSAIDs as anti-tumour agents. Other effects including analgesic, antipyretics, antirheumatic and anti-inflammatory. Several randomized clinical trials have tested the effect of both aspirin and NSAIDs in reducing the risk of CRC and the findings were successful (Temraz et al., 2013). The problem concerned with the use of aspirin is the bleeding effect but in adjuvant setting, the effect of aspirin in reducing the recurrence and as adjuvant treatment may outweigh the risk. To address this, the ADD-Aspirin trial was conducted to evaluate the effect of daily use of aspirin on recurrence and survival after radical cancer treatment in four types of tumours; colorectal, prostate, gastro-oesophageal, and breast cancer. It is an international, phase III, double-blind, randomised, placebo-controlled trial. The results showed that after radical cancer treatment, aspirin is well-tolerated, and the toxicity was low. Also, there was no evidence of a difference in the toxicity between different cancer cohorts or adherence or acceptance of randomisation. Until now, the trial is continued in order to determine if aspirin could offer a potential low cost and well tolerated treatment to enhance cancer outcome (Joharatnam-Hogan et al., 2019).

In addition, it has been suggested that daily use of celecoxib can reduce the risk of CRC up to 69% (Ash and Buggy, 2013). The mechanism of action of NSAIDs including the inhibition of the enzyme cyclooxygenase 1 and 2. COX-1 is the constitutive isoenzyme which is essential to produce the prostaglandin (PG) whereas COX-2 induced during the

inflammatory process by growth factors and cytokines as well as catalyse the production of PG. The production of PG helps to evade the malignant cells to the immune response (Heaney and Buggy, 2012). In CRC, the PGE_2 synthesis and COX-2 enzyme are elevated and the administration of NSAIDs provide a beneficial effect by inhibiting COX-2 enzymes. It also alters the systemic inflammatory response (SIR) of patients with non-metastatic CRC (Park et al., 2014). Other mechanisms including the inhibition of angiogenesis, induce apoptosis and enhance the cellular immunity (Thun et al., 2002). A number of preclinical and clinical studies have suggested a correlation between the use of NSAIDs and the risk of CRC. For example, a prospective cohort study including 301,240 patients of both genders concluded that the use of NSAIDs produced an overall reduction in the risk of CRC (Ruder et al., 2011). Interestingly, celecoxib can prevent the effect of morphine induced the increase of PGE_2, COC-2, angiogenesis, metastasis and tumour growth in a murine breast cancer model (Farooqui et al., 2007). A systematic review with case control and cohort studies has suggested that over-the counter NSAIDs providing a significant composite risk reduction with 43% for colon cancer, 27% for prostate cancer, 25% for breast cancer and 28% for lung cancer. With further subgroup analysis of the studies that used either celecoxib or rofecoxib, the results showed composite risk reduction with 69% for colon cancer, 55% for prostate cancer, 85% for breast cancer and 61% for lung cancer (Harris, 2009). Another meta-analysis examined the effect of high doses of non-aspirin NSAIDs for specific population of patients who had distal colon cancer, aged 40 or older, women, and white people. The results suggested that the non-aspirin NSAIDs possess a significant protective effect by reducing the risk of CRC (Tomić et al., 2019). Some studies show that high dose of celecoxib is better than using a low dose in improving the outcome. It also increases the radio sensitization of colon cancer cells and improving the depression with CRC patients. The use of rofecoxib has been suggested in reducing the risk of CRC; however, it is not recommended for patients with CRC due to the cardiovascular risk effect. A study by Lönnroth and colleagues have reported the

protective effect of indomethacin in CRC (Sada et al., 2019). Furthermore, the use of ibuprofen in CRC patients with elevated CRP may provide a beneficial effect to decrease the inflammatory mediators such as IL-6, CRP and cortisol (McMillan et al., 1995). Despite all the pharmacological effects of NSAIDs, the cardiovascular and renal impairment side effects should be taken into consideration.

The therapeutic effect of aspirin is attributed to the inhibition of both COX-1 and COX-2. The long-term use of aspirin is associated with a decrease in the recurrence of adenoma and mortality with an increase in disease-free and overall survival. A synergistic effect has been found with a concomitant use of aspirin and capecitabine treatment (Sada et al., 2019).

1.6.2 Hormone replacement therapy

More recent attention has focused on the association between the use of hormone therapy such as oestrogen either alone or combined with progesterone and the incidence of CRC, but the results are inconsistent. However, a population-based study in Swedish women who diagnosed with CRC between 2007 up to 2012 and using a hormone therapy after the diagnosis showed that the hormone therapy positively linked to the CRC mortality and all-cause mortality (Ji et al., 2018). These results suggest that sex hormones like oestrogens may produce a protection against CRC among women.

1.6.3 Statin

Statin therapy or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors which was known to be used as cholesterol lowering drugs may have the tendency to moderately lower the risk of colorectal neoplasia and this effect based on the meta-analysis of randomised clinical trials and observational studies. Inducing apoptosis, inhibition of cell proliferation and angiogenesis with an enhancement of immunity are

found as a mechanism of statins in cancer. Also, concomitant use of statin with a low dose of aspirin or NSAIDs may be help in the prevention of CRC (Bardou et al., 2010).

1.6.4 H2 receptor antagonists

High levels of histamine are associated with some types of cancer among them CRC. In particular, H2 receptor is the type of receptor involved in the carcinogenesis of CRC. It may also consider as a pro-angiogenic factor which has been sustained by several in vivo and in vitro studies and influencing the proliferation rate (Losurdo et al., 2018). From a Cochrane meta-analysis which involves six randomised controlled trials has found that the use of cimetidine as an adjuvant treatment improves the survival of patients who underwent for curative surgical resection, however, the studies included were heterogenous (Deva and Jameson, 2012). Furthermore, it has been reported in several studies that H2 receptor antagonists may play a role on CRC patients by enhance the peri-tumoral lymphocyte growth, improve the immune system, anti-angiogenic and anti-oxidant properties with an inhibition of carcinogenesis (Losurdo et al., 2018).

1.6.5 Metformin

Metformin is a commonly used antidiabetic medication for type 2 diabetes mellitus. Patients with type 2 diabetes mellitus are at higher risk of developing CRC. The protective effect of metformin in cancer patients has been studied extensively. At present, many studies have suggested the beneficial effect of metformin in both diabetic and non-diabetic individuals on lowering the risk of development of CRC (Higurashi and Nakajima, 2018). The most important biologic mechanisms associated in patients with diabetes mellitus and cancer are the inflammation and insulin resistance. In this case, a medication that reduce insulin resistance could help to reduce the risk of cancers associated with diabetes mellitus (Novosyadlyy and LeRoith, 2010). Also, the combination between metformin and aspirin

on human CRC cell lines suggested a synergistic effect of aspirin, indicating that metformin can be used as an adjuvant treatment in CRC (Saber et al., 2016).

1.7 Inflammation and cancer

Inflammation is an immune response from the body that can be triggered by a harmful stimulus including toxic compounds, pathogens and damaged cells. These will induce acute or chronic inflammation (Chen et al., 2018a). When the acute inflammatory process fails to resolve any tissue injury, the chronic inflammation takes place in the inflammatory mechanism (Lintermans et al., 2014).

Chronic inflammation is a main hallmark of all cancer types such as CRC. The risk of cancer development increases with a non-resolved chronic inflammation. Inflammation initiates the tumour progression by a pathway in which the inflammatory micro-environment associated with high levels of cytokines, microRNAs, prostaglandins, nuclear factor kappa B (NF-κB) and recepteur d' origine nantais (RON) that affect the cell proliferation rate, cell death, DNA methylation, mutation rate and angiogenesis (Schetter et al., 2010).

The immune response includes a set of events initiated in response to recognition of pathogens or tissue damage, involving cells and soluble mediators, such as cytokines of the innate and adaptive immune system. The main purpose of this inflammatory response is to remove the foreign substance disturbing tissue homeostasis (Medzhitov, 2008). In the normal physiological situation, after tissue repair or pathogen elimination, the inflammation is resolved, and the homeostatic state recovered (Norling and Serhan, 2010).

It is now widely accepted that the risk of cancer increased as a result of inadequate resolved of chronic inflammation. Several pathologies clarify this link, such as endometriosis, chronic gastritis due to Helicobacter pylori (*H. pylori*), IBD, and primary sclerosing cholangitis (PSC). Inflammation can increase the risk of cancer by providing bioactive molecules from cells infiltrating the tumour micro-environment, including

cytokines; growth factors, chemokines that maintain a sustained proliferative rate, cell survival signals to avoid apoptosis, proangiogenic factors, and extracellular matrix modifying enzymes such as metalloproteinases that promote epithelial mesenchymal transition (EMT) and facilitate other carcinogenesis programs, such as genome instability, reprogramming of energy metabolism, and immune evasion (Hanahan and Weinberg, 2011).

An association between the development of cancer and inflammation has long been appreciated (Coussens and Werb, 2002). Epidemiological studies have shown that individuals with chronic inflammation are susceptible to various types of cancer. It has been estimated that 15-20% of all cancer death worldwide mainly due to infections and inflammatory responses (Balkwill and Mantovani, 2001).

1.7.1 Host immune system

The immune system is composed of several types of soluble bioactive molecules, proteins, cytokines, and cells that altogether form a network of biochemical processes that recognize and fight against antigens or “nonself” proteins. To provide protection and maintain the normal state of homeostasis of the host, the immune system consists of two important lines of defence including innate and adaptive immunity (Marshall et al., 2018).

1.7.2 Innate (natural or native) immunity

The innate immune system (non-specific defence) is the first line of defence which respond immediately against pathogens and recognize danger signals (Desmet and Ishii, 2012). The innate immune response involves numerous cells such as phagocytic cells (macrophages and neutrophils), mast cells, dendritic cells, basophils, eosinophils, innate lymphoid cells and natural killer cells (NK). The innate immunity represents the body's “gut reaction” to an abnormality, such as cancer, and does not involve specific recognition

of antigens (immunogenic proteins) (Coussens and Werb, 2002). Microorganisms such as bacteria that infiltrate the epithelial surfaces of the body for the first time are met immediately by cells and molecules that can boost an innate immune response. Phagocytic macrophages conduct the defence against bacteria by means of surface receptors that can recognize and bind common constituents of many bacterial surfaces. Bacterial molecules binding to these receptors trigger the macrophage to engulf the bacterium and induce the secretion of biologically active molecules. Activated macrophages secrete cytokines, which are defined as proteins released by cells that affect the behaviour of other cells that bear receptors for them. They also release proteins known as chemokines that attract cells with chemokine receptors such as neutrophils and monocytes from the bloodstream. An inflammation has been initiated as a result of a release of cytokines and chemokines by macrophages in response to bacterial constituents (Janeway, 2001).

1.7.3 Humoral immunity

Humoral immunity is known as antibody mediated immune response. It starts with an activation of B cell through the recognition of antigens by naïve B cell receptors, then the cells undergo for a process called clonal division of activated B cells. After that a differentiation process of B cells has been occurred to give two types of cells including plasma cells, which are the antibody producing effector cells and memory B cells. By this process, B cells become mature into antibody secreting plasma cells to produce antibodies that bind to antigen. Those antibodies are the effector products of humoral immunity while the memory B cells become as a secondary response which act as immunological memory. If the body re-expose to the same antigen second time, the memory cells will respond more quickly to recognise the antigen and differentiate the plasma cells to produce antibodies (Casadevall and Pirofski, 2003).

1.7.4 Adaptive (acquired or specific) immunity

The adaptive immune system is a specific response to a particular tumour associated antigen and it requires time to prepare. Once the foreign substances entered the body, this immune system is responsible for the destruction of them. There are two types of acquired immune system: humoral immunity, which is mediated via B lymphocytes and their secreted antibodies, which provide protection against extracellular microbes and their toxins, and cell-mediated or cellular immunity, which is mediated via T lymphocytes which mainly protect against intracellular microbes. There are three types of T cells that play a major role in the destruction of antigens. They are cytotoxic T cells (CD8+), helper T cells (CD4+), and regulatory T cells (FOXP3+). Humoral and cellular immunity are linked by a broad family of proteins called cytokines, which play a significant role in immune cell activation, communication, and regulation. Natural killer (NK) cells, which is a third type of lymphocyte, but considered as part of the innate immune system (Marshall et al., 2018). The help from other cells is needed to activate the acquired immune system. The cells of the acquired immune system are coated in receptors. They are highly specific molecules designed to recognize certain particles. The receptors are very specific that each receptor can only recognize only one substance. In the blood, there are many immune cells and each with its own several receptors which means that the body can be protected against many variable challenges (Marshall et al., 2018).

1.8 The post-operative systemic inflammatory response

In 1992, a definition of systemic inflammatory response was proposed by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM). The syndrome may induce by infections and other causes such as burn, trauma and surgical stress. The existence of SIRS is a warning sign for postoperative complications and organ failure (Smajic et al., 2018).

Following surgical injury, the magnitude of post-operative SIR can be assessed by the increase of some markers that can be used in clinical practice such as IL-6, cortisol, white blood cells and CRP. In CRC, a prognostic value of the Glasgow prognostic score (GPS), C-reactive protein (CRP), albumin, modified GPS (mGPS), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) may predict the outcomes of cancer. High GPS scores are significantly associated with cancer-specific survival (Gabay and Kushner, 1999).

In gastrointestinal surgery, there is a strong relationship between surgical stress and SIRS. Several studies confirmed the association between SIRS and the activation of the coagulation system and an increased in the production of pro-inflammatory cytokines. It is known that after surgery the serum level of IL-6 is significantly increased and peaked up to 3-6 hours after surgery and decreased afterward. In addition, the degree of SIRS is related to CRP concentration which stimulated by IL-6. Some evidence ascertains the relation between the magnitude of the severity of surgery and the concentrations of circulating CRP and cytokines, which is the systemic inflammatory response to surgery (Watt et al., 2015b). It was found that the effect of preoperative administration of glucocorticoids reduces the magnitude of the SIR, in particular IL-6 and CRP, and are significantly associated with fewer postoperative infective complications following surgery for gastrointestinal cancer (McSorley et al., 2016a).

1.9 Tumour staging of CRC

Tumour staging is an important issue to evaluate the progression of cancer and help in the prediction of survival for patients. It is considered the first step when the person diagnosed with CRC. Different types of staging systems have been employed including TNM system (Tumour-Node-Metastasis), which has been developed in cooperation by American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), Dukes', Kirklin's and Astler-Coller system. These staging systems are important on the plan of treatment prognosis (CRUK., 2014, Akkoca et al., 2014).

1.9.1 TNM stage

TNM is the most common and applicable used method to all types of tumours. In CRC, the classification of this system based on anatomical information such as the extent of primary tumour (T), the regional lymph node status (N) and the distant metastases (M), grouping the cases with similar prognostic. During the past 20 years, the classification (TNM) staging and histologic grading of rectal cancer has undergone some changes despite their major impact on reporting planning, and outcome of the disease (Haboubi, 2010). The TNM staging definitions are revised every 6–8 years. The 7^{th} revision of TNM staging was published by the AJCC and UICC, and became operational starting with 2010 (Obrocea et al., 2011). In 2018, the 8^{th} edition of the AJCC staging system was implemented worldwide with significant changes of CRC patients with stage IV (Tong et al., 2018).

1.10 Screening and diagnosis of CRC

In the UK, screening programmes for CRC have been operating since in 2006 with the aim of full roll out across the UK by 2009. Screening of CRC is primarily based on the results of faecal occult blood tests, sigmoidoscopy, and colonoscopy and these have been the most studied. CRC screening has improved from guaiac-based faecal occult blood testing (gFOBT), which used a chemical substance called guaiac to detect blood in the stool, to faecal immunochemical tests (FIT), using antibodies to detect blood in the stool. The number of early stage cancer diagnosed is increased while the mortality reduced by using the gFOBT as a screening tool for CRC (Mansouri et al., 2016). Also, the recent meta-analysis has been shown that the average reduction in CRC mortality is estimated to be 12%, varying from 10% to 21% (Massat et al., 2013). However, randomized trials of screening sigmoidoscopy conducted in UK, Italy, and the US have shown an approximately 50% reduction in mortality from distal colorectal cancer (Atkin et al., 2010, Segnan et al., 2011, Schoen et al., 2012). Another test called the stool DNA test (FIT-DNA), which combines the FIT with a test that detects altered DNA in the stool. In USA, colonoscopy is the test of choice for the vast majority of CRC screening (Klabunde et al., 2011). Therefore, screening programs have a significant role on reducing the death rate from CRC.

2 Treatment of CRC

The cure and treatment of CRC depends on the type and stage. Local therapies are those treatment, which treat and cure the tumour without affecting the rest of the body such as surgery (the type of surgery will depend on whether it is for colon or rectal cancer), and radiation therapy. These treatments are more likely to be useful for earlier stage (less advanced) cancers, although they might also be used in some other situations. Other type of treatment using medications, which can be given orally or directly into the bloodstream. These are called systemic therapies because they can reach cancer cells anywhere in the body. Several different types of drugs might be used depending on the type of CRC, including chemotherapy, targeted therapy and immunotherapy.

2.1 TNM stage I and II

2.1.1 Surgery

Surgery remains the primary modality of treatment for all stages of CRC. However, the stress response induced by surgery initiates the cellular immune suppression by activating the sympathetic nervous system and hypothalamic-pituitary adrenal axis. This results in release of hormones including catecholamines, a main driver of pro metastatic effect, glucocorticoids, growth factors, adrenocorticotropic hormone (ACTH), cortisol, cytokines and the acute phase may accelerate the proliferation of residual cancer cells and metastasis (Siekmann et al., 2017a).

The aim of surgery should be to avoid loco-regional recurrence and to achieve cure and remedy. The type of surgery used depends on the stage (extent) of the cancer, where it is, and the goal of the surgery (Pérez-Herrero and Fernández-Medarde, 2015). There are three types of surgery: local excision (by removing the cancer without cutting through the abdominal wall), resection of the colon with anastomosis or colostomy.

It is now well established that laparoscopic surgery for colorectal cancer when compared with conventional open surgery, resulted in an improvement of outcomes such as less pain, shorter length of stay, lower cost, lower complication rates and faster return of bowel function. For this reason, increasing numbers of patients are undergoing laparoscopic surgery (Keller et al., 2016). Another minimally invasive technique by robotic surgery was has gained acceptance in recent years especially for rectal cancer. The technique can be used as a treatment option with feasible and meticulous dissection compared with open colorectal surgery and less favourable compared with laparoscopic approach (Park and Baik, 2016).

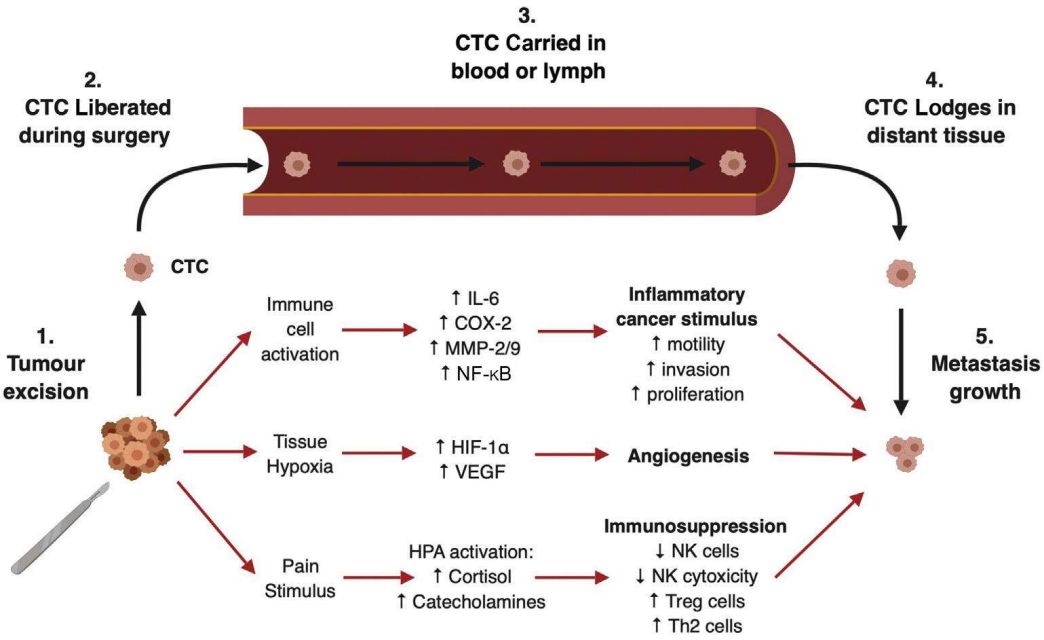


Figure 1.2: The pathophysiological mechanisms enhanced by surgery adopted from (Wall et al., 2019a).

2.1.2 Enhanced recovery after surgery (ERAS)

In recent years there has been a large number of published studies describing the role of ERAS in many gastrointestinal specialities including colorectal, pancreatic, gastric and esophageal cancer (Pisarska et al., 2017).

The ERAS also known as fast recovery program is a multimodal and multi-disciplinary perioperative care protocol which was introduced in 1997 by Professor Henrik Kehlet (Kehlet, 1997). These protocols have been implemented successfully in both colon and rectal resections with a similar outcome, even in those patients with advanced cancer (Pędziwiatr et al., 2017). It involves a multimodal perioperative care pathway designed to achieve early recovery after surgical procedures by maintaining postoperative physiological functions and reducing the profound stress response following surgery. The main elements of the ERAS protocol include pre-operative counselling, avoidance of perioperative fasting and carbohydrate loading up to 2 hours preoperatively, standardized anaesthetic and analgesic regimens (epidural and non-opioid analgesia) and early mobilization (Feldheiser et al., 2016).

In colorectal surgery, it has been known that the implementation of ERAS protocol is the most commonly used practice to improve the clinical outcomes by attenuating the postoperative stress response, organ dysfunction, the postoperative complication rates and the length of hospital stay (Gustafsson et al., 2011). In this context, a number of studies have shown a decrease in morbidity which is an important factor for long term survival with an added beneficial effect in the overall healthcare cost (Lassen et al., 2009).

2.2 TNM stage III and IV

2.2.1 Neo-adjuvant chemo-radiotherapy

Preoperative neo-adjuvant chemo-radiotherapy (CRT) also known as chemo-radiotherapy is considered as a standard treatment for many patients with locally advanced rectal cancer

following radical resection. It helps in reducing the recurrence and tumour size and increasing the anus retention rate and tumour resection rate with minor side effects (Li et al., 2016). A meta-analysis by Chen and colleagues (2019) including 14 randomized clinical trials comparing between eight regimens of CRT treatment, and the results have shown that a regimen of capecitabine combined with oxaliplatin provides the best effective treatment for locally advanced rectal cancer, however, the addition of oxaliplatin to fluorouracil or capecitabine increases the toxicity (Chen et al., 2019a). It has been known in several studies that the preoperative CRT followed by radical resection, the pathologic staging is an important prognostic factor to predict high risk patients for adjuvant treatment in order to reduce the recurrence and improve survival (Hwang et al., 2015).

2.2.2 Adjuvant chemotherapy

The decision to include the adjuvant treatment for colon cancer depends on the differences between the characteristics such as pT3 or pT4 stage and the risk of recurrence (Böckelman and Glimelius, 2017). Since 2004, the standard adjuvant treatment in patients with stage III colon cancer has been the regimen of 6 months duration with oxaliplatin plus a fluoropyrimidine but the neurotoxicity of oxaliplatin should be taken into consideration with less duration of therapy (Grothey et al., 2018). The use of fluoropyrimidines alone, demonstrated an improvement of overall survival rate from 20% to 33% after 5 years in patients with stage III colon cancer, however, its role in stage II disease is controversial.

In 2018, a trial of the Short Course Oncology Therapy (SCOT) was conducted with 6088 patients who had resected high-risk stage II or stage III CRC and were randomised and followed up to 3-8 years. The aim of the trial was to assess and compare the effect, toxicity and cost-effectiveness of 3 months adjuvant oxaliplatin combination chemotherapy with 6 months regimen. The results showed that 3 months treatment was associated with significantly less cost with no significant effect on patients' outcomes; survival and quality

of life. It can be considered as the optimal treatment from an UK health-care perspective. To date, the SCOT trial was the largest randomised study in adjuvant chemotherapy (Robles-Zurita et al., 2018).

Recently, Nozawa and colleagues have reported that the adjuvant chemotherapy should be included in patients with stage IV after curative surgical resection because they found good improvement in both recurrence free survival and overall survival (Nozawa et al., 2020).

3 Anaesthetic agents and techniques

It has been observed that different outcomes may be associated with different anaesthetic agents (inhalational versus total intravenous anaesthesia), different method of analgesic technique (IV opioids versus epidural analgesia), and whether any drug additives or treatments such as blood products, NSAIDs, selective COX-2 inhibitors, and cortico-steroids, β-blockers are used.

There are different components of GA including unconsciousness, analgesia, and paralysis with muscle relaxation. The present thesis focuses mainly on modalities used for analgesia and unconsciousness. With GA, patients are completely unconscious and unresponsive and is administered to mainly insure amnesia, analgesia and paralysis of skeletal muscles. Two stages were involved with GA; induction and maintenance of anaesthesia. The induction state was defined by the transition from awake to anaesthetized state while the maintenance of anaesthesia state to keep a patient unconscious and can be performed by using inhaled volatile anaesthesia or continuous infusion of IV anaesthesia (Urban and Bleckwenn, 2002). It can be given by two routes of administration either by using inhalational, intravenous or combination of both medications which is the most frequently used method (Stollings et al., 2016). GA is not mutually exclusive and used together with RA in most abdominal surgery.

The current literature has demonstrated that different anaesthetic drugs / techniques for surgery have an impact on the innate and cell immune system of the host. For example, general, local and other anaesthetic technique have a significant effect on the postoperative immune cells activity including macrophages, neutrophils, dendritic cells, NK cells and T cells (Tavare et al., 2012). In particular, the pro-inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α may be affected by the anaesthetics by either blocking or unblocking the surgical stress response via the sympathetic nervous system and hypothalamic pituitary

adrenal axis (Dang et al., 2018). Also, it cause an activation of two pathways including the adrenergic-inflammatory pathway and cancer promoting cellular signalling pathway which may lead to tumour recurrence and cancer cell growth or metastasis (Yang et al., 2017, Yap et al., 2019). The influence of anaesthesia can be classified into direct effect on the immune cells or induced indirect regulation of immune system via endocrine and nervous system. A reduction in total circulating T lymphocytes (CD3+ cells) and the ratio of T helper cells (CD4+ cells) to T suppressor cells (CD8+ cells) have been demonstrated in cancer patients along with a decline in the response of T cells to antigens (Ostroumov et al., 2018). Also, anaesthetics may have an effect on stromal, tumour cells and overall effect on recurrence and survival.

As the anaesthetic medications are never applied separately from other medications in the peri-operative period, it would appear difficult to detect the isolated effect of anaesthetic agents on the immunity in the clinical context. Therefore, the preponderance of the studies that determined the immune modulatory properties of anaesthetic drugs are *in vitro* (Rossaint and Zarbock, 2019). Several anaesthetic agents have been used in surgery for colorectal cancer and can be classified into either general or general plus regional anaesthesia. General anaesthesia (GA) can be given by two routes of administration either by using inhalational, intravenous or combination of both medications which is the most frequently used method (Stollings et al., 2016). GA is used for both induction and maintenance of anaesthesia. The drawbacks of GA include the potential for inadequate pain control, high incidence of nausea and vomiting, and increase length of hospitalization. Other controversial effects of GA in oncologic patients are related to the impairment of immune system.

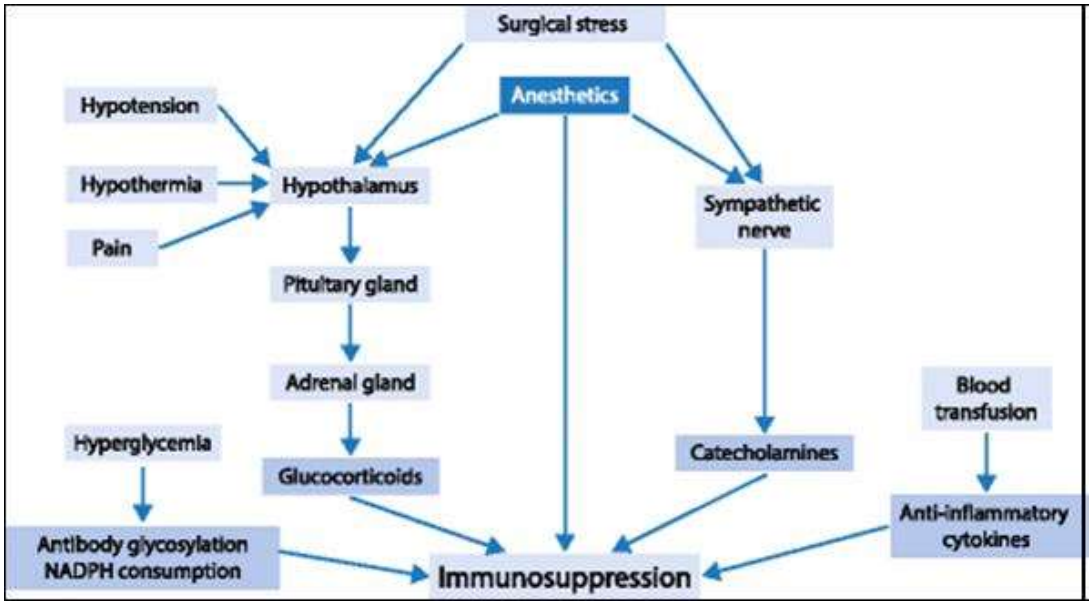


Figure 1.3: The surgical stress and anaesthetic effects through the neuro and immune endocrine interaction adopted from (Aamri and Basnawi, 2017).

Regional anaesthetic techniques may provide superior postoperative pain management than GA. Regional anaesthesia (RA) includes neuraxial block (epidural and spinal techniques) or peripheral nerve blocks such as Transversus abdominis plane block (TAP-block) or rectus sheath block.

In colorectal surgery, many retrospective studies have supported that RA is associated with excellent analgesia. The advantages of RA including the following: First, the combination of both GA with RA can lead to a decrease in the required dose of GA drugs and systemic opioids, and as a result, may avoid the undesirable side effects of opioids. Second, RA attenuates the immunosuppressive effect after major surgical insult (Kaye et al., 2014). However, the results of evaluating the benefits of using RA in colectomy patients are conflicting. There are many key factors involved such as age, timing of epidural, stage and type of colorectal cancer, and American Society of Anaesthesiology physical status classification (ASA grade) (Grandhi et al., 2017b). Therefore, the choice of anaesthetic technique may be a critical component in the progression of cancer cells. The

currently available data suggest that volatile anaesthetics and analgesic opiates may have a harmful effect on cancer outcomes while the propofol based anaesthesia, local and RA techniques may provide a protective effect (Evans et al., 2019). In addition, a considerable amount of literature has been published about the role of RA in ERAS programmes (McIsaac et al., 2015).

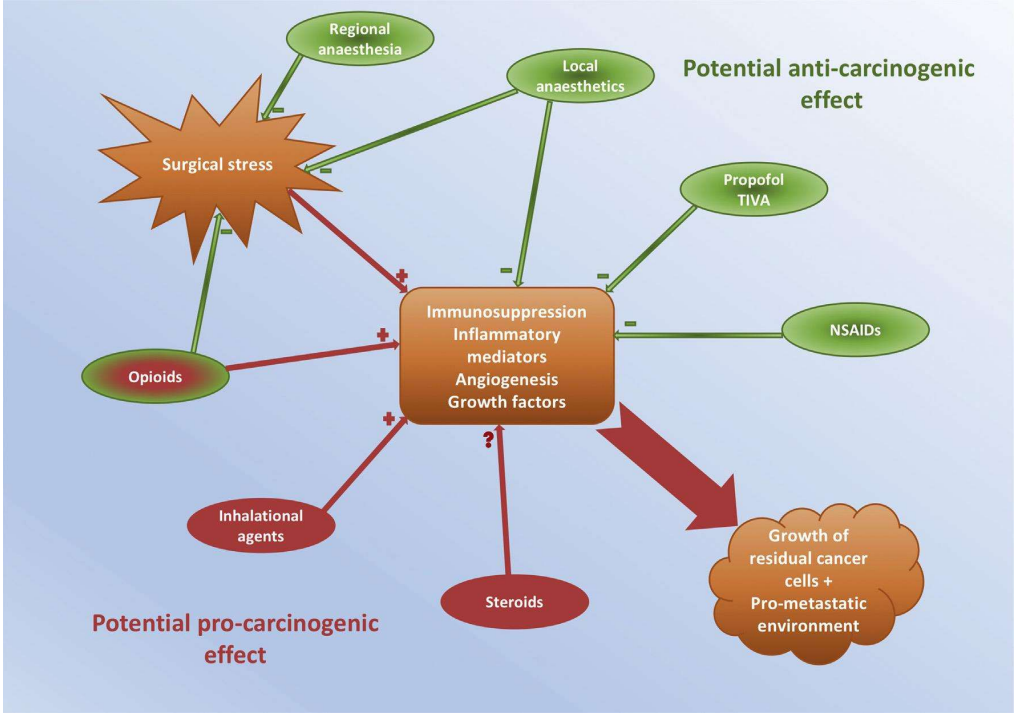


Figure 1.4: The impact of anaesthetic agents during cancer progression, metastasis, and recurrence adopted from (Evans et al., 2019).

3.1 General anaesthesia (GA)

3.1.1 Inhalational anaesthesia (IA)

Inhalational anaesthetics were brought into clinical use in 1842. This type of GA is still used worldwide as a main part of clinical anaesthesia (Zuo, 2012). Halogenated agents such as isoflurane, sevoflurane and desflurane are currently used to provide inhalational

GA. The majority of preclinical studies has suggested that the volatile anaesthetics have a different immunosuppressive property, and this is a dose dependent effect of halogenated anaesthetics on both humoral innate and immune system which are mainly involved in cancer recurrence and metastasis (Stollings et al., 2016, Jin et al., 2019). The results from different studies show inconsistent effect of IAs on apoptosis, cell proliferation and metastasis. For example, isoflurane as well as sevoflurane were found to promote apoptosis of T- lymphocyte and B- lymphocytes in different cell lines by supressing the activity of NK cell, cytotoxic T lymphocyte (CTLs) and the ratio of T-helper 1 to T-helper 2 (Th1/Th2) whilst it increases the levels of pro-tumorigenic cytokines and matrix metalloproteinase (MMPs) (Deegan et al., 2010, Tavare et al., 2012). Conversely, in vitro study has investigated that the exposure of sevoflurane in two different types of tumour cell line produced different results. It showed that sevoflurane did not promote the metastasis in non-small cell lung adenocarcinoma (A549) while it enhances the metastasis in renal carcinoma cell (RCC4) (Ciechanowicz et al., 2018). In another *in vitro* experiment, the CRC cells including HCT116 and SW620 were exposed to different concentrations of sevoflurane for 6 hours and the results showed that sevoflurane prevents the metastasis in CRC cells by inhibiting the cell migration and invasion (Fan et al., 2019). A research conducted by Sugimoto and colleagues who found that sevoflurane increases the proliferation of colon cancer cell line by K (ATP) channels in tumour cells (Sugimoto et al., 2015).

An in vitro study conducted by Kawaraguchi and colleagues found that the short exposure to isoflurane may protect human colon cancer cell lines from apoptosis of TNF- α via caveolin-1 dependent mechanism (Kawaraguchi et al., 2011). In contrast, desflurane was not reported to have a proapoptotic effect (Tavare et al., 2012). Previous research has established that isoflurane can activate the mitogen activated protein kinase (MAPK) including p38 which is needed to regulate the release of proinflammatory cytokines such as

IL-1β, TNF-α and IL-6 (Stollings et al., 2016). Furthermore, the release of cytokines by NK cells such as IL-1β and TNF-α are suppressed in the presence of enflurane and sevoflurane. This is consistent in the abdominal surgery where the low flow of sevoflurane is associated with reducing the lymphocytes and NK cells and increasing the neutrophils and leukocytes (Kaye et al., 2014). It was found that halothane affects the production of reactive oxygen species and chemotaxis (Stollings et al., 2016).

In the literature, there are few studies that have investigated the effect of desflurane on the immune system. A prospective randomized clinical trial reported that the administration of desflurane with propofol in patients underwent for breast cancer surgery may preserve the immune system in particular, the ratio of IL-2/IL-4 and CD4+/CD8+ T cell (Woo et al., 2015).

Many clinical studies have demonstrated that, there is a correlation link between the poor prognosis of colorectal, gastric, breast, hepatocellular and ovarian carcinoma and the high level of hypoxia -inducible factors 1-α (HIFs-1α); a transcription factor which mediate the response to hypoxia and play a main role in the progression, tumour growth and development of cancer (Tavare et al., 2012). Some volatile anaesthetics have the tendency to up regulate HIFs-1α including isoflurane in a dose dependent manner, desflurane and halothane and sevoflurane, however, a study performed by Liang and colleagues has shown that sevoflurane may down regulate HIFs-1α in lung cancer cells and metastasis (Liang et al., 2015). The mechanism by which the IA upregulates the HIFs-1α is beneficial for patients undergoing coronary artery bypass graft surgery as anti-ischemic by protecting the heart and other organs including brain, kidney and liver from ischemia reperfusion injury (Benzonana et al., 2013). In vitro studies have elucidated that the tumorigenic growth factors are enhanced by isoflurane including, insulin- like growth factors (IGFs) (Evans et al., 2019). In addition, sevoflurane and halothane have cytotoxic and anti-

proliferative properties on human cancer including colorectal, larynx carcinoma and pancreatic cancer and advanced differentiated cells of colon cancer (Kvolik et al., 2005).

3.1.2 Intravenous anaesthesia

Propofol is a gamma amino butyric acid receptor agonist, one of the commonly used short acting intravenous anaesthetic with sedative, hypnotic and amnestic effects, that can be used by bolus administration for the induction of anaesthesia or by continuous infusion for the maintenance of anaesthesia.

Several studies have demonstrated that propofol has a more favourable immunomodulating effect than IA. Accumulating evidence from in vivo and in vitro studies has found that propofol possesses anticancer and anti-inflammatory activities by inhibiting the cyclooxygenase 2 (COX-2) activity and prostaglandin E2 (PGE2) which help to reduce the inflammatory cytokines release caused by surgery (Inada et al., 2009). It also reduces the invasion of human colon cancer cells by decreasing the presence of matrix metallo-proteinase enzymes including MMP-2 and 9 which break down the extracellular matrix and accelerate the invasion and progression of tumours (Miao et al., 2010). Propofol has the ability to inactivates the HIF-α in colorectal cancer cells and thus inhibits the glycolysis (Chen et al., 2018b). Moreover, it is increasingly suggested that propofol is able to increase the activity of NK cells particularly in breast cancer surgery in comparison with IA, thus suppress the tumour invasion and metastasis via regulation of beta (β)-adrenoreceptor-mediated signal transduction (Desmond et al., 2015).

According to the literature, the immune modulating property of propofol has been widely discussed and its effect on the pro-inflammatory, inflammatory cytokines and cancer specific biomarkers is conflicting. Data from a randomized clinical study revealed that in colon cancer patients who received propofol with epidural anaesthesia have shown a reduction in all markers of angiogenesis and metastasis such as IL-6, transforming growth

factor-β (TGF-β) and serum-vascular endothelial growth factor-C (VEGF-C) compared with those patients who received sevoflurane with systemic opioids (Xu et al., 2014). A randomized controlled trial by Margarit and colleagues found no significant differences between the effects of TIVA with propofol and isoflurane on IL-6 and IL-10 levels after open colorectal cancer surgery (Margarit et al., 2014). Similar results have been found from another study, which found no significant differences in IL-6, IL-1β, IL-4 and TNF-α concentrations when comparing TIVA using propofol and remifentanil with IA with sevoflurane and fentanyl for patients who scheduled for elective open colorectal surgery (Kvarnström et al., 2012).

3.2 Regional anaesthesia (RA)

RA is a popular method for pain prevention in some surgical procedures. Epidural anaesthesia (EA) can be used in combination with GA in most abdominal and orthopaedic procedures.

A number of studies including retrospective and prospective have been published to compare between general and RA in patients who undergoing oncological surgery. RA includes different techniques such as central or peripheral blocks. Epidural and spinal anaesthetic techniques are examples of central block while TAP-block and rectus sheath block are examples of peripheral nerve blocks. Other analgesic methods used to ameliorate the postoperative pain are patient-controlled analgesia (PCA), systemic lidocaine infusions, wound infiltration and wound infusions (Patel et al., 2012). The drugs that are commonly used for RA are local anaesthetics (LA) such as, lidocaine, bupivacaine and ropivacaine. All of them having a similar analgesic effect with different side effects (Becker and Reed, 2012). The choice of LA for EA depends on the characteristics of the patient either using LA alone, opioids alone or combination of both LA and opioids. The mixture of epidural LA with opioids is the most commonly used regimen following upper

or lower abdominal, thoracic or orthopaedic surgery providing a superior pain control (Mehta et al., 2012).

Epidural anaesthesia (EA) is commonly used in the thoracic region in most abdominal surgeries as this region is linked to the segmental visceral afferent and efferent blockade (Holte and Kehlet, 2000). The results that evaluate the benefit of EA in CRC patients are mixed. Many factors may have a role to detect the exact role of EA including the age, stage or type of CRC, ASA grade and timing of epidural (Grandhi et al., 2017b). Gupta et al, has carried out the effect of EA in colon and rectal cancer patients and found that the improvement in overall survival and reduction in the mortality has been observed for only those who underwent for rectal cancer (Gupta et al., 2011). A randomised trial by Myles et al, found that there was no improvement in 5 year mortality rate or cancer free survival with epidural block for CRC (Myles et al., 2011). Another study by Gottschalk found similar results (Gottschalk et al., 2010). Day et al, found no difference between GA and RA with regards to overall survival in patients underwent for laparoscopic surgery for CRC (Day et al., 2012). However, some evidence showed that the use of EA after abdominal surgery may influence the long-term outcomes of cancer patients by providing attenuation of surgical stress response by blunting the increase of catecholamines and cortisol induced by surgery. This effect has been shown in a study of patients with oesophageal cancer who underwent for thoracic surgery and the epidural block offers a suppression of the increased serum level of cortisol and IL-6 (Gu et al., 2015a). Another advantages of EA, it provides intra and postoperative analgesic effect, lowering the required dose of IA during surgery and opioid consumption (Kettner et al., 2011). Some animal studies have reported that EA can enhance the survival rate after colorectal cancer surgery.

Up to date, only few studies are available which examined the effect of RA on the immune system and cancer recurrence and most of them are retrospective in nature (Kaye et al., 2014). Furthermore, it has been reported that EA preserves the cellular immunity by increasing the ratio of Th1/Th2 cells and preserves NK cell function better than GA. Local anaesthetic agents used in EA has the tendency to reduce the HIF-1α expression (Dang et al., 2018, Iwasaki et al., 2015). A retrospective study has illustrated that the overall survival of colon cancer patients has been improved with epidural analgesia (Vogelaar et al., 2015). EA showed a survival benefit in patients with CRC and liver metastasis (Zimmitti et al., 2016). In addition, a meta-analysis from 13 retrospective and 5 prospective studies showed that the overall survival has been improved in colorectal cancer patients with RA but did not find any effect on cancer recurrence (Chen and Miao, 2013). In contrast to the positive effects of EA, another prospective study, demonstrated negative results in laparoscopic colorectal patients (Day et al., 2012)

The postoperative ileus (POI) is a common problem following colorectal surgeries which affecting the quality of patient recovery and prolong the hospital stay. There is a high evidence in the literature concerning the benefit of EA compared with or without opioids in reducing the ileus and facilitate gastrointestinal recovery (Guay et al., 2016). A meta-analysis has carried out in 2016 to compare between combined general with epidural anaesthesia and GA with opioid analgesia and the results showed that an improvement in pain control and faster return of bowel function in the combined epidural group (Guay et al., 2016).

Spinal anaesthesia (SA) or intrathecal opiate analgesia is another form of central neuraxial blockade, involving only a single injection of LA +/- opioid into the cerebral spinal fluid. It often used for short procedures and exhibits an anti-inflammatory property with a moderate and transient effect compared with EA. SA can be applied for both open and

laparoscopic colorectal resection with superior quality of analgesia than systemic morphine. A randomized controlled trial in patients undergoing for laparoscopic colonic resection with the context of ERAS protocol found that the spinal anaesthesia associated less consumption of postoperative morphine with better analgesia compared with systemic morphine. However, there was no difference between the two groups in return of bowel function, length of hospital stays and postoperative complications (Wongyingsinn et al., 2012).

In comparison to EA, one observational study showed that SA has some advantages over EA in patients undergoing laparoscopic colorectal surgery with shorter hospital stay, earlier return to mobility with a reduced postoperative pain (Virlos et al., 2010).

Regarding to the effect of SA on the systemic modulation of the inflammatory response, one study demonstrated that in patients undergoing knee arthroplasty, there were less inflammatory response in a group who had EA followed by postoperative EA compared with those who received spinal anaesthesia followed by postoperative IV morphine analgesia (Chloropoulou et al., 2013).

TAP- block is one approach of peripheral nerve block that was described by Rafi in 2001. This technique involves an injection of LA in the neurovascular plane between the muscles of internal oblique and transversus abdominis and can provide analgesia of the anterolateral abdominal wall but not for the visceral part. It can be performed for open or laparoscopic colorectal operations and in those for whom the EA is contra-indicated. The question of including this method as analgesia is controversial. In some clinical trials, TAP-block showed an effective pain relief with a lower consumption of postoperative use of opioids after CRC, however, in one study this method did not reduce the pain after laparoscopic colon cancer surgery (Liu et al., 2018, Torup et al., 2016). In comparison with EA, only four studies were conducted in abdominal surgeries that looked at the

analgesic efficacy between the two techniques and none of them providing the superiority of one over the other (Zhang et al., 2015). In contrast, a randomised study has examined that the effect of analgesia with epidural was superior than TAP-block in patients undergoing for lower abdominal surgery (Iyer et al., 2017).

Another technique of peripheral nerve block called rectus sheath block. It does not have the systemic side effect that comes from the sympathetic nerve block. When compared with central neuraxial blocks, it has lesser complications such as urinary retention and safer than GA or central neuraxial blocks particularly for those with severe coexisting disease (Kettner et al., 2011).

3.3 Other anaesthetic adjuvants and medications and post-operative outcome

3.3.1 Opioids

Acute pain causes an activation of the HPA axis which resulted in immunosuppression, decreased NK cell activity, and imbalance of T cell (Dang et al., 2018). Therefore, it is imperative to manage severe pain in cancer patients, whether in the perioperative period of cancer surgery or for long-term treatment of chronic cancer pain during the palliative period (Perry and Douglas, 2019). Opioid drugs are considered as one of the most effective analgesics and another essential part of anaesthesia, and mainly used to manage pain during and after surgery. However, the suppressive effect of opioids on innate and acquired immune system may complicate the treatment of patients with an impaired immunity.

Opioids are classified into natural opiates like morphine and synthetics such as fentanyl, remifentanil, alfentanil, sufentanil, and methadone (Pathan and Williams, 2012). There are three main opioid receptors termed as mu opioid receptor (MOR), kappa opioid receptor (KOR), and delta opioid receptor (DOR). The endogenous ligands for these receptors including the neuropeptides: β-endorphin (MOR), dynorphin (KOR), and methionine-enkephalin (DOR). Opioid receptors can be found in neurons and in immune cells including granulocytes, lymphocytes, monocytes, macrophages, and natural killer cells. Also, it can be found mainly in the CNS, peripheral nervous system and peripheral tissues and in tumour cells originating from breast, colon, glioma, lung, thyroid, pancreatic, endometrial and endocrine cancer (Iwaszkiewicz et al., 2013).

In preclinical studies, it has been noted that opioids may play a role in the maintenance of the homeostasis of gastrointestinal tract (GIT) (Boland et al., 2014). Furthermore, the immunosuppressive effect of opioids has been proven by several studies and the activation

of opioid receptors have both direct and indirect effects on tumour cells. The direct effect leading to proliferation, apoptosis and invasion while the indirect effect including immunosuppression, pro-angiogenesis and pro-inflammatory effect which enhance the development of tumour and cytokine production (Grandhi et al., 2017a).

Morphine, an alkaloid in nature and has a strong MOR agonist. It has the greatest affinity towards MOR and with a lesser affinity to other receptors (Eisenstein, 2019). It was reported that morphine supresses NK cell activity in rats, mice and humans and these immuno-suppressive mechanism by its affinity towards MOR with a dose dependent effect (Eisenstein, 2019). It also inhibits T cell differentiation, monocyte, neutrophil, macrophage and lymphocyte functions (Pathan and Williams, 2012). In addition, there is some evidence from a retrospective study that in patients with cancer and treated with morphine developed more infections than those treated with oxycodone (Suzuki et al., 2013). Morphine inhibits IL-10 and IL-2 production from monocytes and macrophages and supresses IFN-γ and IL-2 production of T-lymphocyte (Sacerdote et al., 2003). On the other hand, a prospective observational study examined the relationship between morphine treatment and immune system in patients with cancer, and the plasma concentration of IL-12 was measured before and after morphine treatment in 44 patients with metastatic cancer and they observed no significant changes in the levels of IL-12 after 8 days of treatment with morphine (Makimura et al., 2011). In comparison to morphine, opioids such as fentanyl, remifentanil, sufentanil and alfentanil have minimal immunosuppressive effect than morphine (Kurosawa and Kato, 2008). In animal studies, fentanyl has been reported to have a suppressive effect on NK cell, but in humans, it increases the activity and number of NK cells, and $CD8^+$ cytotoxic T-lymphocytes (Shavit et al., 2004, Yeager et al., 2002). In 2014, a retrospective study has shown that the use of fentanyl was associated with a reduction of the overall survival (OS) and increased in tumour recurrence in patients with non-small cell lung cancer resection (Cata et al., 2014). In patients underwent for coronary

artery bypass surgery, it has been reported that when fentanyl and remifentanil administered at clinical doses, there were no change in the concentration of IL-6, TNF, IL-10 and IL-2, however, remifentanil was able to reduce the postoperative increase of IFN-γ/IL -10 ratio of greater extent than fentanyl (von Dossow et al., 2008).

Opioids have different effects on the immune system by chronic administration. For example, fentanyl, loperamide, methadone and β-endorphin can mediate a partial anti-inflammatory effect of IL-4 and stimulate the production of IL-4 on human T-lympho-cytes. On the other hand, buprenorphine and morphine leads to a reduction in the level of IL-4 and proteins (Börner et al., 2013). In addition, some previous studies showed that morphine down-regulates cytokine production which are produced by macrophages and T cells (Eisenstein, 2019).

In a study that compared between sufentanil and remifentanil by using target-controlled infusion and in patients underwent laparoscopic surgery for colorectal cancer resection, the concentration of both cortisol and IL-6 increased more in the remifentanil group and the proportion of T cell subsets reduced more in the sufentanil group (Qi et al., 2016). On the other hand, in another randomised clinical trial for elderly patients who underwent for laparoscopic surgery of colon cancer and by comparing between fentanyl combined anaesthesia and remifentanil combined anaesthesia, the concentration of IL-6, IL-8, CRP, TNF-α, and oxidative stress level have reduced significantly in remifentanil combined anaesthesia group (Ding et al., 2019).

A study has shown that a synthetic codeine analogue called tramadol has an apoptotic inducing effect in colon carcinoma cell line Colo320 and this effect was obtained by increasing caspase -3 activity (Özgürbüz et al., 2019).

3.3.2 α-2 adrenoreceptor agonists

α-2 adrenoceptor agonists are used frequently as sedative and analgesic but their effects on cancer have rarely been studied. Dexmedetomidine is a selective α-2 adrenoceptor agonist, with an analgesic, anxiolytic, sedative, sympatholytic, and opioid-sparing effect. It can be administered as analgesic adjuvant providing a safe respiratory property or anaesthetic adjuvant to reduce the requirements of opioids, intravenous and inhalational anaesthesia (Lee, 2019). Clonidine is another α-2 agonist that used to control postoperative pain.

A systematic review and meta-analysis indicated that when a systemic dexmedetomidine combined with local anaesthetic in a TAP-block after abdominal surgery provide an ideal pain control, reduce the consumption of opioids, and prolong the duration of local anaesthetic (Sun et al., 2019). Also, the anti-inflammatory effect of dexmedetomidine have demonstrated by several studies and lowering the serum levels of IL-6, IL-8, and TNF-α (Wu et al., 2018a). Recently, it has been shown that the adjuvant use of dexmedetomidine with sufentanil via IV patient-controlled analgesia after esophageal cancer surgery is significantly lowering IL-6 and TNF-α concentrations and increased IL-10 level, reduce both the postoperative delirium and the consumption of opioids, and hasten the recovery (Tang et al., 2020). With regards to CRC, a randomized double-blind clinical study showed that in 60 patients underwent for laparoscopic colorectal surgery, the gastrointestinal motility function has improved with intraoperative administration of dexmedetomidine (Chen et al., 2016). Another randomised clinical trial reported that in elderly patients undergoing laparoscopic radical resection of colorectal cancer, dexmedetomidine was an effective analgesia with a relieve of stress response, reduce the release of inflammatory markers and modulation of the immune function (Zhang et al., 2017a).

3.3.3 β-adrenoreceptor antagonists

β-blockers are drugs that have a cardioprotective effect and commonly used for treating hypertension and coronary artery disease. They have been considered for cancer treatment by antagonising adrenergic receptor activation and may help to minimize the surgical stress insult after major abdominal surgery (Ahl et al., 2020b). The results from a large retrospective cohort study demonstrated that preoperative β-blockers therapy for colon cancer patients underwent for elective surgery was strongly associated with a significant reduction in post-operative short and long-term mortality (Ahl et al., 2020b). Moreover, it has been reported in a previous multicentre study that patients underwent for abdominal resection of rectal cancer and exposed to pre-operative β-blockers, that the survival rate was increased up to one year as well as reduction in post-operative complications (Ahl et al., 2020a).

4 Summary and Aims

CRC is one type of solid tumour cancer that is the third most diagnosed cancer and world-wide is the fourth most common cause of cancer death (Ferlay et al., 2015). Surgery is a fundamental treatment for most of solid tumours, however, accumulating evidence suggested that surgical trauma potentially promotes the development of micro-metastasis, angiogenesis and affects the long-term prognosis of cancer patients. Following surgical trauma, wide range of endocrinological, immunological and haematological changes were occurred. These encompasses an activation of the SNS resulted in secretion of catechol-amines, pro-inflammatory cytokines and production of acute phase proteins from the liver such as CRP. The post-operative systemic inflammatory response can be used as an early predictor for the development of infective complications. The magnitude of the post-operative systemic inflammatory response can be assessed by IL-6 and CRP. In addition, post-operative CRP concentrations >150mg/L on day 3, 4 and 5 were associated with postoperative complications.

Volatile or IV anaesthesia and/or opiates are received for up to 80% of patients undergoing oncological surgery. Together with surgery, they have different impact on the host immune system.

The aim of the present thesis was to examine the effect of perioperative anaesthesia on the postoperative SIR of patients undergoing surgery for colorectal cancer and in particular to address the following;

1. The effect of anaesthesia on the postoperative systemic inflammatory response in patients undergoing surgery: A systematic review and meta-analysis.

2. The relationship between anaesthetic technique, clinicopathological characteristics and the magnitude of the postoperative systemic inflammatory response in patients undergoing elective surgery for colon cancer.

3. The effect of anaesthesia on the magnitude of the postoperative systemic inflammatory response in patients undergoing elective surgery for colorectal cancer in the context of an enhanced recovery pathway.

4. The relationship between pre-operative medications, the type of anaesthesia and post-operative sequelae in patients undergoing surgery for colorectal cancer.

5. The relationship between nutritional status, anaesthetic approach, and peri-operative characteristics of patients undergoing surgery for colorectal cancer.

6. The relationship between opioid administration, type of anaesthesia and clinico-pathological characteristics in patients undergoing surgery for colorectal cancer.

5 The effect of anaesthesia on the postoperative systemic inflammatory response in patients undergoing surgery: A systematic review and meta-analysis.

5.1 Introduction

The surgical stress response is defined as the systemic reaction of the human body to a surgical procedure. It has long been recognised that a surgical injury results in stereotypical changes of the neuroendocrinological, metabolic, immunological and haematological systems in humans (Desborough, 2000). The neuroendocrine response to surgery involves the stimulation of the sympathetic nervous system and resultant tachycardia, hypertension and stimulation of the hypothalamic-pituitary adrenal axis (HPA). This induces the release of hormones such as adrenocorticotropic hormone (ACTH), catecholamines (norepinephrine and epinephrine) and cortisol. Increasing circulating concentrations of such mediators are associated with the suppression of pro-inflammatory T cell responses (Finnerty et al., 2013). For example, an increase in the white cell count is associated with a decrease in the number of lymphocytes including CD4+ and CD8+ and is proposed to have a detrimental effect on the post-operative immunity (Dabrowska and Slotwinski, 2014).

Furthermore, the production of pro-inflammatory cytokines including interleukin (IL) IL-1, IL-6, IL-8 and tumour necrosis factor (TNF) alpha by innate immune cells such as neutrophils and macrophages, interacting with damaged cells and platelets, leads to the production of acute phase proteins from the liver such as C- reactive protein (CRP), fibrinogen and complement proteins. The existence of other factors including the pre-existing co-morbid condition, adjuvant chemo or radio therapy, blood transfusion and type of surgical procedure may amplify the surgical stress response (Watt et al., 2017b). An exaggerated post-operative systemic inflammatory response (SIR) is associated with increased post-operative morbidity and mortality (Giannoudis et al., 2006, McSorley et al., 2016a).

In terms of routine clinical assessment of the magnitude of surgical injury, circulating concentrations of IL-6 and CRP are particularly useful in the 12-24 hour and 24-96 hour periods respectively following surgical injury (Watt et al., 2015a). Indeed, in colorectal surgery, postoperative threshold concentrations of CRP >150mg/L on day 3 and 4 are associated with increased post-operative infections precluding safe discharge (McSorley et al., 2015, McDermott et al., 2015).

In addition to host factors, and surgical factors, different anaesthetic techniques used in surgery may have a differential effect on the postoperative SIR and post-operative complications (Cassinello et al., 2015). Some anaesthetic techniques may affect the immune system by decreasing the levels of pro-inflammatory cytokines and modify the function of innate and adaptive immune cells. For example, the immunomodulatory effect of propofol has been reported in several studies and more favourable than inhalational agents and that combined regional anaesthesia has a greater effect than single use of general anaesthesia in reducing the surgery induced inflammatory response. Furthermore, the modification of perioperative anaesthetic technique may play an important role in cancer patients to reduce the incidence of metastasis and improve the long-term survival (Perry et al., 2019, Ke et al., 2008).

The aim of the present systematic review and meta-analysis was to examine the relationship between different anaesthetic techniques and the magnitude of the postoperative SIR in particular that of IL-6 and CRP, and the postoperative infective complications in patients undergoing surgery of different degrees of severity. The results of this review may help to delineate which anaesthetic techniques reduce the magnitude of the SIR.

5.2 Methods

5.2.1 Outcomes of Interest

The primary outcome of interest was the impact of anaesthesia on the postoperative SIR in particular IL-6 and CRP in patients following surgery. The secondary outcome of interest was the impact of anaesthesia on postoperative complications, in particular infective complications, following surgery.

5.2.2 Literature Search

A systematic search of the scientific literature was conducted from 1987 until March 2018 using PubMed, the Excerpta Medica Database (EMBASE), Web of Science databases and the Cochrane Database of Systematic Reviews (CDSR).

5.2.3 Study Selection and Data Extraction

The following search terms were used in free text and medical subject heading (MeSH) together with the usual Boolean meaning of "OR" and "AND" including ("anaesthesia and analgesia"/ OR analgesia, epidural/ OR analgesia, patient controlled/ OR anesthesia/ OR anesthesia, general/ OR anesthesia, inhalation/ OR balanced anesthesia/ OR anesthesia, endotracheal/ OR anesthesia, intravenous [Mesh]) AND "systemic inflammation OR stress response OR systemic inflammatory response" [Mesh]) AND ("General Surgery"[Mesh] OR "Surgical Procedures, Operative"[Mesh] AND "IL-6" AND "CRP" AND "postoperative complication".

A search of the bibliographies of selected papers was carried out to identify any relevant articles missed during the primary search. The duplicated studies were removed manually. Additional studies were hands searched from the reference list of included studies. The literature search and data extraction were carried out by a single author (AA). Any uncertainty regarding the inclusion, or otherwise, of a paper was discussed with the senior

author (DM). Data on study characteristics including authors, year of publication, country of origin, number of patients, type and severity of surgery, anaesthetic agents used type of complications and inflammatory response markers were extracted to preconstructed tables for each individual study. Study quality was assessed using the Jadad scale.

5.2.4 Study Eligibility Criteria

The study question was performed according to the PICO classification including; Population: patients undergoing surgery. Intervention: anaesthetic technique. Comparison: different general and regional anaesthetic techniques (general anaesthesia; general plus regional anaesthesia; regional anaesthesia; miscellaneous adjuvants). Outcome: IL-6, CRP, and postoperative infective complications.

Only controlled, randomized clinical trials published in the English language, including, patients older than 18 years, undergoing surgery of any type were included in the review. All titles and abstracts were reviewed to assess their relevance for inclusion. There were no restrictions in terms of ethnicity, and stage of cancer or surgical approach.

5.2.5 Meta-analysis

In the present review, some studies were amenable to meta-analysis using random or fixed effects model to calculate the combined mean difference and its 95% confidence interval in postoperative IL-6 and CRP. Where data were expressed as a median and range or interquartile range, the calculation of mean and standard deviation was derived from the methods of Hozo et al. and Wan et al.

With regards to the effect of anaesthesia on the postoperative complications, OR_S and 95% confidence interval (CI) were obtained from each study and shown in a forest plot graph and combined using a random effects model.

In the present review, the majority of studies were heterogeneous and therefore the use of random effects model was considered more appropriate than fixed effects model as it was not assumed that they shared a common effect.

Meta-analysis was performed by using the Review Manager software version 5.3 (RevMan v5.3 Nordic Cochrane Collaboration). Statistical heterogeneity was determined by the I^2 test. P-values <0.05 a were considered to be statistically significant.

5.2.6 Evaluation of Clinical Trial Studies

The methodological quality of each study was evaluated using the Jadad scale tool, also known as the Oxford quality scoring system. This is a 3-question, 5-point system with superior validity and reliability evidence compared with other scoring systems (Olivo et al., 2008).

Points for randomization, double-blinding, and description of withdrawals and dropouts are included within the score with points omitted for inappropriate description of randomization or blinding. Studies scoring ≥ 3 points are considered to represent satisfactory methodological quality, with studies scoring, ≤ 2 points considered to be of low quality. Studies in which double-blinding is not possible may be assessed as high quality if the total score ≥ 2 points (Chung et al., 2012, Jadad et al., 1996).

5.3 Results

5.3.1 Study Selection Process

The results of the literature review are shown in the PRISMA Flow Diagram (**Figure 5.1**; (Moher et al., 2010).

In total, 395 studies were identified through the databases. Records were excluded including 165 review articles, 30 articles not in English, 20 animal studies and 2 studies which include non-infective complications. In addition, studies not meeting the inclusion criteria, such as those not reporting IL-6 or CRP or reporting these markers at time points out with the study specifications, were excluded. Sixty studies examined the impact of different anaesthetic techniques on the postoperative SIR and postoperative infective complications. The mean or median values of IL-6 and CRP were taken for each study and the mean value was calculated for each anaesthetic group at sampling points of 12–24 and 24–72 hours for IL-6 and, CRP respectively.

5.3.2 The Effect of General Anaesthesia on the Postoperative SIR

In total, 12 studies compared different types of general anaesthetic (GA) agents (intravenous or inhalational) on the postoperative SIR (**Table 5.1**). The mean peak IL-6 and CRP were 484 pg/mL (n=425) and 107 mg/L (n=195) respectively. Note: The mean peak IL-6 was 86 pg/mL if the study of Li et al., is excluded from the results.

5.3.3 Studies Comparing Inhalational Anaesthetic Drugs

One study with minor severity of surgery (n = 40) reported no significant effect on the mean peak IL-6 when halothane plus nitrous oxide was compared with isoflurane plus nitrous oxide for maintenance of anaesthesia after induction with propofol and fentanyl (30 pg/mL versus 31 pg/mL, P-value not given) (Helmy and Al-Attiyah, 2000).

5.3.4 Studies Comparing Total Intravenous Anaesthesia (TIVA) to Inhalational

Six studies (Schneemilch et al., 2005, Kvarnstrom et al., 2012, Mazoti et al., 2013, Sayed et al., 2015, Ke et al., 2008, Margarit et al., 2014) with 272 patients compared the use of TIVA to inhalational anaesthesia and measured IL-6 at 12 to 24 hours after surgery (**Figure 5.2.1**). On meta-analysis using a random effects model, TIVA was associated with a non-significant difference in IL-6 concentration (mean difference = −1.35, 95% CI–7.02 9.72, P = 0.75). There was a wide variation in heterogeneity between studies (I^2 = 94%, P <0.00001).

Three studies (Sayed et al., 2015, Yoo et al., 2014, Nakanuno et al., 2015) with 172 patients compared the use of TIVA to inhalational anaesthesia and measured CRP at 24 to 48 hours after surgery (**Figure 5.3.1**). On meta-analysis using a random effects model, TIVA was associated with a significant difference in CRP concentration (mean difference = −43.24, 95% CI–84.72, −1.76, P = 0.04). There was a wide variation in heterogeneity between studies (I^2=100%, P <0.00001).

Of note, patients in the study by Nakanuno et al received postoperative sedation with either propofol or midazolam resulting in longer duration of drug administration than in other studies where anaesthetic agents were only administered during surgery. If this study is removed from the meta-analysis, TIVA is associated with a non-significant difference in CRP concentration.

5.3.5 Studies Comparing Drugs Used in TIVA

One study in emergency orthopedic surgery (n = 60), reported a significant reduction of the mean peak IL-6 in patients given TIVA using etomidate versus TIVA with propofol (3240 pg/mL versus 9000 pg/mL, P = 0.001) (Li et al., 2017). It should be noted that etomidate inhibits the conversion of 11-deoxycortisol to cortisol resulting in transient HPA axis

suppression. Another study in patients undergoing esophagectomy (n = 30), reported a significant reduction of the mean peak IL-6 in patients given TIVA using dexmedetomedine compared to TIVA with propofol (180 pg/mL versus 310 pg/mL, P <0.05) (Jiang et al., 2016). In a further study (n = 23), a significant reduction of the mean peak IL-6 was observed when dexmedetomedine was added to propofol TIVA compared with propofol TIVA alone in mini-cardiopulmonary bypass surgery (130 vs 160 pg/mL, P < 0.0001) although the mean peak CRP was not different in both groups (150 vs 120 mg/L, P > 0.05) (Bulow et al., 2016).

5.3.6 The Effect of Regional Anaesthesia/Analgesia on the Postoperative SIR

A total of 24 studies including 1034 patients compared the effects of different regional or neuraxial anaesthetic or analgesic techniques on the postoperative SIR (**Tables 5.2.1 and 5.2.2)**.

5.3.7 Studies comparing regional anaesthetic techniques in patients also receiving general anaesthesia

One study in colonic resection compared thoracic epidural to intravenous lidocaine and a placebo control group in patients undergoing GA with desflurane maintenance for colonic surgery, finding a significant difference in IL-6 concentration 12 hours after surgery (P <0.0001) with the lowest in the epidural group (14 pg/mL), followed by the IV lidocaine group (20 pg/mL) and the highest in the placebo control group (29 pg/mL) (Kuo et al., 2006).

Only one study, in patients undergoing laparoscopic colorectal resection, (n =120) compared the combination of GA plus spinal anaesthesia (bupivacaine and diamorphine) to GA plus postoperative patient-controlled analgesia (PCA) with morphine and did not show any significant effect on the mean peak CRP (42 mg/L versus58 mg/L, P-value not given)

(Day et al., 2015). In addition, a single study in cardiac surgery (n = 30), compared GA with or without intercostal nerve block, reporting significantly lower peak IL-6 in the combined intercostal / GA group (2200 pg/mL versus 1300 pg/mL, P < 0.001) (Zhan et al., 2017).

One randomized study (n = 60) compared the effect of four different anaesthetic techniques on the inflammatory response to cardiac surgery with CPB. All patients received TIVA with Propofol plus either; alfentanil infusion; high dose remifentanil infusion; low dose remifentanil infusion; or low dose remifentanil infusion plus thoracic epidural. An increase in the mean peak IL-6 was seen in the group receiving low dose remifentanil infusion plus thoracic epidural (P = 0.006), although the mean peak difference of CRP was not statistically significant between the groups (Heijmans et al., 2007). A further study in patients undergoing laparoscopic cholecystectomy under GA (n=60), reported no significant difference in mean peak IL-6 when four different thoracic epidural analgesia regimens were compared; saline; fentanyl; fentanyl plus bupivacaine; or fentanyl plus levobupivacaine (P-value not given) (Ozcan et al., 2016).

Twelve studies (Brix-Christensen et al., 1998, Yokoyama et al., 2005, Moselli et al., 2011, Hadimioglu et al., 2012, Gasiunaite et al., 2012, Ezhevskaya et al., 2013, Fant et al., 2013, Fares et al., 2014, Xu et al., 2014, Gu et al., 2015b, Atia and Abdel-Rahman, 2016, Salem et al., 2017) with 529 patients compared the use of epidural anaesthesia in combination with GA to GA alone or with postoperative patient controlled parenteral opiates and measured IL-6 20 to 24 hours after surgery (**Figure 5.2.2**). On meta-analysis using a random effects model, epidural was associated with a non-significant difference in IL-6 concentration (mean difference =4.16, 95% CI -4.83-13.15, P= 0.36). There was a wide variation in heterogeneity between studies (I^2= 94%, P < 0.00001).

Seven studies (281 patients) (Brix-Christensen et al., 1998, Yokoyama et al., 2005, Gasiunaite et al., 2012, Palomero Rodriguez et al., 2008, Papadima et al., 2009, Chen et al., 2015, Sidiropoulou et al., 2016) compared the use of epidural anaesthesia in combination with GA to GA alone or with postoperative patient controlled parenteral opiates and measured CRP 24 to 72 hours after surgery (**Figure 5.3.2**). On meta-analysis using a random effects model, epidural was associated with a non-significant difference in CRP concentration (mean difference= −14.62, 95% CI -37.60-8.35, P =0.21). There was a wide variation in heterogeneity between studies (I^2= 95%, P <0.00001).

5.3.8 Studies Comparing General Anaesthesia with Central Neuraxial Anaesthesia

One study in patients undergoing hemorrhoidectomy (n = 58), showed no significant difference of the mean peak CRP when "saddle block" spinal anaesthesia without GA was compared to GA (18 mg/L versus 15 mg/L, P = 0.531) (Buyukkocak et al., 2006). In another study of patients undergoing major lower limb surgery (n = 60), there were no significant difference of the mean peak CRP in patients given epidural anaesthesia without GA versus GA (62.1 mg/L versus 64.1 mg/L, P =0.917) (Kahveci et al., 2014).

5.3.9 Studies Comparing Central Neuraxial Anaesthetic Techniques Without GA

A single study in patients undergoing total knee arthroplasty (n = 56) reported no significant difference of the mean peak IL-6 (0.67 pg/mL versus 0.73 pg/mL, P = 0.626) and CRP at 24 hours (5.5 mg/L versus 6.2 mg/L, P= 0.443) when spinal anaesthesia was compared to epidural anaesthesia (Chloropoulou et al., 2013).

5.3.10 The Effect of Miscellaneous and Adjuvant Drugs with General and Regional Anaesthesia on the Postoperative SIR

The addition of some adjuvant drugs with general and regional anaesthesia may play a role in mitigating the inflammatory mediators. Sixteen studies were included with the results shown in **Table 5.3**.

5.3.11 Studies of Cyclo-Oxygenase Inhibitors Administered Perioperatively

Two studies reported the impact of cyclo-oxygenase (COX) 2 inhibitors. In the first study (n = 120), a single dose of IV parecoxib 40 mg was administered in patients who had undergone percutaneous nephrolithotomy on the day of surgery followed by 40 mg every 12 hours for 48 hours demonstrating significant reduction of the mean peak IL-6 (17 pg/mL versus 26 pg/mL, $P < 0.05$) and CRP (19.7 mg/L versus 28.6 mg/L, $P < 0.05$) (Huang et al., 2016). In the second study, 37 patients undergoing total knee replacement were randomized to receive pre-operative oral rofecoxib or placebo one hour before surgery. Both groups received GA plus epidural during surgery with patient controlled epidural analgesia postoperatively. Mean peak IL-6 was reduced significantly in the rofecoxib group (38 pg/mL versus 63 pg/mL, $P < 0.05$) (Feng et al., 2008).

5.3.12 Studies Comparing Opioid Regimens as Part of GA

Two studies reported the impact of different opioids during and after anaesthesia on the postoperative systemic inflammatory response. In the first study (n = 113), there was a significant reduction in the mean peak IL-6 in those treated with oxycodone versus sufentanil in patients undergoing resection of rectal carcinoma under TIVA (43 pg/mL versus 55 pg/mL, $P < 0.05$) (Liu et al., 2017). In the second study (n = 92), IV nalbuphine was associated with a significantly lower mean peak IL-6 when administered prior to induction of anaesthesia in patients underwent to thoracoscopic lobectomy (126.49 pg/mL versus 153.36 pg/mL, $P < 0.001$) (Zhang et al., 2017b).

5.3.13 Studies of Ketamine Administered as an Analgesic Adjunct

Three studies (Roytblat et al., 1998, Cho et al., 2009, Luggya et al., 2017) with 120 patients compared the use of ketamine to either placebo or opiates during GA and measured IL-6 at 24 hours after surgery (**Figure 5.2.3**). On meta-analysis using a fixed effects model, ketamine was associated with a non-significant difference in IL-6 concentration (mean difference = −2.25, 95% CI -81.69-77.18, P = 0.96). There was minimal heterogeneity between studies (I^2 = 3%, P = 0.36).

Two studies (Cho et al., 2009, Welters et al., 2011) with 178 patients compared the use of ketamine to either placebo or opiates during GA and measured CRP at 24 hours after surgery (**Figure 5.3.3**). On meta-analysis using a fixed effects model, ketamine was associated with a significant difference in CRP concentration (mean difference = 0.74, 95% CI 0.65–0.83, P <0.001). There was minimal heterogeneity between studies (I^2 =0%, P = 0.94).

5.3.14 Other/Miscellaneous

Six studies investigated the impact of other / miscellaneous adjuvant drugs on the postoperative SIR during GA. In a study of 40 patients randomized to receive IV pentoxyphylline infusion or placebo before GA for colorectal surgery, mean peak IL-6 levels were reduced when compared with control (20 pg/mL versus 35.5 pg/mL, P <0.0001) (Lu et al., 2004). In patients undergoing laparoscopic gastrectomy (n=39), those who received a clinical dose of the beta blocker esmolol had a lower mean peak CRP versus placebo (24 mg/L versus 59 mg/L, P =0.043) (Kim et al., 2015).

In a study comparing prostaglandin E1 (PGE1) to placebo (n=14), there was a significant reduction of the mean peak IL-6 when a small dose of PGE1 was added during anaesthesia (33 pg/mL versus 67 pg/mL, P <0.05) (Nakazawa et al., 2004). In a study of cardiac

surgery on cardiopulmonary bypass (n =24), there was no significant difference in the mean peak IL-6 (52 pg/mL versus 45.72 pg/mL, P <0.01) and CRP (99.3 mg/L versus 105.1mg/L, P <0.01) between patients who received amiodarone versus control (Rahman et al., 2009). In another cardiac surgery study (n = 81), there was no significant difference in the mean peak IL-6 (100 pg/mL versus 106 pg/mL, P= 0.17) and CRP (111.5mg/L versus 118 mg/L, P= 0.11) between patients who received IV selenium before induction of anaesthesia and placebo (Sedighinejad et al., 2016a). Finally, a further study of patients requiring cardiopulmonary bypass (n = 37) which compared a short infusion of dexmedetomedine to placebo for 10 minutes after aortic cross clamp during CBP in addition to TIVA with propofol reported a significant association with lower peak IL-6 concentrations in the treatment arm (20 pg/mL versus 56 pg/mL, P = 0.0026). Of note, both groups received 1 g methylprednisolone during surgery (Ueki et al., 2014).

5.3.15 Epidural Adjuncts

Two studies reported the impact of adjuvant drugs used in epidural infusions on the postoperative SIR. The first study compared epidural using ropivacaine and morphine with the addition of clonidine during GA to epidural ropivacaine and morphine without clonidine in patients undergoing colorectal surgery, reporting a significantly reduced mean peak IL-6 in the treatment group (n = 40) (11.5 pg/mL versus 17 pg/mL) (Wu et al., 2004). In a further study in patients undergoing open gynecological surgery (n = 40), there was no significant difference in mean peak IL-6 when different doses of epidural neostigmine were administered before induction of GA (Masaki et al., 2004).

5.4 The effect of regional and general anaesthetic techniques on postoperative complications

Fourteen studies including 1755 patients reported the impact of general and regional anaesthetic techniques on postoperative complications across a variety of surgical specialities and severities (**Table 5.4**).

5.4.1 Infective Complications

Eight studies (Moselli et al., 2011, Fares et al., 2014, Chen et al., 2015, Yeager et al., 1987, Jayr et al., 1993, Scott et al., 2001, Svircevic et al., 2011, Tyagi et al., 2017) with 1446 patients compared the use of epidural anaesthesia in combination with GA to GA alone and reported rates of infective complications after surgery (**Figure 5.4.1**). On meta-analysis using a random effects model, epidural was associated with a non-significant difference in infective complications (OR=0.98, 95% CI 0.49–1.95, P= 0.94). There was a wide variation in heterogeneity between studies (I^2 = 69%, P = 0.002).

Four studies (Nakanuno et al., 2015, Lee et al., 2012, Liu et al., 2016, Markovic-Bozic et al., 2016) with 166 patients compared the use of anaesthetic maintenance with TIVA to inhalational agents and reported rates of infective complications after surgery (**Figure 5.4.2**). On meta-analysis using a random effects model, TIVA was associated with a non-significant difference in infective complications (OR = 0.47, 95% CI 0.14 –1.56, P= 0.21). There was minimal heterogeneity between studies (I^2 =0%, P= 0.82).

5.4.2 Lower Respiratory Tract Infection

Six studies (Moselli et al., 2011, Fares et al., 2014, Yeager et al., 1987, Jayr et al., 1993, Scott et al., 2001, Svircevic et al., 2011) with 166 patients compared the use of epidural anaesthesia in combination with GA to GA and reported rates of lower respiratory tract infection after surgery (**Figure 5.5**). On meta-analysis using a random effects model,

epidural was associated with a non-significant difference in lower respiratory tract infections (OR = 0.60, 95% CI 0.28–1.26, P = 0.17). There was a wide variation in heterogeneity between studies heterogeneity (I^2 = 73%, P = 0.002).

5.4.3 Anastomotic Leak

Four studies (Moselli et al., 2011, Fares et al., 2014, Chen et al., 2015, Tyagi et al., 2017), 1 in esophagectomy and 3 in colorectal surgery, with 178 patients compared the use of epidural anaesthesia in combination with GA to GA and reported rates of anastomotic leak (**Figure 5.6.1**). On meta-analysis using a random effects model, epidural was associated with a non-significant difference in anastomotic leak (OR = 0.72, 95% CI 0.18–2.79, P = 0.63). There was minimal heterogeneity between studies (I^2=0%, P = 0.41).

Two studies (Nakanuno et al., 2015, Lee et al., 2012) both in esophagectomy, with 68 patients compared anaesthetic maintenance with TIVA to inhalational agents and reported rates of anastomotic leak (**Figure 5.6.2**). On meta-analysis using a random effects model, TIVA was associated with a non-significant difference in anastomotic leak (OR = 0.71, 95% CI 0.06 – 8.56, P= 0.79). There was minimal heterogeneity between studies (I^2 = 37%, P = 0.21).

A single study (n=53) in laparoscopic colorectal surgery compared epidural anaesthesia in combination with GA to GA alone and reported no significant difference in anastomotic permeability (11.5% versus 14.8%, P >0.05) (Gasiunaite et al., 2012).

5.4.4 Wound Infection

One study (n = 58) comparing TIVA with propofol to inhalational anaesthesia in laparoscopic hysterectomy for cervical cancer reported no significant difference in wound infection rates, with no wound infection in either group (Liu et al., 2016). A further study (n= 40) comparing TIVA with propofol to inhalational anaesthesia in craniotomy also

reported no significant difference in wound infection rates with 1 wound infection in each group (Markovic-Bozic et al., 2016).

5.4.5 Ileus

A single study (n=35) in colonic cancer resection compared epidural anaesthesia in combination with GA to GA including remifentanil and reported no significant difference in rates of postoperative ileus (2 versus 0, $P > 0.05$) (Moselli et al., 2011). A further study (n=120) in laparoscopic colorectal surgery compared GA plus spinal anaesthesia (bupivacaine and diamorphine) to GA plus postoperative analgesia with PCA morphine, reporting a significant reduction in rates of ileus in the group of patients given spinal opioid (2 versus 11, $P < 0.05$) (Day et al., 2015).

5.5 Discussion

In the present systematic review and meta-analysis, there were 60 randomized controlled, clinical studies that examined the relationship between anaesthesia and the objective markers of the postoperative SIR following surgical operations of varying severity. Most of the studies involved in this review had a small study population (<50 patients per trial arm). The majority of studies measured IL-6 in the postoperative period; however, there was considerable variability in the values reported. In contrast, fewer studies reported CRP values with less variability. Irrespective, the majority of studies did not report a significant difference in the magnitude of the postoperative systemic inflammatory response when different general and regional anaesthetic techniques were compared. Only 14 randomized studies reported the influence of anaesthesia on postoperative infective complications and the results from the present meta-analysis did not find any difference in postoperative complications between different anaesthetic groups.

There is good evidence that both IL-6 and CRP reflect the magnitude of surgical injury (Watt et al., 2015c). For example, laparoscopic surgery, compared with open surgery, is associated with a smaller surgical injury and lower peak IL-6 and CRP. Furthermore, it has been established that there are certain threshold values of CRP that when measured are associated with the development of postoperative infective complications, particularly in colorectal surgery, but increasingly in other surgical specialities (Watt et al., 2017b, McDermott et al., 2015). However, although not routinely measured in clinical laboratories, the majority of studies in the present review examined IL-6 in the postoperative period. It is likely that the peak IL-6 measurement, rather than CRP, was made as it could be sampled earlier in the postoperative period. Therefore, given the relationship between peak CRP and infective complications, it would be important that in future studies peak CRP is measured when anaesthetic regimens are being tested, especially in the context of postoperative complications.

Experimental and clinical studies have long suggested that the choice of anaesthetic agents may influence the immune system, in particular, that some anaesthetic regimens may be associated with less immunosuppression. This is likely to be very important in cancer surgery (Dang et al., 2018). With the enhanced recovery protocols now being used in cancer surgery there is an opportunity to move towards standardized anaesthetic and perioperative care protocols that are known to reduce the magnitude of the postoperative systemic inflammatory response and therefore reduce the relative postoperative immunosuppression, with the aim of reducing postoperative morbidity, and disease recurrence in the context of cancer surgery.

From the results of the present systematic review and meta-analysis it would appear that total intravenous anaesthesia, in particular the use of propofol, was associated with a consistent moderation of the postoperative SIR (CRP not IL-6) in moderate to major severity of surgery. Therefore, it may be that intravenous anaesthetic regimens in moderate to major severity of surgery have the potential to reduce the postoperative SIR. Indeed, it is of interest that there is some experimental evidence that propofol, a GABA receptor agonist, is less immunosuppressive compared with inhalational anaesthesia. For example, it has been reported that propofol preserves NK function, inhibits COX-2 and the production of PGE-2 and pro-inflammatory cytokines such as IL-1, TNF-α and IL-6 (Cassinello et al., 2015, Markovic-Bozic et al., 2016, González-Correa et al., 2008, Piegeler and Beck-Schimmer, 2016, Cruz et al., 2017). In contrast, inhalational anaesthetics such as sevoflurane and isoflurane may increase the pro inflammatory cytokines especially IL-6, inhibit neutrophil function and reduce lymphocyte proliferation (Ke et al., 2008, Lee et al., 2015).

The administration of dexmedetomedine, an alpha 2 receptor agonist, an adjunct to general anaesthesia leads to a significant decrease in plasma concentration of IL-6 but without any

significant effect on CRP level (Li et al., 2015). In addition to the anaesthetic effect of dexmedetomedine, it also exhibits some clinical benefits among them the anti-inflammatory, sedative, analgesic, and anxiolytic effects (Li et al., 2013).

Ketamine, an NMDA receptor antagonist, is thought to have both anti-inflammatory and sedative effects with a suppressive effect of NK cell function and pain transmission (Piegeler and Beck-Schimmer, 2016, Cruz et al., 2017). It produces an analgesic effect in low or small sub-anaesthetic dose. However, the results of meta-analysis reported that the use of ketamine at analgesic doses did not show any significant reduction in IL-6 concentration, but it shows a significant reduction in CRP concentrations.

The efficacy of combining epidural with general anaesthesia as compared with general anaesthetic alone has been reported by multiple clinical studies to maintain postoperative immune function and provide better pain control during perioperative period (Song et al., 2017). Epidural anaesthesia can be associated with negative effects such as hypotension resulting in excessive fluid administration and local complications such as insertion site / epidural infection. However, the results of the present meta-analysis suggest that the use of epidural with general versus general anaesthesia alone has no significant impact on either postoperative IL-6 or CRP.

Some other drugs, used before or after induction of anaesthesia as adjuvant therapy, appear to have a significant effect in reducing the mean peak of IL-6 and CRP. Among these are anti-inflammatory drugs including corticosteroids, NSAIDs, and selective COX-2 inhibitors, and other agents not typically known for their anti-inflammatory effects including nalbuphine, oxycodone, epidural clonidine, pentoxifylline and esmolol. Further work is required to define the role, if any, of these agents in the perioperative period.

The main limitation of this review is the small number of sample size in each arm. In addition, the majority of the studies reported low quality of evidence along with high level of heterogeneity and this may affect the overall summary estimate of the meta-analysis. The severity of surgical injury was variable from mild to moderate to severe, and a variety of different surgical procedures and specialities were included, and this may have had an effect on the efficacy of the anaesthetic agent examined. Patients at higher risk of postoperative complications and patients undergoing higher severity of surgery may be more likely to receive additional anaesthetic techniques such as epidurals resulting in the potential for unmeasured confounding by indication.

In the present systematic review and meta-analysis, we have included timepoints of 24-72 hours for CRP concentration because some of the included studies measured the CRP level from 24-48 hours while the other studies measured the CRP level from 48-72 hours. However, although the 24-72 hours captured all the data in the literature it should be recognised that this may include patients on the upwards trajectory, plateau and downwards trajectory of the post-operative CRP profile and may make some of the results difficult to interpret.

In general, when carrying out such systematic review and meta-analysis the sample size is important since it determines the precision of the estimates and the power of the study to determine whether or not there is a real effect. Therefore, where there were small numbers of studies with few observations then the conclusions that can be made from such a systematic review and meta-analysis is limited. Further studies are required controlling for the anaesthetic agent (s) administered, the severity of surgery and the postoperative biomarker used.

In conclusion, this systematic review and meta-analysis reported the current randomized controlled trials evidence of the association between general anaesthesia, regional

anaesthesia or both combined to moderate the magnitude of the postoperative SIR as well as infective complications. There was a suggestion that TIVA using propofol or ketamine at analgesic doses is associated with a reduction in the magnitude of the postoperative systemic inflammatory response as measured by CRP although not IL6. However, there were no other observed differences in anaesthetic techniques which favoured a reduction in the magnitude of the postoperative SIR and infective complications.

Further, adequately powered studies in patients undergoing moderate / major severity of surgery using postoperative CRP measurements are required to clarify the effect of perioperative anaesthesia on the postoperative SIR and infective complications. Such work is of clinical importance due to the associations between postoperative systemic inflammation and postoperative morbidity

5.6 Figures and Legends

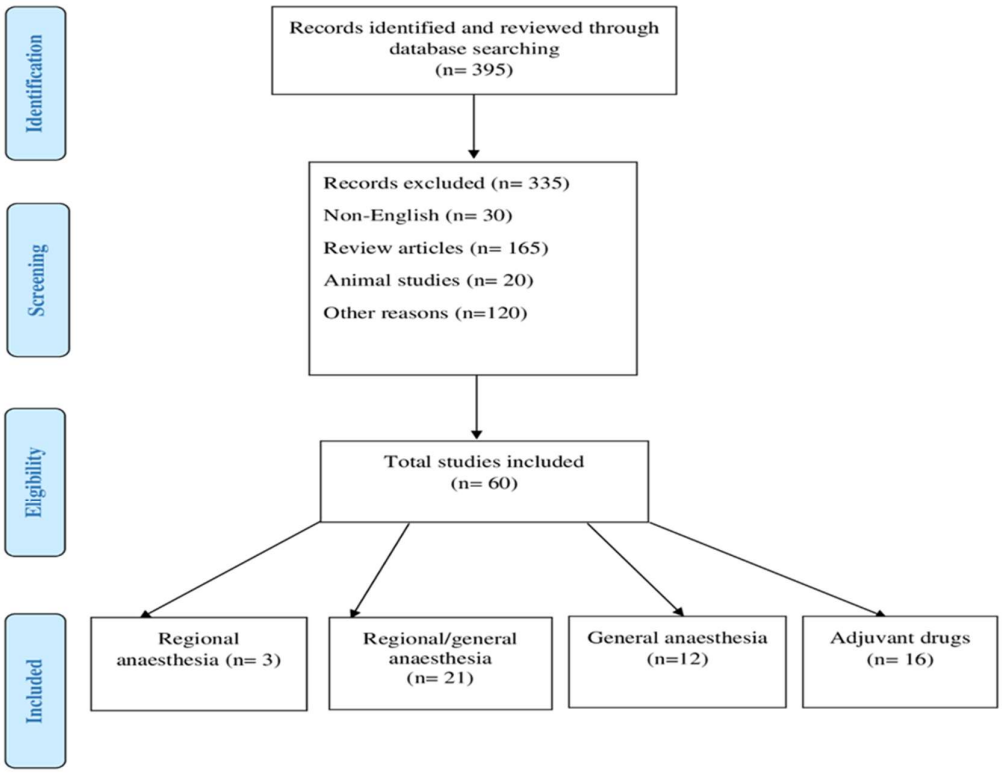
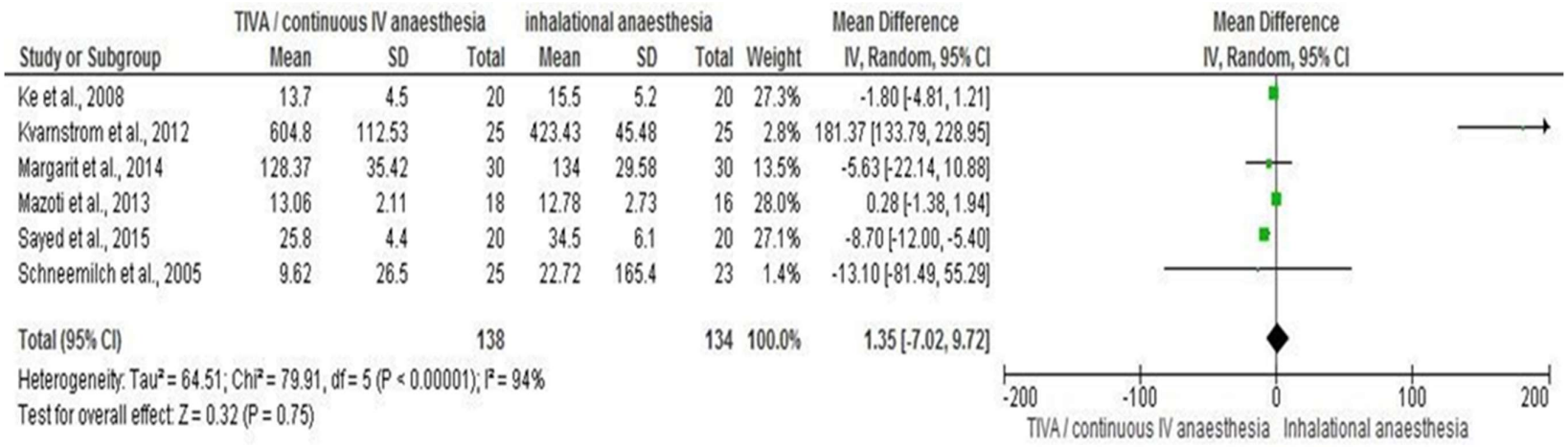


Figure 5.1: Flow diagram chart illustrated the process of article selection. Some studies measured both IL-6 and CRP and showing the postoperative complications and 8 studies showing only the postoperative complications.

1. Total intravenous anaesthesia compared with inhalational anaesthesia.



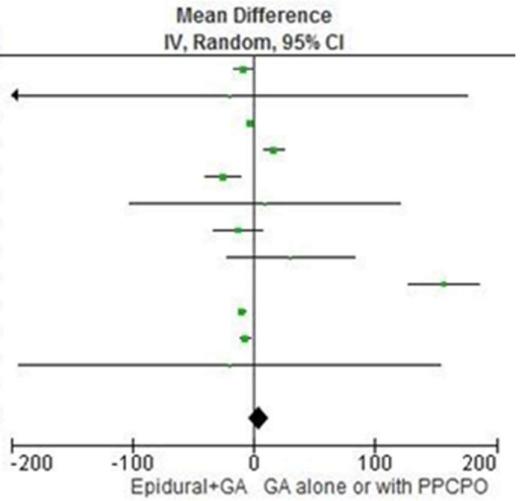
Study or Subgroup	TIVA / continuous IV anaesthesia Mean	SD	Total	inhalational anaesthesia Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ke et al., 2008	13.7	4.5	20	15.5	5.2	20	27.3%	-1.80 [-4.81, 1.21]
Kvarnstrom et al., 2012	604.8	112.53	25	423.43	45.48	25	2.8%	181.37 [133.79, 228.95]
Margarit et al., 2014	128.37	35.42	30	134	29.58	30	13.5%	-5.63 [-22.14, 10.88]
Mazoti et al., 2013	13.06	2.11	18	12.78	2.73	16	28.0%	0.28 [-1.38, 1.94]
Sayed et al., 2015	25.8	4.4	20	34.5	6.1	20	27.1%	-8.70 [-12.00, -5.40]
Schneemilch et al., 2005	9.62	26.5	25	22.72	165.4	23	1.4%	-13.10 [-81.49, 55.29]
Total (95% CI)			**138**			**134**	**100.0%**	**1.35 [-7.02, 9.72]**

Heterogeneity: Tau² = 64.51; Chi² = 79.91, df = 5 (P < 0.00001); I² = 94%
Test for overall effect: Z = 0.32 (P = 0.75)

2. Epidural anaesthesia in combination with general anaesthesia to either general anaesthesia alone or with postoperative patient controlled parenteral opiates.

	Epidural+GA			GA alone or with POCPO				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Atia and Abdul-Rahman, 2016	58	16.5	40	66.9	20	40	13.4%	-8.90 [-16.93, -0.87]
Brix-Christensen et al., 1998	200	210	8	220	190	8	0.2%	-20.00 [-216.24, 176.24]
Ezhevskaya et al., 2013	9	2.12	45	12	4	40	15.0%	-3.00 [-4.39, -1.61]
Fant et al., 2013	51.8	13.7	12	35.27	4.27	14	13.4%	16.53 [8.46, 24.60]
Fares et al., 2014	55.2	24.6	15	80.6	13.7	15	10.9%	-25.40 [-39.65, -11.15]
Gasiunaite et al., 2012	61.7	215.3	26	52.2	197.5	27	0.6%	9.50 [-101.85, 120.85]
Gu et al., 2015	117.3	25.5	15	130	29.8	15	8.7%	-12.70 [-32.55, 7.15]
Hadimioglu et al., 2012	80	103.2	21	50	72.1	25	2.5%	30.00 [-22.41, 82.41]
Moselli et al., 2011	173.5	43.9	18	17.1	43.6	17	5.9%	156.40 [127.40, 185.40]
Salem et al., 2017	31.7	6.5	44	41.3	9	44	14.7%	-9.60 [-12.88, -6.32]
Xu et al., 2014	26.7	6.8	20	33.6	8.3	20	14.4%	-6.90 [-11.60, -2.20]
Yokoyama et al., 2005	310	210	15	330	270	15	0.3%	-20.00 [-193.10, 153.10]
Total (95% CI)			**279**			**280**	**100.0%**	**4.16 [-4.83, 13.15]**

Heterogeneity: Tau² = 139.87; Chi² = 169.45, df = 11 (P < 0.00001); I² = 94%
Test for overall effect: Z = 0.91 (P = 0.36)



3. Ketamine compared with placebo or opiates.

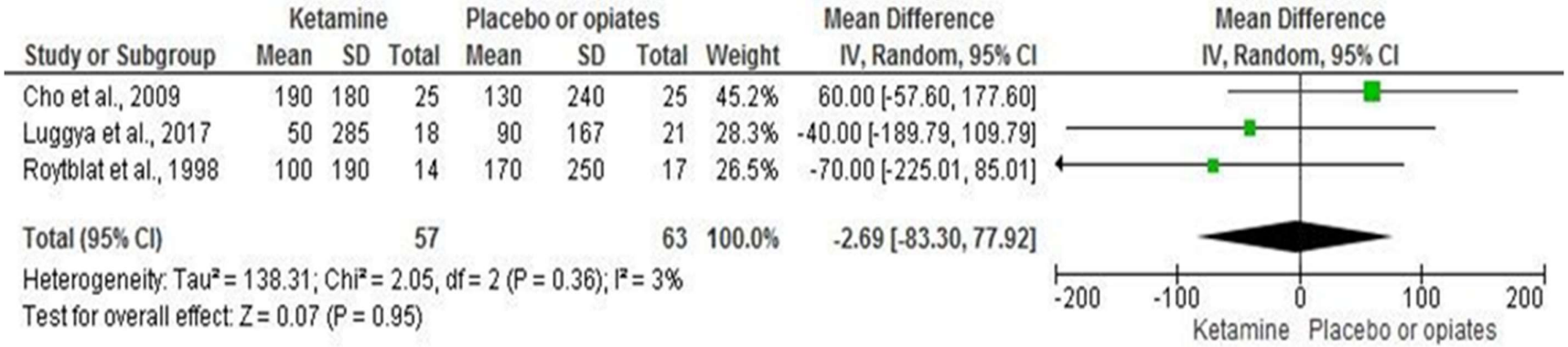
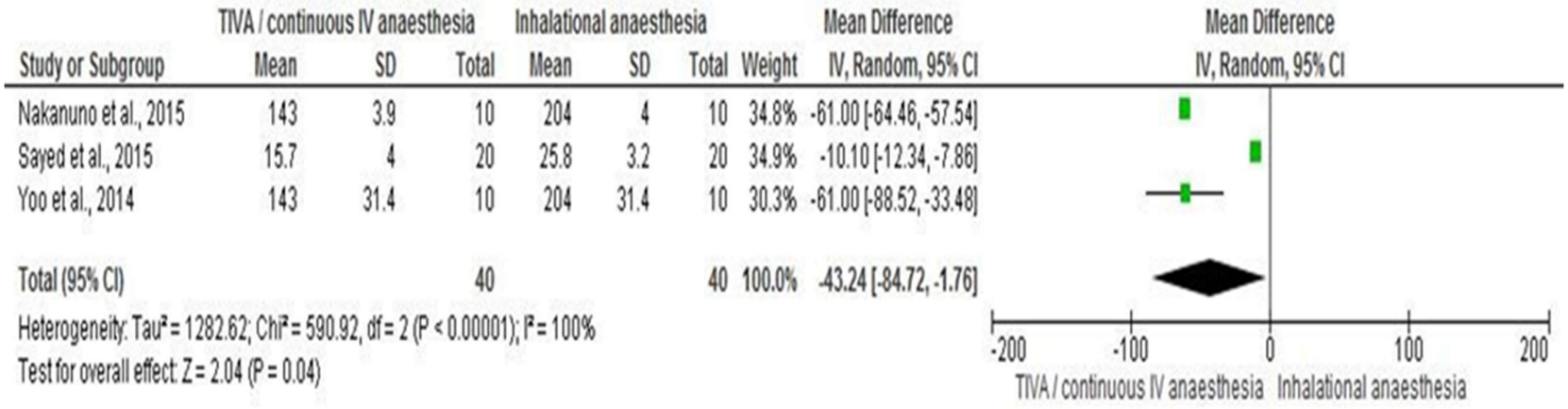


Figure 5.2 : Forest graph of studies that compared the use of different anaesthetics on the plasma level of IL-6 following surgery of varying severity.

1. Total intravenous anaesthesia compared with inhalational anaesthesia.

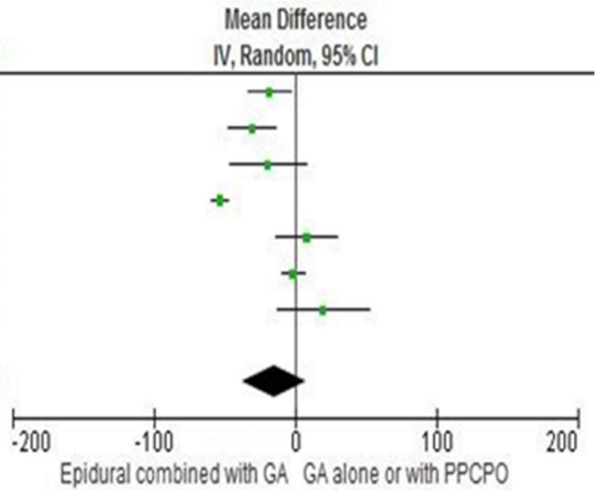


2. Epidural anaesthesia in combination with general anaesthesia to either general anaesthesia alone or with postoperative patient controlled parenteral opiates.

	Epidural combined with GA			GA alone or with PPCPO				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Brix-Christensen et al., 1998	132	17.4	8	150	13	8	14.9%	-18.00 [-33.05, -2.95]
Chen et al., 2015	60	20	26	90	40	27	14.7%	-30.00 [-46.93, -13.07]
Gasiunaite et al., 2012	42.6	26.9	26	62	66.4	27	13.0%	-19.40 [-46.50, 7.70]
Palomero Rodriguez et al., 2008	145	3.32	10	198.1	10.3	12	15.7%	-53.10 [-59.28, -46.92]
Papadima et al., 2009	133.8	34.6	21	125.5	35	19	14.0%	8.30 [-13.30, 29.90]
Sidiropoulou et al., 2016	48.1	11.7	30	49.6	19.6	30	15.6%	-1.50 [-9.67, 6.67]
Yokoyama et al., 2005	90	40	15	70	50	15	12.1%	20.00 [-12.40, 52.40]
Total (95% CI)			136			138	100.0%	-14.62 [-37.60, 8.35]

Heterogeneity: $Tau^2 = 862.87$; $Chi^2 = 124.66$, df = 6 ($P < 0.00001$); $I^2 = 95\%$

Test for overall effect: $Z = 1.25$ ($P = 0.21$)



3. Ketamine compared with placebo or opiates.

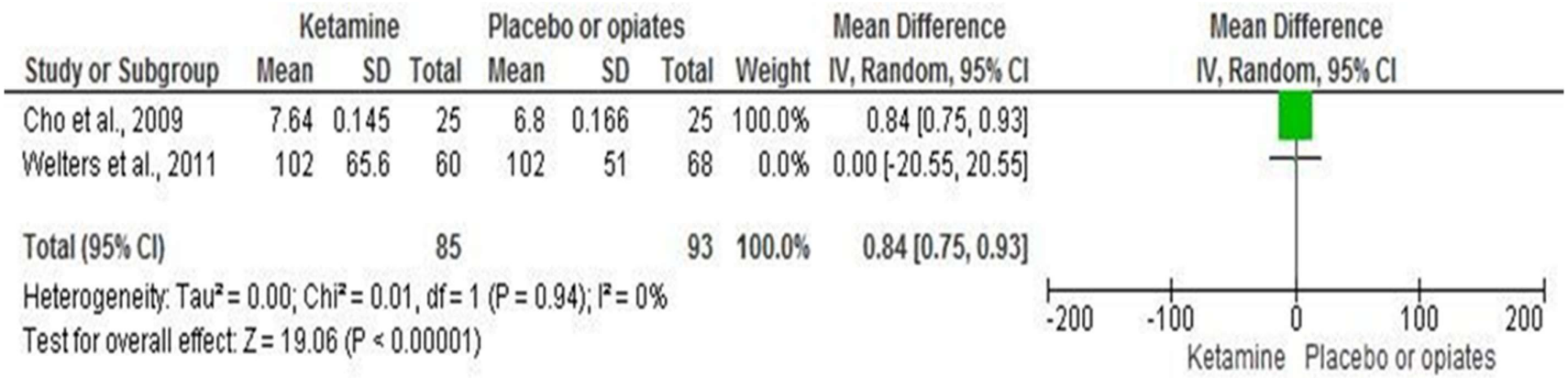
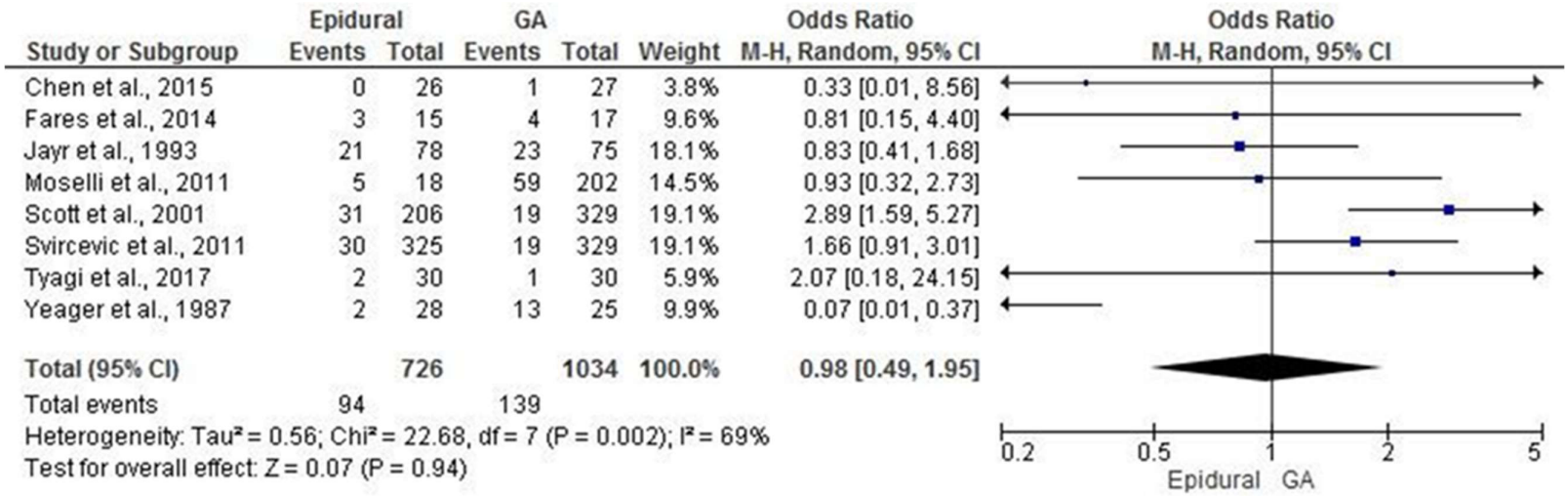


Figure 5.3: Forest graph of studies that compared the use of different anaesthetics on the plasma level of CRP following surgery of varying severity.

1. Forest graph of studies that compared the use of epidural to general anaesthesia and reported rates of infective complications after surgery.



2. Forest graph of studies that compared the use of total intravenous anaesthesia to inhalational anaesthesia and reported rates of infective complications after surgery.

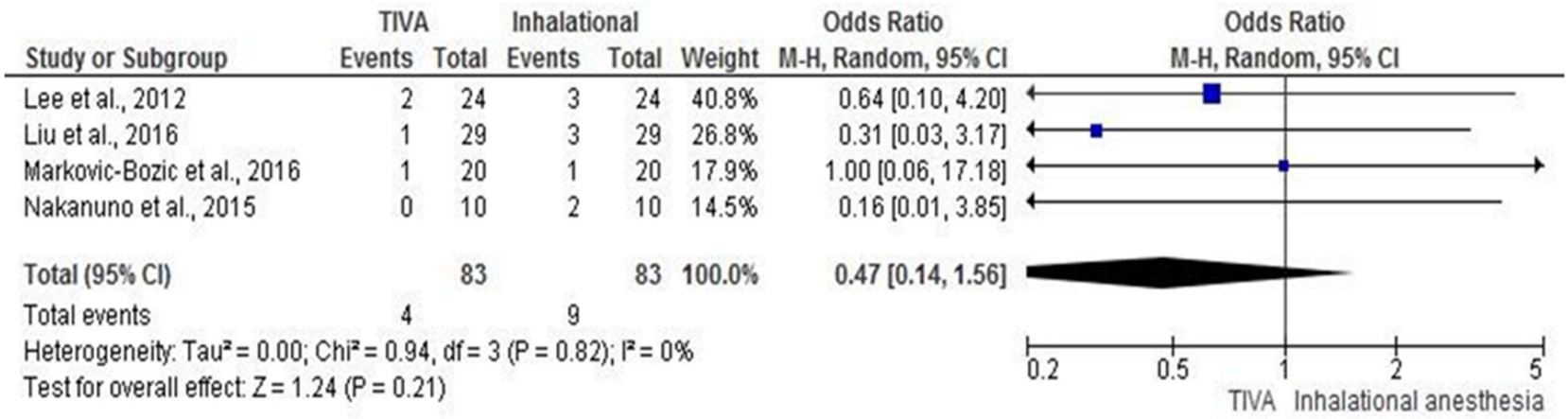


Figure 5.4: Comparison of anaesthetic techniques reporting infective complications after surgery.

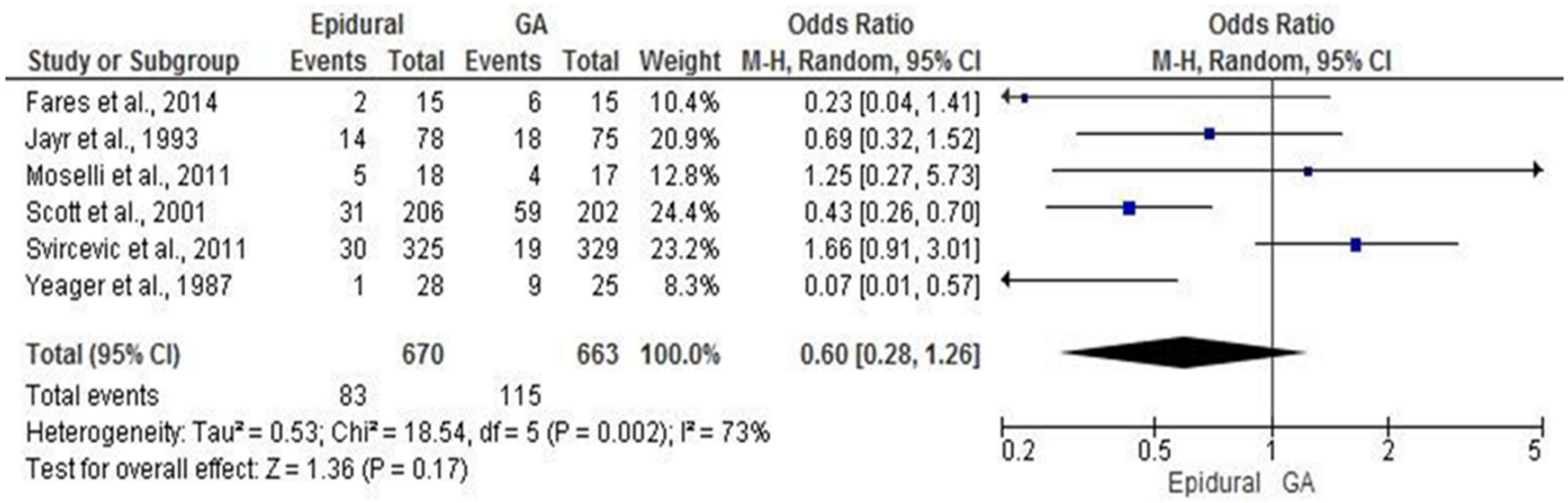
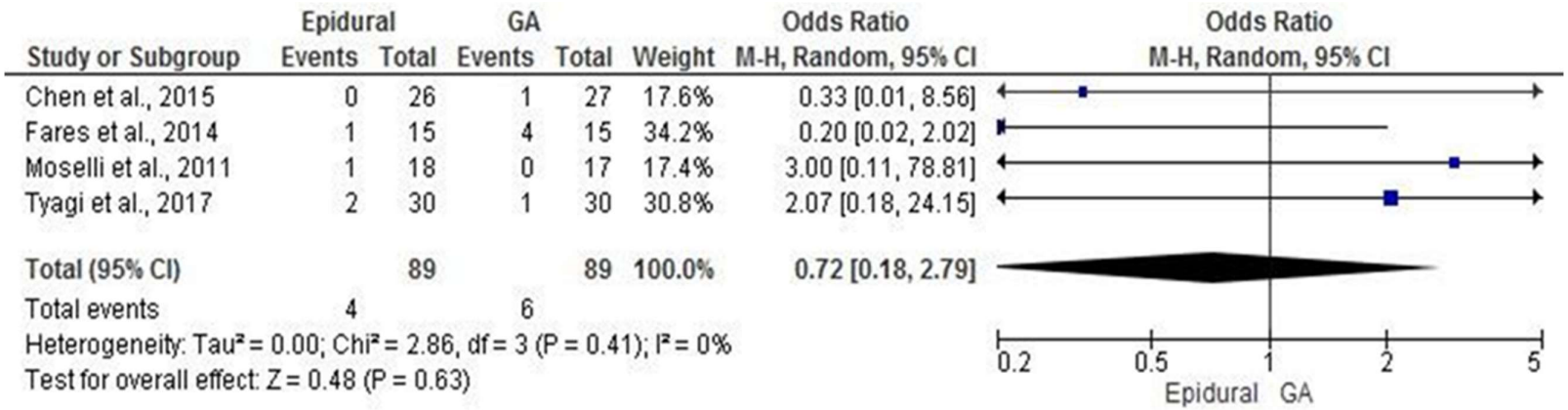


Figure 5.5: Forest graph of studies that compared the use of epidural anaesthesia in combination with general anaesthesia to general anaesthesia and reported rates of lower respiratory tract infection after surgery.

1. Forest graph of studies that compared the use of epidural anaesthesia in combination with general anaesthesia to general anaesthesia.



2. Forest graph of studies that compared the use of total intravenous anaesthesia to inhalational anaesthesia.

Figure 5.6: Comparison of anaesthetic techniques reporting anastomotic leak after surgery.

5.7 Tables and Footnotes

Table 5.1: The relationship between the general anaesthesia and post-operative systemic inflammatory response in patients undergoing different types of surgery in the context of a randomised controlled trial.

No	Author (s) and year	Country	Type of surgery	Severity of surgery	Patients (n)	Anaesthetics used	Inflammatory response marker	Post-operative sampling point	Findings	Comments	Quality of study
1.	(Helmy and Al-Attiyah, 2000)	Egypt	Minor elective surgery.	Minor	40	Halothane group. Isoflurane group.	IL-6*	24 hours	Halothane group, IL-6=30 pg/ml Isoflurane group, IL-6=31 pg/ml	No significant difference between groups.	Low range of quality score.
2.	(Schneemilch et al., 2005)	Germany	Minimal invasive partial diskectomy.	Moderate	48	TIVA§ with propofol and sufentanil compared with BAL§ with sevoflurane.	IL-6	24 hours	TIVA, IL-6=15 pg/ml, P<0.05 BAL, IL-6=35 pg/ml, P<0.05	Significant reduction in IL-6 in TIVA group versus BAL group.	Low range of quality score.
3.	(Ke et al., 2008)	China	Open cholecystectomy.	Moderate	40	TIVA with propofol and remifentanil compared with BAL‖ with isoflurane.	IL-6	12 hours	TIVA group, IL-6= 13.7±4.5 pg/ml, P<0.001 IA group, IL-6=15.5±5.2 pg/ml, P<0.001	Significant reduction in IL-6 in TIVA versus IA group.	Low range of quality score.
4.	(Kvarnstrom et al., 2012)	Sweden	Colorectal cancer.	Moderate	50	TIVA with propofol and remifentanil compared with inhalational anaesthesia with sevoflurane and fentanyl.	IL-6	24 hours	TIVA, 24 hours, IL-6=505 (129.4-1370) pg/ml. Inhalational, 24 hours, IL-6=370 (198-810) pg/ml.	No significant difference between groups.	Low range of quality score.
5.	(Mazoti et al., 2013)	Brazil	Otorhinological surgery.	Minor	34	TIVA with propofol compared with inhaled anaesthesia with isoflurane.	IL-6	24 hours	Propofol, 24 hours, IL-6=22 pg/ml Isoflurane, 24 hours, IL-6=20 pg/ml	No significant difference between groups.	Low range of quality score.
6.	(Yoo et al., 2014)	Korea	Cardiopulmonary bypass surgery.	Major	112	Group P= propofol with sufentanil. Group S=sevoflurane with sufentanil.	CRP†	24 hours	Group P, 24 hours, CRP= 80 (13.108, (1.483-24.733) mg/L, P=0.05 Group S, 24 hours, CRP=120 (13.108,	Significant reduction in CRP in group P versus group S.	Low range of quality score.

									(1.483-24.733) mg/L, P=0.05		
7.	(Margarit et al., 2014)	Romania	Colorectal cancer.	Moderate	60	TIVA with propofol compared with inhalational anaesthesia with isoflurane.	IL-6	24 hours	TIVA+propofol, 24 hours, IL-6=88 (5.8-349) pg/ml, P=0.6 Inhalational, 24 hours, IL-6=101(23-428) pg/ml, P=0.6	No significant difference between groups.	Low range of quality score.
8.	(Sayed et al., 2015)	UK	Cardiopulmonary bypass surgery.	Major	40	Group P = Propofol and fentanyl group. Group I = Isoflurane and fentanyl group.	IL-6 CRP	24 hours 24 hours	Group P, 24 hours, IL-6=25.8 (4.4) pg/ml, P<0.001 Group I, 24 hours, IL-6=34.5 (6.1) pg/ml, P<0.001 Group P, 24 hours, CRP=15.7 (4) mg/L, P<0.001 Group I, 24 hours, CRP=25.8 (3.2) mg/L, P<0.001	Significant reduction in IL-6 in group P versus group I. Significant reduction in CRP in group P versus group I.	High range of quality score.
9.	(Nakanuno et al., 2015)	Japan	Thoracoabdominal esophagectomy.	Major	20	Group P= propofol anaesthesia followed by propofol sedation. Group S= sevoflurane anaesthesia followed by midazolam sedation.	CRP	48 hours	Group P, 48 hours, CRP=143 ±3.9 mg/L, P<0.05 Group S, 48 hours, CRP= 204±4 mg/L, P<0.05	Significant reduction in CRP in group P versus group S.	Low range of quality score.
10.	(Jiang et al., 2016)	China	Open esophagectomy	Major	30	TIVA with propofol compared with dexmedetomedine.	IL-6	24 hours	TIVA+propofol, 24 hours, IL-6= 310 pg/ml, P<0.05 Dexmedetomedine, 24 hours, IL-6=180 pg/ml	Significant reduction in IL-6 in dexmedetomedine group versus TIVA+Propofol group.	Low range of quality score.
11.	(Bulow et al., 2016)	Brasil	Mini-cardiopulmonary bypass surgery.	Major	23	TIVA + DEX ‡ group= Propofol, sufentanil and DEX. TIVA group= propofol and sufentanil.	IL-6 CRP	24 hours 24 hours	TIVA + DEX group, 24 hours, IL-6= 130 pg/ml, P<0.0001 TIVA group, 24 hours, IL-6=160 pg/ml, P<0.0001 TIVA + DEX group, 24 hours, CRP= 150 mg/L	Significant reduction in IL-6 in TIVA + DEX group versus TIVA group. No significant difference between groups.	High range of quality score.

									TIVA group, 24 hours, CRP=120 mg/L		
12.	(Li et al., 2017)	China	Tibial fracture surgery.	Moderate	60	Control group= patients received propofol with remifentanil. Etomidate group= patients received etomidate with remifentanil.	IL-6	24 hours	Control, 24 hours, IL-6=9000 ±0.48 pg/ml, P=0.001 Etomidate, 24 hours, IL-6=3240 ±1.24pg/ml, P=0.001	Significant reduction in IL-6 in etomidate group versus control group.	Low range of quality score.

* IL-6=Interleukin 6, † CRP=C-reactive protein, ‡ DEX = dexmedetomedine, § TIVA=total intravenous anaesthesia, || BAL=balanced inhalational anaesthesia.

Table 5.2: The relationship between combined general and regional or neuraxial anaesthesia/analgesia and general anaesthesia alone (including postoperative intravenous opiate analgesia) on the post-operative systemic inflammatory response in patients undergoing different types of surgery in the context of a randomised controlled trial.

No	Author (s) and year	Country	Type of surgery	Severity of surgery	Patients (n)	Anaesthetics used	Inflammatory response marker	Post-operative sampling point	Findings	Comments	Quality of study
1.	(Brix-Christensen et al., 1998)	Denmark	Coronary artery bypass grafting surgery.	Major	16	Group I=TEA‡ combined with inhalational anaesthesia. Group II= high dose fentanyl group.	IL-6* CRP†	24 hours 48 hours	Group I, IL-6=200 pg/ml. Group II= IL-6=230 pg/ml. Group I, CRP=132 mg/L (±17.4) Group II= CRP=150 mg/L (±13)	No significant difference between groups. No significant difference between groups.	Low range of quality score.
2.	(Yokoyama et al., 2005)	Japan	Oesophageal cancer.	Major	30	Group E= GA§ with continuous epidural infusion for postoperative analgesia compared with group G= intraoperative GA and postoperative IV morphine infusion.	IL-6 CRP	24 hours 24 and 72 hours	Group E, 24 hours, IL-6= 310 pg/ml Group G, 24 hours, IL-6 = 330 pg/ml Group E, 24 hours, CRP=90 mg/L 72 hours, CRP=100 mg/L Group G, 24 hours, CRP=70 mg/L 72 hours, CRP=100 mg/L	No significant difference between groups. No significant difference between groups.	Low range of quality score.
3.	(Kuo et al., 2006)	Taiwan	Colon cancer.	Moderate	60	Thoracic epidural analgesia with lidocaine compared with IV infusion with lidocaine and control group.	IL-6	12 hours	Control ,12 hours, IL-6= 29 pg/ml, P<0.0001 TEA, 12 hours, IL-6= 14 pg/ml, P<0.0001 IV group, 12 hours, IL-6=20 pg/ml, P<0.0001	Significant reduction in IL-6 in TEA group versus other groups and IV group was better than the control group.	Low range of quality score.
4.	(Heijmans et al., 2007)	Netherlands	Coronary artery bypass surgery.	Major	60	AG= alfentanil group HDRG= high-dose remifentanil group.	IL-6	18 hours	AG, IL-6=0.18 pg/ml, P=0.006 HDRG, IL-6=0.14 pg/ml, P=0.006	Significant increase in IL-6 in TEA group versus other groups.	Low range of quality score.

						LDRG= low-dose remifentanil group. TEA= thoracic epidural analgesia in combination with propofol-TCI technique.	CRP	24,48 and 72 hours	LDRG, IL-6=0.15 pg/ml, P=0.006 TEA, IL-6=0.46 pg/ml, P=0.006 AG, 24 hours, CRP=80 mg/L 48 hours, CRP=170 mg/L 72 hours, CRP=120 mg/L HDRG, 24hours, CRP=70 mg/L 48 hours, CRP=180 mg/L 72 hours, CRP=120 mg/L LDRG, 24 hours, CRP=80 mg/L 48 hours, CRP=220 mg/L 72 hours, CRP=145 mg/L TEA, 24 hours, CRP=50 mg/L 48 hours, CRP=200 mg/L 72 hours, CRP=135 mg/L	No significant difference between groups.	
5.	(Palomero Rodriguez et al., 2008)	Spain	Coronary artery bypass graft surgery with cardiopulmonary bypass.	Major	22	GA= GA with postop IV morphine infusion TEA with bupivacaine combined with GA.	CRP	24 and 36 hours	GA, 24 hours, CRP=200 mg/L, P=0.047 36 hours, CRP=250 mg/L TEA, 24 hours, CRP= 160 mg/L, P=0.047 36 hours, CRP=200 mg/L	Significant reduction in CRP in TEA group versus GA group.	High range of quality score.
6.	(Papadima et al., 2009)	Greece	Abdominal colectomy.	Major	40	Group G= GA with postop PCA[#] Group C= GA combined with epidural analgesia.	CRP	24 hours	Group G, 24 hours, CRP= 120.40 mg/L (125.53±35.03) Group C, 24 hours, CRP= 139 mg/L (133.87±34.65), P=0.045	Significant increase in CRP in group C versus group G.	Low range of quality score.
7.	(Moselli et al., 2011)	Italy	Colon cancer.	Moderate	35	IEA= GA with intraoperative epidural analgesia compared with IA=	IL-6	24 hours	IEA, 24 hours, IL-6=173.5 pg/ml. IA, 24 hours, IL-6= 171.2 pg/ml.	No significant difference between groups.	Low range of quality score.

						GA with IV analgesia.					
8.	(Hadimioglu et al., 2012)	Turkey	Renal transplantation surgery.	Major	46	Group I= GA alone. Group II= EA|| combined with GA.	IL-6	24 hours	Group I, 24 hours, IL-6=80 pg/ml, P<0.05 Group II, 24 hours, IL-6=50 pg/ml, P<0.05	Significant reduction in IL-6 in group II versus group I.	Low range of quality score.
9.	(Gasiunaite et al., 2012)	Lithuania	Laparoscopic colorectal surgery.	Moderate	53	GA compared with combined GA with EA.	IL-6 CRP	24 hours 24 and 48 hours	GA, 24 hours, IL-6= 52.2 (197.56) pg/ml. EA, 24 hours, IL-6= 61.78 (215.31) pg/ml. GA, 24 hours, CRP=128.6 (0) mg/L 48 hours, 62.07 (66.43) mg/L EA, 24 hours, CRP= 64 (38.47) mg/L 48 hours, 42.62 (26.98) mg/L	No significant difference between groups. No significant difference between groups.	Low range of quality score.
10.	(Ezhevskaya et al., 2013)	Philadelphia	Major spinal surgery.	Major	85	Group E= EA and endotracheal anaesthesia with sevoflurane during surgery and continuous epidural analgesia with ropivacaine, fentanyl and epinephrine after surgery. Group G=GA with sevoflurane and fentanyl and systemically administered opioids after surgery.	IL-6	24 hours	Group E, 24 hours, IL-6=9 pg/ml Group G, 24 hours, IL-6=12 pg/ml	No significant difference between groups.	Low range of quality score.

11.	(Fant et al., 2013)	Sweden	Radical retro-pubic prostatectomy.	Moderate	26	Group E= PCEA[**] received epidural analgesia using LA[¶] during operation and a combination of LA and opioids after operation. Group P= PCIA[#] has IV opioid-based analgesia.	IL-6 CRP	24 hours 24 and 72 hours	Group E, 24 hours, IL-6=35.7 pg/ml, P=0.953 Group P, 24 hours, IL-6=29.1 pg/ml, P=0.953 Group E, 24 hours, CRP= 69 (36) mg/L, P=0.907 72 hours, CRP=98 (68) mg/L, P=0.515 Group P, 24 hours, CRP=67 (25) mg/L, P=0.907 72 hours, CRP=112 (32) mg/L, P=0.515	No significant difference between groups. No significant difference between groups.	Low range of quality score.
12.	(Fares et al., 2014)	Egypt	Ivor Lewis esophagectomy	Major	30	Group I= GA and postoperative PCA[#] morphine Group II= Thoracic epidural analgesia combined with GA.	IL-6	20 hours	Group I, 20 hours, IL-6=80.6±13.7, P=0.033 Group II, 20 hours, IL-6=55.2±24.6, P=0.033	Significant reduction in IL-6 in group II versus group I.	Low range of quality score.
13.	(Xu et al., 2014)	China	Colon cancer.	Moderate	40	PEA = Thoracic propofol epidural anaesthesia GA with PCA IV sufentanil	IL-6	24 hours	TPEA, 24 hours, IL-6=26.75 (6.84) pg/ml, P=0.007 GA, 24 hours, IL-6=33.60 (8.32) pg/ml, P=0.007	Significant reduction in IL-6 in TPEA versus GA group.	Low range of quality score.
14.	(Day et al., 2015)	UK	Laparoscopic colorectal surgery.	Moderate	120	PCA compared with spinal analgesia.	IL-6	24 hours	PCA, 24 hours, IL-6=58 pg/ml, Spinal, 24 hours, IL-6=42 pg/ml	No significant difference between groups.	Low range of quality score.
15.	(Chen et al., 2015)	China	Colon cancer.	Moderate	53	G = GA with postoperative PCIV opiate E = GA combined with EA.	CRP	48 hours	GA,48 hours, CRP=90 mg/L, P<0.01 Epidural, 48 hours, CRP= 65 mg/L, P<0.01	Significant reduction in CRP in EA group versus GA group.	Low range of quality score.
16.	(Gu et al., 2015b)	China	Oesophageal carcinoma undergoing thoracic surgery.	Major	57	Group I = GA+PCIA Group II= GA+PCEA Group III=GA+TEA+PCIA	IL-6	24 hours	Group I, 24 hours, IL-6=140±56.3 pg/ml, P=0.46 Group II, 24 hours, IL-6=128.7±29.7 pg/ml,	No significant difference between groups.	Low range of quality score.

						Group IV= GA+TEA+PCEA			Group III, 24 hours, IL -6=130±29.8pg/ml, P=0.46 Group IV, 24 hours, IL-6=117.3±25.5 pg/ml, P=0.46		
17.	(Sidiropoulou et al., 2016)	Greece	Laparoscopic cholecystectomy.	Minor	60	GA compared with lumbar epidural anaesthesia and GA.	CRP	24 hours	GA, 24 hours, CRP = 49.68±19.69 mg/L EGA, 24 hours, CRP = 48.15±11.73 mg/L	No significant difference between groups.	High range of quality score.
18.	(Atia and Abdel-Rahman, 2016)	Egypt	Major abdominal surgery.	Major	80	Group I= combined TIVA with TEA. Group II= GA with TIVA[††]	IL-6	24 hours	Group I, IL-6, 24 hours=58 ±16.59 pg/ml, P=0.033 Group II, IL-6, 24 hours=66.93 ±20.06 pg/ml, P=0.033	Significant reduction in IL-6 in group I versus group II.	Low range of quality score.
19.	(Ozcan et al., 2016)	Turkey	Laparoscopic cholecystectomy.	Minor	60	TEA= combination of GA and thoracic epidural analgesia divided into four groups: Group S = saline, Group F=fentanyl, Group B= bupivacaine and group L= levobupivacaine were infused with saline, saline and fentanyl, bupivacaine and fentanyl, and levobupivacaine and fentanyl, respectively via epidural catheter before surgical incision.	IL-6	24 hours	Group S, 24 hours, IL-6=17 pg/ml Group F, 24 hours, IL-6= 17 pg/ml Group B, 24 hours, IL-6=15 pg/ml Group L, 24 hours, IL-6= 14 pg/ml.	No significant difference between groups.	Low range of quality score.
20.	(Zhan et al., 2017)	China	Minimally invasive mitral valve surgery.	Major	30	Group A= patients received intercostal	IL-6	24 hours	Group A, 24 hours, IL-6=1300 pg/ml, P<0.001 Group B, 24 hours, IL-6=2200 pg/ml, P<0.001	Significant reduction in IL-6 in group A versus group B.	Low range of quality score.

						nerve block combined with GA. Group B= patients received GA alone.					
21.	(Salem et al., 2017)	Egypt	Coronary artery bypass graft surgery.	Major	88	GA= GA alone. TEA+GA= thoracic epidural analgesia combined with GA.	IL-6	24 hours	GA, 24 hours, IL-6=41.38 pg/ml TEA+GA, 24 hours, IL-6=31.7 pg/ml	Significant reduction in IL-6 in TEA combined with GA group versus GA group.	High range of quality score.

* IL-6=Interleukin 6, † CRP= C-reactive protein, ‡ TEA= thoracic epidural anaesthesia, § GA= general anaesthesia, || EA= epidural anaesthesia, ¶ LA= local anaesthesia, # PCIA/PCA= patient-controlled intravenous analgesia, ** PCEA= patient-controlled epidural analgesia, †† TIVA=total intravenous anaesthesia.

Table 5.3: The relationship between regional anaesthesia and post-operative systemic inflammatory response in patients undergoing different types of surgery in the context of a randomised controlled trial.

No	Author (s) and year	Country	Type of surgery	Severity of surgery	Patients (n)	Anaesthetics used	Inflammatory response marker	Post-operative sampling point	Findings	Comments	Quality of study
1.	(Buyukkocak et al., 2006)	Turkey	Anorectal Surgery.	Minor	58	ITGA= intratracheal GA[‡] compared with regional (saddle block) anaesthesia.	CRP [†]	24 hours	ITGA, CRP=15.08±14.36 mg/L, P=0.531 Regional, CRP=18.06±21.01 mg/L, P=0.531	No significant difference between groups.	Low range of quality score.
2.	(Chloropoulou et al., 2013)	Greece	Total knee arthoplasty.	Moderate	56	Group A= Spinal anaesthesia followed by IV morphine analgesia. Group B= EA[§] followed by epidural analgesia.	IL-6 [*] CRP	24 hours 24 and 48 hours	Group A, 24 hours, IL-6=0.67 pg/ml Group B, 24hours, IL-6=0.73 pg/ml Group A, 24 hours, CRP=5.5 mg/L 48hours, CRP=93.5mg/L Group B, 24hours, CRP=6.2 mg/L 48 hours, CRP=85.8 mg/L	No significant difference between groups. No significant difference between groups.	Low range of quality score.
3.	(Kahveci et al., 2014)	Turkey	Major lower extremity surgery.	Major	60	Group E= EA group. Group G= standard GA group.	CRP	24 hours	Group E, 24 hours, CRP=62.1±31.2 mg/L, P=0.917 Group G, 24 hours, CRP=64.1 ±38.4 mg/L, P=0.917	No significant difference between groups.	Low range of quality score.

[*] IL-6=Interleukin 6, [†] CRP=C-reactive protein, [‡] GA= general anaesthesia, [§] EA= epidural anaesthesia.

Table 5.4: The relationship between the effects of adjuvant drugs with general anaesthetics on the post-operative systemic inflammatory response in patients undergoing different types of surgery in the context of a randomised controlled trial.

No	Author (s) and year	Country	Type of surgery	Severity of surgery	Patients (n)	Anaesthetics used	Inflammatory response marker	Post-operative sampling point	Findings	Comments	Quality of study
1.	(Roytblat et al., 1998)	Israel	Coronary artery bypass grafting surgery.	Major	31	Control group= large dose of fentanyl. Ketamine group= small dose of ketamine added to GA‡.	IL-6 *	24 hours	Control, IL-6=170 pg/ml. P<0.05 Ketamine, IL-6=100 pg/ml, P<0.05	Significant reduction in IL-6 in ketamine group versus control group.	High range of quality score.
2.	(Wu et al., 2004)	China	Colorectal cancer.	Moderate	40	Control group received only PCEA§ with morphine and ropivacaine. Clonidine group received preoperative epidural clonidine and postoperative PCEA with clonidine+morphine + ropivacaine.	IL-6	12-24 hours	Control, 12 hours, IL-6=25 pg/ml, P<0.0001 24 hours, IL6=9 pg/ml, P<0.0001 Clonidine, 12 hours, IL-6= 16 pg/ml, P<0.0001 24 hours, IL6=7 pg/ml, P<0.0001	Significant reduction in IL-6 in clonidine group versus control.	Low range of quality score.
3.	(Nakazawa et al., 2004)	Japan	Oesophageal cancer surgery.	Major	14	Control group= did not receive PGE1‖ PGE1 group= received IV PGE1 during anaesthesia.	IL-6	24 hours	Control, IL-6=66.7 (35.5-159.3) pg/ml, P<0.05 PGE1, IL-6=32.8 (17.9-86.9) pg/ml, P<0.05	Significant reduction in IL-6 in PGE1 group versus control.	High range of quality score.
4.	(Masaki et al., 2004)	Japan	Lower open abdominal surgery.	Major	40	Different doses of pre-incisional epidural neostigmine with mepivacaine before the induction of GA	IL-6	24 hours	Control, IL-6= 8000 % (0.27±0.10) N-0.05 mg, IL6= 9000 % (0.12±0.04) N-0.1 mg, IL-6=13,000 % (0.40±0.19) N-0.15 mg, IL-6= 13,000 % (0.66±0.37)	No significant difference between groups.	Low range of quality score.

5.	(Lu et al., 2004)	China	Colorectal cancer.	Moderate	40	Pre-incisional IV pentoxifylline compared to control group.	IL-6	12-24 hours	Control, 12 hours, IL-6= 50 pg/ml, P<0.0001 24 hours, IL6= 21 pg/ml, P<0.0001 PTX, 12 hours, IL-6= 23 pg/ml, P<0.0001 24 hours, IL-6=17 pg/ml, P<0.0001	Significant reduction in IL-6 in pentoxifylline group versus control group.	Low range of quality score.
6.	(Feng et al., 2008)	China	Total knee joint replacement surgery.	Moderate	37	Control group= placebo was given 1 hour before surgery. All patients received epidural combined with isoflurane anaesthesia during operation and PCEA postoperatively. Study group=oral rofecoxib 1 hour before surgery.	IL-6	12 hours	Control,12 hours, IL-6=63 pg/ml, P<0.05 Rofecoxib, 12 hours, IL-6=38 pg/ml, P<0.05	Significant reduction in IL-6 in rofecoxib group versus control group.	Low range of quality score.
7.	(Cho et al., 2009)	Korea	Off-pump coronary artery bypass graft surgery.	Major	50	Control group= saline during induction of anaesthesia with sevoflurane. Ketamine group= 0.5 mg kg-1 of ketamine during induction of anaesthesia.	IL-6 CRP†	24 hours 24-48 hours	Control, IL-6=130 pg/ml. Ketamine, IL-6=190 pg/ml. Control, 24 hours, CRP=70 mg/L 48 hours, CRP=150 md/L Ketamine, 24 hours, CRP=73 mg/L 48 hours, CRP=160 mg/L	No significant difference between groups. No significant difference between groups.	High range of quality score.
8.	(Rahman et al., 2009)	Turkey	Cardiopulmonary bypass surgery.	Major	24	Intra-operative amiodarone group compared with control.	IL-6 CRP	24 hours 24 hours	Control, 24 hours, IL-6=45.72±17.35) pg/ml. Amiodarone, 24 hours, IL-6=52.09±4.40) pg/ml Control, 24 hours, CRP=105.13 (105.13±0.57) mg/L	No significant difference between groups. No significant difference between groups.	High range of quality score.

									Amiodarone, 24 hours, CRP=99.25 (99.25±19.27) mg/L		
9.	(Welters et al., 2011)	UK	Coronary artery bypass surgery with cardiopulmonary bypass.	Major	128	Ketamine based anaesthetics compared with standard anaesthesia with propofol and sufentanil.	CRP	24 hours	Ketamine, 24 hours, CRP=102 (65.6) mg/L, P=0.299 Propofol, 24 hours, CRP=102 (51) mg/L, P=0.299	No significant difference between groups.	Low range of quality score.
10.	(Ueki et al., 2014)	Japan	Cardiopulmonary bypass surgery.	Major	37	Group D= Dexmedetomedine group. Group S= Saline group.	IL-6	24 hours	Group D, 24 hours, IL-6=20 pg/ml, P=0.0026 Group S, 24 hours, IL-6=56 pg/ml, P=0.0026	Significant reduction in IL-6 in group D versus group S.	High range of quality score.
							CRP	24,48 and 72 hours	Group D, 24 hours, CRP=52.5 mg/L 48 hours, CRP=72.5 mg/L 72 hours, CRP=53.9 mg/L Group S, 24 hours, CRP=58.9 mg/L 48 hours, CRP=64.7mg/L 72 hours, CRP=39.8 mg/L	No significant difference between groups.	
11.	(Kim et al., 2015)	Korea	Laparoscopic gastrectomy.	Moderate	39	Saline group, were infused with an equal volume of normal saline. Clinical dose group were infused with a loading dose of 0.5 mg/kg esmolol followed by infusion at a constant rate of 30 µg/kg/min, subclinical dose group were infused with a loading dose of 0.25 mg/kg esmolol and followed by constant infusion of 15 µg/kg/min.	CRP	24 hours	Saline, 24 hours, CRP =59 mg/L, P=0.043 Clinical, 24 hours, CRP = 24 mg/L, P=0.043 Subclinical, 24 hours, CRP =44 mg/L	Significant reduction in CRP in clinical dose group versus saline group.	High range of quality score.

12.	(Sedighinejad et al., 2016b)	Iran	Coronary artery bypass graft surgery with cardiopulmonary bypass surgery.	Major	81	Selenium group= IV bolus of 600 µg Se before induction of anaesthesia. Placebo group= normal saline.	IL-6 CRP	24 hours 24 and 48 hours	Selenium, 24 hours, IL-6=100 pg/ml, P=0.17 Placebo, 24 hours, IL-6=106 pg/ml, P=0.17 Selenium, 24 hours, CRP=100 mg/L, P=0.075 48 hours, CRP=123 mg/L, P=0.11 Placebo, 24 hours, CRP=106 mg/L, P=0.075 48 hours, CRP=130 mg/L, P=0.11	No significant difference between groups. No significant difference between groups.	High range of quality score.
13.	(Huang et al., 2016)	China	Percutaneous nephrolithotomy.	Minor	120	Parecoxib group and control group.	IL-6 CRP	24 hours 24, 48 and 72 hours	Control, 24 hours, IL-6=26 pg/ml, P<0.05 Parecoxib, 24 hours, IL-6=17 pg/ml, P<0.05 Control, 24 hours, CRP=24 mg/L, P<0.05 48 hours, CRP=28 mg/L, P<0.05 72 hours, CRP=34 mg/L, P<0.05 Parecoxib, 24 hours, CRP=17 mg/L, P<0.05 48 hours, CRP=19 mg/L, P<0.05 72 hours, CRP=23 mg/L, P<0.05	Significant reduction in IL-6 in parecoxib versus control group. Significant reduction in CRP in parecoxib versus control group.	High range of quality score.
14.	(Zhang et al., 2017b)	China	Thoracoscopic lobectomy.	Major	92	Control group= patients received saline. Nalbuphine HCL group= patients received IV nalbuphine HCL prior to induction of anaesthesia.	IL-6	24 hours	Control group, 24 hours, IL-6=153.36 ±6.77 pg/ml, P<0.001 Nalbuphine HCL group, 24 hours, IL-6=126.49±6.68 pg/ml, P<0.001	Significant reduction in IL-6 in nalbuphine group versus control group.	Low range of quality score.

15.	(Liu et al., 2017)	China	Laparoscopic cholecystectomy.	Minor	113	Control group= patients received sufentanil. Observation group= patients received oxycodone HCL.	IL-6	24 hours	Control, 24 hours, IL-6=55.16±8.05 pg/ml, P<0.05 Observation, 24 hours, IL-6=43.17 ±6.66 pg/ml, P<0.05	Significant reduction in IL-6 in observation group versus control group.	Low range of quality score.
16.	(Luggya et al., 2017)	USA	Abdominal or perineal surgery.	Major	39	Ketamine group and placebo group.	IL-6	24 hours	Ketamine, 24 hours, IL-6 =50 ±285pg/m, P=0.402 Placebo, 24 hours, IL-6 =90±167 pg/ml, P=0.402	No significant difference between groups.	High range of quality score.

* IL-6= Interleukin 6, † CRP= C-reactive protein, ‡ GA= general anaesthesia, § PCEA= patient-controlled epidural analgesia, ‖ PGE1=prostaglandin E1.

Table 5.5: Comparison between different types of anaesthesia on the post-operative infective complications following different types of surgery in the context of a randomised controlled trial.

No	Author (s) and year	Country	Type of surgery	Severity of surgery	Patients (n)	Type of complications	Anaesthetics used	Findings	Comments	Quality of study
1.	(Yeager et al., 1987)	California	Intra-thoracic, intra-abdominal or major (non-cerebral) vascular surgery.	Major	53	* Pneumonia * Sepsis	Group I= EA† and postoperative analgesia. Group II= GA* and parenteral narcotic administration for post-operative pain relief.	Group I, 1 case of pneumonia and one case of sepsis. Group II, 9 cases of pneumonia and 4 cases of sepsis.	Significant reduction in post-operative complications in group I compared with group II.	Low range of quality score.
2.	(Jayr et al., 1993)	France	Major abdominal surgery.	Major	153	* Pulmonary complication.	Group I= GA with IV fentanyl and postoperative analgesia with subcutaneous morphine. Group II= GA combined with epidural bupivacaine and epidural bupivacaine with morphine for postoperative pain relief.	Group I, 23 cases with pulmonary complication. Group II, 21 cases with pulmonary complication.	No significant difference between the groups.	Low range of quality score.
3.	(Scott et al., 2001)	UK	Coronary artery bypass graft surgery.	Major	408	* Lower respiratory tract infection.	Group TEA‡ = GA with perioperative TEA. Group GA= GA with postoperative opioid analgesia.	Group TEA, 31 cases of lower respiratory tract infection. Group GA, 59 cases of lower respiratory tract infection.	Significant reduction in lower respiratory tract infection in TEA group compared with GA group.	High range of quality score.
4.	(Moselli et al., 2011)	Italy	Colon cancer	Moderate	35	* Anastomosis leakage (AL). * Pneumonia * Ileus	IEA= GA with intraoperative epidural analgesia compared with IA= GA with IV analgesia.	IEA group, one case of AL, 5 cases of pneumonia and 2 cases of ileus. IA, no cases of AL or ileus and 4 cases of pneumonia.	No significant difference between the groups.	Low range of quality score.
5.	(Svircevic et al., 2011)	The Netherlands	Cardiac surgery.	Major	654	* Pneumonia	Group I= GA alone. Group II= combined GA and TEA.	Group I, 19 cases of Pneumonia. Group II, 30 cases of Pneumonia.	No significant difference between the groups.	High range of quality score.
6.	(Lee et al., 2012)	South Korea	Ivor Lewis operation for oesophageal cancer.	Major	48	* Anastomosis leakage (AL). * Sepsis	Group S= sevoflurane. Group P= TIVA§ with propofol and remifentanil.	Group S, 1 case of AL and 2 cases of sepsis. Group P, 2 cases of AL with no cases of sepsis.	No significant difference between the groups.	Low range of quality score.

7.	(Gasiunaite et al., 2012)	Lithuania	Laparoscopic colorectal surgery.	Moderate	53	* Anastomotic permeability.	GA compared with combined GA with EA.	GA group, anastomotic permeability is 14.8% GA+EA group, anastomotic permeability is 11.5%	No significant difference between the groups.	Low range of quality score.
8.	(Fares et al., 2014)	Egypt	Ivor Lewis esophagectomy	Major	30	* Anastomosis leakage (AL). * Pneumonia * Septic shock	Group I= GA Group II= Thoracic epidural analgesia combined with GA.	GA group, 4 cases of AL, 6 cases of pneumonia and 2 cases of septic shock. GA+TEA, 1 case of AL, 2 cases of pneumonia and one case of septic shock.	No significant difference between the groups.	Low range of quality score.
9.	(Chen et al., 2015)	China	Colon cancer.	Moderate	53	* Anastomosis leakage (AL). * Wound infection. * Urinary tract infection (UTI).	GA alone compared with GA combined with epidural anaesthesia.	GA group, 1 case of AL, 1 case of wound infection and with no case of UTI. GA+EA, no case of AL, 1 case of wound infection and with no case of UTI.	No significant difference between the groups.	Low range of quality score.
10.	(Day et al., 2015)	UK	Laparoscopic colorectal surgery.	Moderate	120	* Ileus	PCA ‖ compared with spinal analgesia.	PCA group, 11 cases of ileus. Spinal analgesia group, 2 cases of ileus.	Significant reduction in ileus in spinal analgesia compared with PCA.	Low range of quality score.
11.	(Nakanuno et al., 2015)	Japan	Thoraco-abdominal esophagectomy.	Major	20	* Anastomosis leakage (AL).	Group P= propofol anaesthesia followed by propofol sedation. Group S= sevoflurane anaesthesia followed by midazolam sedation.	Group P, no cases with AL. Group S, 2 cases with AL.	No significant difference between the groups.	Low range of quality score.
12.	(Liu et al., 2016)	China	Laparoscopic radical hysterectomy for cervical cancer.	Moderate	58	*Wound infection. *Urinary tract infection (UTI).	Group S= sevoflurane. Group P= TIVA with propofol.	Group S, no cases have shown with wound infection but 3 cases with UTI. Group P, , no cases have shown with wound infection but 1 case with UTI.	No significant difference between the groups.	Low range of quality score.
13.	(Markovic-Bozic et al., 2016)	Slovenia	Craniotomy	Major	40	*Wound infection.	Group P= propofol. Group S= Sevoflurane.	Group P, one case of wound infection. Group S, one case of wound infection.	No significant difference between the groups.	High range of quality score.
14.	(Tyagi et al., 2017)	India	Abdominal laparotomy.	Major	60	*Anastomosis leakage (AL).	TEB group= patients received GA along with thoracic epidural block. GA group= patients received GA alone.	Group TEB, 2 of AL Group GA, 1 of AL.	No significant difference between the groups.	High range of quality score.

*GA= general anaesthesia, † EA= epidural anaesthesia, ‡ TEA= thoracic epidural anaesthesia, § TIVA= total intravenous anaesthesia, ‖ PCA= patient-controlled analgesia.

6. The relationship between anaesthetic technique, clinicopathological characteristics and the magnitude of the postoperative systemic inflammatory response in patients undergoing elective surgery for colon cancer

6.1 Introduction

Surgical resection remains the mainstay of treatment for patients with non-metastatic solid tumours. However, the magnitude of the stress response from surgical injury may lead to alterations in the immune function, neuroendocrine and metabolic responses and in turn may instigate the progression and recurrence of cancer (Diakos et al., 2014).

Routinely, the magnitude of the post-operative SIR, is evidenced by CRP concentration in the blood (Watt et al., 2015c, Gabay and Kushner, 1999). In turn, the magnitude of the post-operative CRP response has been shown to be associated with post-operative complications (Watt et al., 2017b). More recently, a threshold of a CRP >150 mg/L on day 3 or day 4 has been shown to be associated with the development of post-operative complications and greater hospital stay (Straatman et al., 2015). With the establishment of a post-operative CRP threshold, potential factors giving rise to an elevated post-operative CRP are being increasingly identified in operable colorectal cancer. To date the pre-operative factors identified to independently modulate the SIR following surgery include age, ASA grade, BMI, pre-operative mGPS, and most recently preoperative corticosteroids (Watt et al., 2017b, McSorley et al., 2016a) and these should be incorporated into any analysis of the effect of anaesthesia.

A systematic review and meta-analysis in chapter 5, reported that due to the heterogeneity of previous studies, it is not clear whether different anaesthetic approaches modulate the magnitude of the post-operative SIR as evidenced by IL-6 and CRP (Perry et al., 2019,

Alhayyan et al., 2020a). However, the systematic review was not able to account for a number of potential confounding factors, in particular the type of surgery since open and laparoscopic surgical techniques are recognised to be associated with a different magnitude of the SIR (Ramanathan et al., 2015, Watt et al., 2015c).

Regional anaesthesia is an integral component of enhanced recovery programmes which aim to; reduce the perioperative neural and hormonal stress responses, manage pain, optimise post-operative mobilisation, aid return to oral nutrition, and facilitate recovery. The provision of multi-modal, balanced analgesia has the advantage of reducing opioid consumption and associated adverse effects. Whilst epidural analgesia was traditionally considered the gold standard for analgesia in patients undergoing open colorectal surgery, the evolution of minimally invasive surgery in combination with alternative analgesic techniques such as intrathecal opioid administration, abdominal wall blocks, continuous wound infusions and intravenous lignocaine now forms a central component of most accelerated surgical pathways (Gustafsson et al., 2019).

The aim of the present study was to examine the association between different anaesthetic technique, clinicopathological characteristics and the magnitude of the post-operative SIR in patients undergoing elective surgery for colon cancer.

6.2 Patients and Methods

6.2.1 Patients

A prospective database consisted of 543 patients who underwent for elective open or laparoscopic colon cancer resection was retrospectively reviewed in a single surgical unit at Glasgow Royal Infirmary hospital between 2008 and 2016. The total number of patients who had documented anaesthetic regimen was 409; for either open (n=241) or laparoscopic approach (n=168). Only 61 patients received general anaesthesia alone with the remaining 348 receiving general anaesthesia plus a regional anaesthetic technique. Regional anaesthesia was subdivided into four subgroups; (general plus epidural (GA+E) n=156; general plus spinal opioid (GA+Sp) n=91; general plus Transversus Abdominus Plane block (GA+TAP) n=60; general plus local anaesthetic infiltration (GA+LA) n=41. More details on clinical and pathological characteristics including 194 patients with hypertension, 72 diabetics; 24 patients with type 1 diabetes mellitus and 38 patients with type II. In addition, 130 patients received adjuvant therapy while only 10 who received neoadjuvant therapy.

6.2.2 Methods

All data were anonymised, and the emergency cases were excluded from the analysis. All tumours were staged according to TNM staging system (tumour, node and metastasis). The American Society of Anaesthesiologists (ASA) grading system was used to assess patient comorbidity (Fitz-Henry, 2011b). The modified Glasgow Prognostic Score (mGPS) from 0-2, was used to assess the preoperative systemic inflammatory response. Patients with normal CRP concentration (<10 mg/L) scored zero. Patients with high CRP concentration (>10 mg/L) scored 1 and patients with high CRP concentration (>10 mg/L) and hypoalbuminaemia (<35 g/L) scored 2 (McMillan, 2013a). The measurement of post-

operative C-reactive protein (CRP) on the second, third and fourth day was used to assess the magnitude of the postoperative SIR.

Patients' data were collected from a prospective database from January to December 2016 from the academic department of surgery at Glasgow Royal Infirmary hospital. The study was approved by the West of Scotland Research Ethics Committee, Glasgow.

6.2.3 Data analysis

All data were analysed using SPSS version 25.0 for windows (IBM Corporation, Armonk, NY, USA). Analysis of frequency was used to calculate the total numbers of each explanatory variable. The X^2 (Chi-square) statistical method was used to test the statistical significance between the anaesthetic agents, surgical technique and clinicopathological variables. The chi square test was used to examine which anaesthetic group differ significantly on the POD 2 CRP in patients undergoing elective open colon surgery. A p-value of <0.05 was considered statistically significant.

6.3 Results

The clinicopathological data of 409 patients who underwent for elective open or laparoscopic colon cancer surgery were summarized in Table 6.1. The year of operation was divided into two periods; 2008-2012, (n=149) and 2013-2016, (n=260). Patients were divided into two main groups; open surgery (n=241) and laparoscopic surgery (n=168). Patients received either general anaesthesia alone or general anaesthesia plus a regional anaesthetic technique. Preoperative dexamethasone was administered to 104 patients (43%) undergoing open surgery and 129 patients (76%) undergoing laparoscopic surgery.

The majority of patients were younger than 75 years old (40%), male (54%), were normal weight or obese (65%) and underwent open surgery (59%) for colon cancer resection. Regional anaesthesia was administered in 85% of patients, with epidural the most commonly performed technique (38%). Most patients were not systemically inflamed prior to surgery mGPS (78%) and had a CRP <150 mg/L on day 3 (56%) and 4 (67%) following surgery.

The comparison between open versus laparoscopic surgery, anaesthetic technique and clinicopathological data of patients undergoing elective colon cancer surgery is shown in Table 6.1. There was a significant association between surgical approach, anaesthetic technique ($p < 0.001$), year of operation ($p < 0.001$), BMI ($p < 0.01$), ASA grade ($p < 0.01$), POD 2 CRP > 150 ($p < 0.001$), POD 3 CRP > 150 ($p < 0.001$), POD 4 CRP > 150 ($p < 0.05$), preoperative dexamethasone ($p < 0.001$) and overall complications ($p < 0.001$).

The relationship between anaesthetic technique and clinicopathological data of patients undergoing elective open surgery for colon cancer is shown in Table 6.2. There was a significant association between anaesthetic agents and POD 2 CRP > 150 ($p < 0.001$), year of operation ($p < 0.01$), and preoperative dexamethasone ($p < 0.01$).

The relationship between anaesthetic technique and clinicopathological data of patients undergoing elective laparoscopic surgery for colon cancer is shown in Table 6.3. There were no significant associations between anaesthetic agents and clinicopathological characteristics including year of operation ($p = 0.99$), preoperative dexamethasone ($p = 0.70$) and POD 2 CRP ($p = 0.62$).

The relationship between the administration of dexamethasone versus no dexamethasone and clinicopathological variables of patients undergoing elective laparoscopic surgery for colon cancer is shown in Table 6.4. There was a significant association between the administration of preoperative dexamethasone, sex ($p=0.05$), year of operation ($p = 0.002$), POD2 CRP ($p<0.001$), POD3 CRP ($p=0.01$) and any complication ($p=0.04$).

The relationship between each anaesthetic group and POD 2 CRP > 150 mg/L of patients undergoing elective open surgery for colon cancer is shown in Table 6.5. There was a significant association between anaesthetic technique in particular, general + epidural ($p= 0.02$) and general + spinal ($p = 0.01$) with POD 2 CRP > 150 mg/L.

6.4 Discussion

In this retrospective observational study, there was a significant association between type of anaesthesia, and the magnitude of the postoperative day 2 CRP in patients who underwent open but not laparoscopic surgical resection for colorectal cancer. There was a reduction in patients with POD 2 CRP >150 mg/L in the GA+TAP, GA+LA and GA+Sp groups. Patients receiving GA + epidural seemed more likely to have a POD 2 CRP >150 mg/L. Although a number of confounding factors were examined, this may reflect a higher risk patient cohort and confounding by indication. The exact nature of the relationship between type of anaesthesia and post-operative SIR remains unclear and requires further investigation. However, it is clear that the type of anaesthesia is secondary to the effect of surgical approach, in particular laparoscopic surgery on the postoperative SIR.

In the present study, the association between anaesthesia type and post-operative SIR in open colorectal surgery provides new information in an area of clinical uncertainty. To our knowledge, few studies have examined the effect of specific anaesthetic techniques on the post-operative SIR. In particular, the effect of anaesthesia on the post-operative CRP concentration is not clear. Chen and co-workers (2015), in 53 patients undergoing open resection of colon cancer, reported a significant reduction on day 2 post-operative CRP with general plus epidural anaesthesia compared with general anaesthesia (Chen et al., 2015). Papadima and co-workers, in 40 patients receiving open surgery for colon cancer, reported a decrease of post-operative day 2 CRP in patients receiving general anaesthesia compared with epidural analgesia (Papadima et al., 2009). In contrast, Gasiunaite and co-workers, in 53 patients receiving laparoscopic colorectal resection, reported no significant difference in the post-operative CRP concentration on day 2 and 3 in patients receiving general anaesthesia versus general plus epidural anaesthesia (Gasiunaite et al., 2012). Taken together with the present results in 409 patients and given that the magnitude of the

postoperative SIR is greater in open surgery (Watt et al., 2015c), it may be that regional anaesthetic techniques have a greater potential to modulate the magnitude of the postoperative SIR when compared with laparoscopic surgery.

The anaesthetic technique varied with time with a notable increase in spinal opioid analgesia and general anaesthesia without regional analgesia. This is consistent with the evolution of anaesthesia according to ERAS principles. The benefits of epidural analgesia are less apparent in the ERAS setting and may even be disadvantageous in its association with hypotension, urinary retention, failure rates and rare but serious complications such as epidural haematoma and abscess. However, epidural anaesthesia is still recommended in high-risk patient groups, patients with chronic pain and those considered likely to convert to an open procedure (Popping et al., 2014, Borzellino et al., 2016a).

In addition to central neuraxial blockade, other regional anaesthetic techniques including TAP-block or local anaesthetic infiltration, can be used for postoperative pain management in abdominal surgery. A renewed interest in the use of abdominal wall blocks has resulted in a large number of studies examining pain scores and the consumption of opioids after surgery. TAP block remains the most studied of these techniques though evidence remains heterogeneous, and questions remain as to the optimal technique, method of administration, dosage and efficacy in different types of surgery. TAP blocks are recommended by ERAS guidelines in the performance of minimally invasive colorectal surgery (Gustafsson et al., 2019) . However, their effect on the post-operative SIR remains to be defined.

Preoperative adjuvants such as the intravenous administration of dexamethasone, are commonly used in the anaesthetic practice to reduce the postoperative nausea and vomiting. Following abdominal surgery, preoperative use of dexamethasone may significantly reduce the magnitude of the postoperative SIR and postoperative complications (McSorley et al., 2017a, McSorley et al., 2019) though its potential immunosuppressive effects are as yet to be undetermined. To date, dexamethasone has been considered as a part of fast track or

enhanced recovery after surgery (ERAS) (Watt et al., 2015d, McSorley et al., 2016a). Therefore, the administration of dexamethasone represents a potential confounder to any effects of anaesthesia type on the postoperative SIR.

Therefore, anaesthetic practices may vary widely within and across surgical approaches and even within enhanced recovery protocols (McIsaac et al., 2015). Against this background it is difficult to speculate what anaesthetic regimen has the most profound effect on the postoperative SIR. Also, it is difficult to speculate on what mechanism of action may be most efficacious to target to reduce the magnitude of the postoperative SIR. Therefore, it will require prospective examination of anaesthetic practice across multiple institutions to tease out the effects of anaesthesia on the postoperative SIR. Such work will provide the foundations of an evidenced based approach to developing an anaesthetic protocol to be used alongside existing enhanced recovery protocols.

Several limitations to this study need to be acknowledged. Firstly, this study includes patients from a single centre and is subject to the well-described limitations of retrospective analysis. For example, due to the granularity of the data collected retrospectively, it was not possible to account for all the agents that may have been used in the provision of general anaesthesia and that may have influenced the postoperative SIR. Also, it was not possible to correct for all potentially confounding factors in the analysis. Therefore, further prospective work is required to examine the relationship between anaesthetic technique and the magnitude of the postoperative SIR in more detail.

In summary, in the largest study to date and in patients undergoing elective surgery for colon cancer, the anaesthetic approach may affect the magnitude of the postoperative SIR, as evidenced by post-operative CRP concentrations. Further prospective studies are required to confirm these findings.

6.5 Tables and Footnotes

Table 6.1: Demographic characteristics for patients undergoing surgery for elective colon cancer and the comparison between open and laparoscopic surgery for different anaesthetic groups, (n=409).

Characteristic	Number of patients (%)	Open surgery	Laparoscopic surgery	p-value
Age (<65/65-74/>75)	125 (31)/163 (40)/121 (29)	98 (31)/122 (38)/96 (30)	62 (31)/81 (41)/55 (28)	0.68
Sex (male/female)	220 (54)/189 (46)	169 (53)/147 (46)	108 (54)/90 (45)	0.44
BMI (<20/20-25/26-30/>30)	24 (6)/122 (31)/115 (29)/133 (34)	25 (9)/101 (35)/75 (26)/83 (29)	10 (5)/50 (26)/62 (32)/72 (37)	0.005
Year of operation (2008-2012/ 2013-2016)	149 (36)/260 (64)	159 (50)/157 (50)	68 (34)/130 (66)	<0.001
ASA grade (1/2/3/4)	77 (19)/185 (46)/129 (32)/11 (3)	50 (16)/124 (41)/115 (38)/15 (5)	39 (20)/95 (50)/53 (28)/4 (2)	0.007
TNM stage (I/II/III/IV)	89 (22)/166 (41)/135 (34)/13 (3)	60 (19)/128 (42)/101 (33)/18 (6)	50 (26)/71 (37)/69 (36)/2 (1)	0.08
Preop mGPS (0/1/2)	291 (78)/39 (10)/45 (12)	207 (74)/25 (9)/47 (17)	141 (81)/22 (12)/11 (6)	0.01

Surgical technique (open/laparoscopic)	241 (59)/168 (41)	-	-	-
Anaesthetic approach (G/G +E/G +TAP-B/G + LI/G +S)	61 (15)/156 (38)/60 (15)/41 (10)/91 (22)	23 (9)/144 (59)/22 (9)/11 (4)/42 (17)	38 (23)/12 (7)/38 (23)/30 (18)/49 (29)	<0.001
POD 2 CRP > 150 mg/L (no/yes) [a]	182 (50)/181 (50)	97 (36)/171 (64)	111 (66)/57 (34)	<0.001
POD 3 CRP > 150 mg/L (no/yes)	215 (56)/172 (44)	132 (43)/172 (56)	115 (64)/63 (35)	<0.001
POD 4 CRP > 150 mg/L (no/yes) [b]	217 (67)/106 (33)	169 (60)/113 (40)	91 (69)/41 (31)	0.04
Dexamethasone (no/yes)	177 (43)/231 (57)	137 (57)/104 (43)	40 (24)/129 (76)	<0.001
Any complication (no/yes)	251 (62)/156 (38)	159 (54)/137 (46)	134 (71)/55 (29)	<0.001

ASA American Society of Anaesthesiology Grading system; *BMI* body mass index; *CRP* C-reactive protein; *TNM* Tumour Node Metastases; *Preop mGPS* preoperative modified Glasgow Prognostic score; *POD* postoperative day, [a] n=363, [b] n=323, *G* General anaesthesia; *E* Epidural anaesthesia; *TAP-b* TAP-block; *LI* Local infiltration; S Spinal anaesthesia.

Table 6.2: The relationship between anaesthetic techniques and clinicopathological variables of patients undergoing elective open surgery for colon cancer, (n=241).

Characteristic	**Anaesthetic agents**					
	General alone (n=23)	**GA + Epidural** (n=143)	**GA + TAP - block** (n=22)	**GA + Local-infiltration** (n=11)	**GA + Spinal** (n=42)	**P-value**
Age (<65/65-74/>75)	6 (26)/9 (39)/8 (35)	49 (34)/57 (40)/37 (26)	8 (36)/6 (27)/8 (36)	2 (18)/2 (18)/7 (63)	10 (24)/18 (43)/15 (33)	0.13
Sex (male/female)	10 (43)/13 (56)	80 (56)/63 (44)	9 (41)/13 (59)	2 (18)/9 (82)	26 (62)/16 (38)	0.77
BMI (<20/20-25/26-30/>30)	0 (0)/13 (56)/2 (9)/8 (35)	10 (7)/40 (31)/41 (31)/39 (30)	4 (18)/8 (36)/4 (18)/6 (27)	1 (9)/2 (18)/3 (27)/5 (45)	2 (5)/13 (32)/15 (36)/11 (27)	0.69
Year of operation (2008-2012/2013-2016)	0 (0)/23 (100)	79 (55)/64 (45)	12 (54)/10 (45)	7 (63)/4 (36)	4 (9)/38 (90)	0.005
ASA grade (1/2/3/4)	7 (30)/10 (43)/5 (22)/1 (4)	24 (17)/62 (44)/52 (36)/4 (3)	5 (23)/8 (36)/9 (41)/0 (0)	1 (9)/5 (45)/4 (36)/1 (9)	7 (18)/18 (46)/12 (31)/2 (5)	0.53

TNM stage (I/II/III/IV)	5 (23)/9 (41)/8 (36)/0 (0)	27 (19)/63 (45)/43 (31)/7 (5)	3 (13)/14 (63)/4 (18)/1 (4)	0 (0)/4 (36)/7 (63)/0 (0)	12 (29)/15 (37)/10 (24)/4 (10)	0.84
Preop mGPS (0/1/2)	16 (73)/2 (9)/4 (18)	99 (75)/12 (9)/21 (16)	15 (79)/0 (0)/4 (21)	9 (90)/0 (0)/1 (10)	30 (75)/4 (10)/6 (15)	0.68
POD 2 CRP > 150 mg/L (no/yes)	5 (25)/15 (75)	42 (32)/88 (68)	8 (42)/11 (58)	6 (67)/3 (33)	22 (59)/15 (40)	<0.001
POD 3 CRP > 150 mg/L (no/yes)	12 (57)/9 (43)	61 (44)/78 (56)	10 (45)/12 (54)	8 (80)/2 (20)	21 (51)/20 (49)	0.32
POD 4 CRP > 150 mg/L (no/yes)	13 (72)/5 (28)	81 (64)/45 (36)	12 (60)/8 (40)	7 (87)/1 (12)	25 (66)/13 (34)	0.78
Dexamethasone (no/yes)	10 (45)/12 (54)	96 (67)/47 (33)	9 (41)/13 (59)	7 (63)/4 (36)	15 (36)/27 (64)	0.006
Any complication (no/yes)	11 (50)/11 (50)	80 (56)/63 (44)	14 (67)/8 (36)	11 (100)/0 (0)	16 (39)/25 (61)	0.48

ASA American Society of Anaesthesiology Grading system; *BMI* body mass index; *CRP* C-reactive protein; *TNM* Tumour Node Metastases; *Preop mGPS* preoperative modified Glasgow Prognostic score; *POD* postoperative day.

Table 6.3: The relationship between anaesthetic techniques and clinicopathological variables of patients undergoing elective laparoscopic surgery for colon cancer, (n=168).

Characteristic	**Anaesthetic agents**					
	General alone (n=38)	**GA + Epidural** (n=13)	**GA + TAP-block** (n=38)	**GA + Local-infiltration** (n=30)	**GA + Spinal** (n=49)	**P-value**
Age (<65/65-74/>75)	10 (26)/17 (45)/11 (29)	4 (31)/4 (31)/5 (38)	17 (45)/12 (32)/9 (24)	6 (20)/14 (47)/10 (33)	13 (26)/24 (49)/12 (24)	0.83
Sex (male/female)	20 (53)/18 (47)	12 (92)/1 (7)	20 (53)/18 (47)	15 (50)/15 (50)	26 (53)/23 (47)	0.46
BMI (<20/20-25/26-30/>30)	1 (2)/15 (39)/10 (26)/12 (32)	1 (8)/0 (0)/1 (8)/11 (84)	0 (0)/10 (26)/13 (34)/15 (39)	1 (3)/8 (27)/10 (33)/11 (37)	4 (8)/13 (27)/16 (33)/15 (31)	0.44
Year of operation (2008-2012/2013-2016)	2 (5)/36 (95)	6 (46)/7 (54)	21 (55)/17 (45)	11 (37)/19 (63)	7 (14)/42 (86)	0.99
ASA grade (1/2/3/4)	10 (26)/16 (42)/11 (29)/1 (2)	0 (0)/7 (54)/6 (46)/0 (0)	9 (24)/19 (50)/10 (26)/0 (0)	3 (10)/15 (52)/10 (34)/1 (3)	11 (23)/25 (53)/10 (21)/1 (2)	0.81

TNM stage (I/II/III/IV)	8 (21)/15 (39)/15 (39)/0 (0)	6 (46)/4 (31)/3 (23)/0 (0)	7 (18)/17 (45)/14 (37)/0 (0)	5 (17)/10 (33)/14 (47)/1 (3)	16 (33)/15 (31)/17 (35)/0 (0)	0.92
Preop mGPS (0/1/2)	30 (81)/3 (8)/4 (11)	6 (60)/2 (20)/2 (20)	28 (87)/4 (12)/0 (0)	23 (82)/4 (14)/1 (7)	35 (78)/8 (18)/2 (4)	0.58
POD 2 CRP > 150 mg/L (no/yes)	23 (68)/11 (32)	5 (38)/8 (61)	24 (75)/8 (25)	19 (68)/9 (32)	28 (68)/13 (32)	0.62
POD 3 CRP > 150 mg/L (no/yes)	24 (69)/11 (31)	8 (61)/5 (38)	24 (67)/12 (33)	20 (77)/6 (23)	27 (61)/17 (39)	0.82
POD 4 CRP > 150 mg/L (no/yes)	14 (64)/8 (36)	9 (82)/2 (18)	15 (65)/8 (35)	17 (89)/2 (10)	24 (63)/14 (37)	0.90
Dexamethasone (no/yes)	8 (21)/30 (79)	7 (54)/6 (46)	7 (18)/31 (82)	7 (23)/23 (77)	11 (22)/38 (78)	0.70
Any complication (no/yes)	30 (79)/8 (21)	7 (54)/6 (56)	30 (79)/8 (21)	24 (80)/6 (20)	28 (57)/21 (43)	0.10

Table 6.4: The relationship between the administration of dexamethasone and clinicopathological variables of patients undergoing elective laparoscopic surgery for colon cancer, (n=168).

Characteristics	**No dexamethasone** (n=40)	**Dexamethasone** (n=128)	**P-value**
Age (<65/65-74/>75)	13 (32)/15 (38)/12 (30)	37 (29)/56 (44)/35 (27)	0.94
Sex (male/female)	27(68)/13 (32)	66 (52)/62 (48)	0.05
BMI (<20/20-25/26-30/>30)	2 (5)/8 (20)/8 (20)/21 (55)	5 (4)/38 (30)/42 (33)/43 (33)	0.10
Year of operation (2008-2012/2013-2016)	19 (48)/21 (52)	28 (30)/ 100 (78)	0.002
ASA grade (1/2/3/4)	6 (15)/19 (48)/13 (32)/2 (5)	27 (22)/63 (50)/34 (27)/1 (1)	0.13
TNM stage (I/II/III/IV)	10 (25)/17 (44)/12 (31)/0 (0)	32 (25)/44 (34)/51 (40)/1 (1)	0.44
Preop mGPS (0/1/2)	26 (72)/8 (22)/2 (6)	96 (83)/13 (11)/7 (6)	0.34

POD 2 CRP > 150 mg/L (no/yes)	13 (37)/22 (63)	86 (76)/27 (24)	<0.001
POD 3 CRP > 150 mg/L (no/yes)	18 (50)/18 (50)	85 (72)/33 (28)	0.01
POD 4 CRP > 150 mg/L (no/yes)	22 (67)/11 (33)	57 (71)/23 (29)	0.39
Anaesthetic approach (G/G +G/E+G/TAP-B+ G/LI +G/S)	8 (20)/7 (17)/7 (17)/7 (17)/11 (29)	30 (23)/6 (5)/31 (24)/23 (18)/38 (30)	0.70
Any complication (no/yes)	23 (58)/17 (42)	97 (76)/31 (24)	0.04

Table 6.5: The relationship between each anaesthetic technique and POD 2 CRP of patients undergoing elective open surgery for colon cancer.

Group of anaesthesia	Number of patients	Adjusted Z Score	P-value
General alone	15	1	0.15
General + Epidural	89	2.2	0.02
General + TAP-block	10	-0.5	0.58
General + Local infiltration	3	-1.4	0.15
General + Spinal	16	-2.5	0.01

7. The effect of anaesthesia on the magnitude of the postoperative systemic inflammatory response in patients undergoing elective surgery for colorectal cancer in the context of an enhanced recovery pathway. A prospective cohort study.

7.1 Introduction

The perioperative period is a complex process that may influence the outcome of cancer surgery (Tohme et al., 2017). In particular, both surgery and anaesthesia have been reported to depress the cellular immunity during the postoperative period and to potentiate recurrence and metastasis of cancer (Kim, 2018). The surgical stress response and its magnitude are strongly associated with IL-6 and CRP (Watt et al., 2015c). However, although the impact of surgery on the postoperative SIR is well delineated, the impact of anaesthesia is not clear.

Regional anaesthetic techniques can be used combined with GA in most abdominal surgery which involving either neuraxial or peripheral nerve block. The available evidence suggests the benefits of RA on the surgical stress response, recovery of the gastrointestinal function and reducing the postoperative pain outcome and opioid consumption (Dang et al., 2018).

Specifically, a systematic review and meta-analysis in chapter 5, reported that it was not clear in the literature whether anaesthetic technique has an effect on the magnitude of the postoperative SIR. This was due to the heterogeneity and poor quality of identified studies (Alhayyan et al., 2020a). Furthermore, these authors, in a retrospective audit of the effect of anaesthetic technique on the magnitude of the postoperative CRP in patients undergoing elective open or laparoscopic surgery for colon cancer, reported that the magnitude of the postoperative SIR in particular, POD 2 CRP, was modulated by the induction of RA in patients who underwent open surgery, but not laparoscopic surgery for colorectal cancer (Alhayyan et al., 2020b).

With the introduction of enhanced recovery pathways (ERPs), there has been a focus on laparoscopic surgery and early mobilisation of patients undergoing surgery for colorectal cancer, however, few studies have examined the effect of anaesthetic technique (Cortez et al., 2019). In terms of the postoperative SIR, few components of ERP have been proven to reduce the postoperative SIR with the exception of minimally invasive surgery (Watt et al., 2015d).

The aim of the present study was to examine the effect of anaesthesia using a prospective proforma within the context of ERP, on the magnitude of the postoperative SIR in patients undergoing elective surgery for colorectal cancer.

7.2 Patients and Methods

7.2.1 Study Design

The study was designed by preparing a proforma including clinicopathological data, all the anaesthetic technique or agents and all the medications administered before and after induction of anaesthesia such as neuromuscular blockers, steroids, antibiotics, and benzodiazepines in patients who underwent elective surgery for colorectal cancer (Table 7.1).

7.2.2 Patients

519 consecutive patients who underwent for elective open or laparoscopic surgery for colorectal cancer from 2015 – 2019 within an ERAS pathway were identified from a prospectively maintained database at single centre. Of these only 507 patients who had documented anaesthetic records. All data were anonymised, and all patients underwent either open (n=304) or laparoscopic surgery (n=203). Propofol had been given for the induction of GA either with or without remifentanil. Most patients received inhalational anaesthesia for the maintenance of anaesthesia (n=449) while only few patients received intravenous anaesthesia mainly propofol for both induction and maintenance of anaesthesia (n=53). In addition, 309 patients underwent for colon resection while 196 patients underwent for rectal resection. Anaesthetic regimens were grouped according to the anaesthetic methods applied into GA or GA + RA. Within the RA technique, three groups were included either epidural (n= 115), spinal (n= 213), or local anaesthesia (n= 80).

All clinicopathological data were anonymised, and all the emergency cases were excluded from the analysis. The preoperative modified Glasgow Prognostic Score (mGPS) from 0-2, was used to assess the preoperative systemic inflammatory response. Patients with normal CRP concentration (<10 mg/L) = 0. Patients with high CRP concentration (>10 mg/L) = 1

and patients with high CRP concentration (>10 mg/L) and hypoalbuminaemia (<35 g/L) = 2 (McMillan, 2013b). The magnitude of the postoperative SIR was assessed by the measurement of post-operative C-reactive protein (CRP ≤150 /> 150 mg/L), on the second, third and fourth postoperative days. Tumours were staged according to TNM staging system (tumour, node and metastasis). The patient comorbidity was assessed by using the American Society of Anaesthesiologists (ASA) grading system while severity of surgical complications has been classified by using the Clavien-Dindo scale (Fitz-Henry, 2011b, Dindo et al., 2004a).

Patients' data were collected from a prospective database from January to December 2016 from the academic department of surgery at Glasgow Royal Infirmary hospital. The study was approved by the West of Scotland Research Ethics Committee, Glasgow.

7.2.3 Data Analysis

All data were analysed using SPSS version 25.0 for windows (IBM Corporation, Armonk, NY, USA). Based on previous retrospective study, greater than 400 patients were recruited to the present study. The X^2 (Chi-square) statistical method was used to test the statistical significance between the anaesthetic regimens and clinicopathological variables. A p-value of <0.05 were considered statistically significant.

Binary logistic regression model was used to examine the relationship between the clinicopathological variables and the postoperative CRP with the calculation of odds ratio (OR) and 95% confidence interval (CI). On univariate analysis, all the clinicopathological variables with a p-value <0.10 were included into a multivariate analysis using a backward conditional model to identify independently significant variables.

7.3 Results

Most patients were male (275, 54%), younger than 65 years old (207, 41%), normal or overweight (319, 64%) and were non-smokers (235, 47%). The majority of patients had the surgical resection for open colorectal cancer (304, 60%). The GA was only administered to 99 patients while GA plus RA was the most commonly performed technique (408, 80%). The epidural anaesthetic technique was given to (115, 23%), spinal to (213, 42%), and local anaesthesia to (80, 16%) respectively.

IV dexamethasone was administered at the induction of anaesthesia to 373 patients (74%) and 133 patients (26%) did not receive dexamethasone. Also, 489 patients received opioids. In theatre, NSAID-COX2 inhibitors was administered to 79 patients and IV local anaesthesia such as lidocaine or lignocaine was administered to 54 patients. In addition, most patients did not receive NSAID-COX2 (n=504) or steroid (n=503) postoperatively. The basis of this was not clear but may reflect institutional anaesthetic practice to prefer opioids to NSAID-COX2.

Preoperative antibiotics were given to most patients (n=491) to reduce the risk of infections. All patients received muscle relaxant and neuromuscular reversal was given to 277 patients. Benzodiazepine medication was administered to 145 patients. In addition, most patients did not receive NSAID-COX2 (n=504) or steroids (n=503) postoperatively. The majority of patients were not systemically inflamed prior to surgery (322, 65%) and had a CRP <150 mg/L on day 2, 3 and 4 following surgery.

The relationship between GA versus GA + RA and clinicopathological data of patients undergoing elective surgery for colorectal cancer is shown in Table 7.2. There was a significant association between GA versus GA + RA, surgical approach ($p = 0.02$), TNM stage ($p = 0.003$), preoperative dexamethasone ($p = 0.05$), neoadjuvant therapy ($p = 0.006$), and POD 4 CRP ($p = 0.005$).

The relationship between GA versus GA + RA and clinicopathological data of patients undergoing elective surgery for colon cancer is shown in Table 7.3. There was a significant association between GA versus GA + RA, surgical approach (p =0.01), and POD 4 CRP (p =0.01).

Binary logistic regression of clinicopathological variables that significantly associated with low (≤150 mg/L) v.s high (>150 mg/L) POD 4 CRP concentration in patients undergoing elective surgery for colorectal cancer is shown in Table 7.4. On univariate analysis, POD 4 CRP was associated with anaesthetic technique (OR 0.58; CI 0.31-1.07; p =0.086), age (OR 0.70; CI 0.50-0.98; p =0.043), sex (OR 1.15; CI 0.95-2.52; p =0.074), smoking (OR 1.57; CI 1.13-2.19; p =0.006), preoperative mGPS (OR 1.55; CI 1.15-2.10; p =0.004), and preoperative dexamethasone (OR 0.70; CI 0.47-1.03; p =0.072). On multivariate analysis, POD 4 CRP was independently associated with anaesthetic technique, (OR 0.56; CI 0.32-0.97; p =0.039), age (OR 0.74; CI 0.55-0.99; p =0.045), smoking (OR 1.58; CI 1.18-2.12; p =0.002), preoperative mGPS (OR 1.41; CI 1.08-1.84; p =0.012), and preoperative dexamethasone (OR 0.68; CI 0.50-0.92; p =0.014).

7.4 Discussion

The results of the present prospective observational study showed that RA, within the context of an ERP, had a modest and an independent effect on the magnitude of the postoperative SIR in elective surgery for colorectal cancer. This would suggest that there is a role for anaesthetic technique in modulating the postoperative SIR.

To date, there has been one previous study that addressed the effect of anaesthesia on postoperative CRP within an ERAS program. Chen et al (2015) conducted a randomized study and reported that in open colon cancer patients who underwent for fast-track protocol, GA combined with epidural anaesthesia (n=26) showed a significant reduction on postoperative day 2 CRP level compared with a group of GA alone (n=27). In contrast, in the pre-ERP era, Papadima et al conducted a randomized study and reported no significant difference in postoperative CRP concentrations in both techniques of anaesthesia (GA, n=19 v.s combined GA with RA, n=21) in patients underwent for open colectomy. Therefore, the present observational study is the largest to date to examine this relationship in the ERP era.

The application of an ERP in colorectal surgery has been studied extensively and now established as a best care method. It is an evidence-based multimodal care pathway that contains several components during the preoperative, intraoperative and postoperative periods to attain faster recovery and shorter hospital stay with a focus on reducing the postoperative stress response and postoperative complication rates (Pedziwiatr et al., 2018). A randomized controlled trial conducted by Veenhof and colleagues (2012) who examined the effect of fast track and standard care on immune status and stress response within open or laparoscopic surgery for non-metastasized colon cancer patients, reported that the immune function was significantly improved for those who underwent for minimally invasive surgery with fast-track protocol. This result was consistent with the hypothesis that

laparoscopic technique in combination with fast track protocol enhanced the immune function and thereby reducing the stress response and lowering the postoperative concentration of CRP (Watt et al., 2015d).

There is a recognition that RA, in particular neuraxial block with epidural technique have been reported to protect the immune system. This includes modulation of surgical stress response with an optimal postoperative pain relief. With regards to the postoperative outcomes and in patients undergoing abdominal surgery, the most studied technique in RA is the epidural analgesia (Baldini and Carli, 2015, Dang et al., 2018). The use of RA has been reported to reduce the dose of opioids and thus minimise the risk of immune suppressive effect of opioids (Zajaczkowska et al., 2018). However, in the present study and even within RA patients, opioids were extensively administered to control pain in the perioperative period. However, the immunosuppressive effects of opioids have been reported in many previous and recent studies. Therefore, there is significant work to be done to reduce the reliance on opioids postoperatively (McIsaac et al., 2015).

Propofol, is the most commonly intravenous anaesthetic agent used for induction by bolus administration and maintenance of anaesthesia by continuous infusion. It has been reported that propofol based IV anaesthesia has an anti-inflammatory, antioxidant and antitumor effect providing some protection against immune suppression. In addition, previous research has established that propofol based IV anaesthesia was favourable in the long-term outcome in patients underwent for surgical resection of gastric, oesophagus and colon (Sessler and Riedel, 2019). Therefore, with the appropriate use of propofol it may be that the use of opioids in the postoperative period may be reduced or removed (Thota et al., 2019, Guerrero Orriach et al., 2020).

The concept of ERP was introduced by Prof. Kehlet and Wilmore. The role of ERAS has been proven in multiple surgical disciplines and aims to minimize the perioperative surgical

stress response, maintain the body physiological function and facilitate recovery after surgery (Kehlet, 2015).

There is increasing interest in moderating the post-operative systemic inflammatory response using anaesthesia to improve recovery from surgery (Watt et al., 2015d, Piegeler and Beck-Schimmer, 2016). However, to date there has been little data to guide how we might proceed and therefore there is a pressing need for more information on the effect of anaesthesia on the post-operative systemic inflammatory response taking account of other peri-operative treatments (Kehlet, 2020). Recently, a retrospective study of 543 patients who underwent for elective curative surgery for CRC examined the relationship between two types of anaesthesia, inhalational or TIVA within a standardized ERP and the post-operative complications, survival, recurrence, and recovery. The results of this study showed that those patients who exposed to inhalational anaesthesia had a significant lower chance of discharge and bowel movement per post-operative day while no significant difference for other the outcomes was reported (Crone et al., 2020). Clearly, further studies are required if evidenced based anaesthesia is to be practised within an enhanced recovery pathway.

In the present study, in the context of ERP, approximately 19 % of patients had GA solely. These patients were less likely to have advanced disease and less likely to have undergone open surgery and therefore is not clear what drives this apparently suboptimal anaesthetic practice. However, it may simply reflect existing anaesthetic practice.

In major open colorectal surgery, epidural anaesthesia is recommended, however, it may superfluous in laparoscopic colorectal surgery. A recent meta-analysis showed that there was no additional clinical benefit with epidural analgesia for patients undergoing laparoscopic colorectal surgery within an ERP (Borzellino et al., 2016b). Indeed, the commonly used analgesic techniques in laparoscopic abdominal surgery are spinal analgesia, continuous IV local infusion and TAP block, which has been a recommended technique in laparoscopic abdominal surgery (Hughes et al., 2015, Baldini and Carli, 2015).

Both TAP block and rectus sheath block including a block of abdominal nerve wall and applied by a surgeon. In the TAP block, an injection of local anaesthetic agents in the neuromuscular plane between transversus abdominis muscle and internal oblique muscle of the anterior abdominal wall was applied while a rectus sheath block includes an injection of local anaesthetic on the posterior wall of the rectus sheath (Yarwood and Berrill, 2010, Bharti et al., 2011). However, success of such blocks is recognised to be variable.

A recent randomised clinical study reported that, in a comparison between GA + continuous TAP block performed before laparoscopic colorectal surgery with GA + thoracic epidural anaesthesia, both anaesthetic techniques were able to significantly attenuate the surgical stress response including IL-6. Also, the continuous TAP-block anaesthesia was associated with an acceleration in the recovery of gastrointestinal function and shorted hospital stay (Xu et al., 2020b).

The present prospective observational cohort study has some limitations. The use of surgical and anaesthetic techniques was variable, and it was a single centre study. Also, the administration of preoperative steroids to the majority of patients (74%) may have affected the relationship between the type of anaesthesia and the postoperative SIR since dexamethasone has been shown recently in reducing the postoperative SIR and complications after elective colorectal cancer surgery (McSorley et al., 2017b). However, this study was carried in a relatively large well documented group of patients undergoing surgery for colorectal cancer.

In summary, the results of the present study suggest that the application of RA within an ERP reduces the magnitude of the postoperative SIR in patients undergoing elective surgery for colorectal resection. Further studies are needed to examine the relationship between anaesthesia and the magnitude of the postoperative SIR in large multicentre randomized trials to provide an optimal ERP in patients undergoing surgery for colorectal cancer.

7.5 Tables and Footnotes

Table 7.1: Pro-forma for patients undergoing surgery for elective open or laparoscopic surgery of colorectal cancer.

1-	CRC master number	
2-	CHI	
3-	Age	☐ <65 ☐ 65-74 ☐ >75
4-	Sex	☐ male ☐ female
5-	BMI	☐ <20 ☐ 20-25 ☐ 26-30 ☐ >30
6-	Smoking	☐ never ☐ ex ☐ current
7-	ASA grade	☐ 1 ☐ 2 ☐ 3 ☐ 4
8-	TNM stage	☐ 1 ☐ 2 ☐ 3 ☐ 4
9-	Tumour site	☐ right ☐ left
10-	Preop mGPS	☐ 0 ☐ 1 ☐ 2
11-	Open surgery	☐ no ☐ yes
	Laparoscopic surgery	☐ no ☐ yes
12-	Induction agent	☐ Inhalational ☐ Propofol ☐ Thiopentone ☐ Etomidate

13- Total Intravenous anaesthesia ☐ no ☐ yes, if yes specify ☐ Propofol TCI ☐ Propofol TCI+remifentanil

14- Inhalational anaesthesia ☐ no ☐ yes, if yes specify ☐ Sevoflurane ☐ Desflurane ☐ Isoflurane

15- Remifentanil ☐ no ☐ yes TCI

16- Total dose of opioid in theatre ☐ morphine 25mg ☐ fentanyl ___mg

17- General + epidural ☐ no ☐ yes, if yes specify ☐ plain bupivacaine bag ☐ bupivacaine plus opioid

18- General + Abdo wall-block ☐ no ☐ yes, if yes specify ☐ TAP block ☐ TAP catheter ☐ Rectus sheath block ☐ Rectus sheath catheter

19- General + local infiltration ☐ no ☐ yes, if yes specify ☐ Simple local infiltration ☐ Wound infiltration catheters

20- General + spinal ☐ no ☐ yes, if yes specify ☐ Local anaesthetic + opioid ☐ Opioid alone

21- Dexamethasone given in theatre ☐ no ☐ yes

22- NSAID / COX 2 given in theatre ☐ no ☐ yes, if yes specify ☐ Diclofenac ☐ Ketorolac ☐ Others _____

23- IV local anaesthetics given in theatre ☐ no ☐ yes

24- NSAID / COX2 Given post-op? ☐ no ☐ yes, if yes specify ☐ Diclofenac ☐ Ibuprofen ☐ Others _____

25- Steroids given post-op? ☐ no ☐ yes, if yes specify, dose _____mg

26- Morphine Given post-op? ☐ no ☐ yes, if yes specify Total dose in 72 hrs = _____ mg (this will be a combination of oral and IV. Need to work out equivalent IV dose)

27- Neostigmine/glycopyrrolate ☐ no ☐ yes

28- Amoxicillin + Gentamicin + Metronidazole ☐ no ☐ yes

29- Muscle relaxant ☐ no ☐ yes

30- Midazolam ☐ no ☐ yes

31- POD 2 CRP >150 mg/L ☐ no ☐ yes

32- POD 3 CRP >150 mg/L ☐ no ☐ yes

33- POD 4 CRP >150 mg/L ☐ no ☐ yes

34- Neoadjuvant therapy ☐ no ☐ yes

35- Adjuvant therapy ☐ no ☐ yes

36- Stoma type ☐ no ☐ ileostomy ☐ colostomy

37- Any complication ☐ no ☐ yes

38- Infective complications ☐ no ☐ yes

39- Clavien-Dindo grade ☐ 0 ☐ 1-2 ☐ 3-4 ☐

Table 7.2: The relationship between general vs general + regional anaesthesia and clinicopathological variables in patients undergoing elective surgery for colorectal cancer in ERP, (n=507).

Characteristic	**GA, (n= 99)**	**GA + RA, (n= 408)**	**P-value**
Age			0.80
<65	40 (40)	167 (41)	
65-74	36 (36)	135 (33)	
>75	23 (23)	106 (26)	
Sex			0.09
Male	60 (61)	215 (53)	
Female	39 (39)	193 (47)	
BMI			0.26
<20	3 (3)	21 (5)	
20-25	38 (39)	104 (26)	
26-30	28 (29)	149 (37)	
>30	28 (29)	125 (31)	
Smoking			0.56
Never	45 (47)	190 (47)	
Ex	31 (33)	154 (38)	
Current	19 (20)	60 (15)	
ASA grade			0.24
1	10 (10)	37 (9)	
2	47 (47)	208 (53)	
3	35 (35)	138 (35)	
4	7 (7)	10 (2)	
TNM stage			0.003
I	26 (28)	79 (20)	
II	41 (44)	129 (32)	
III	20 (21)	155 (39)	
IV	4 (4)	29 (7)	

Surgical approach Open Laparoscopic	 50 (51) 49 (49)	 254 (62) 154 (38)	0.02
Tumour site Colon Rectum	 65 (65) 34 (34)	 244 (60) 162 (40)	0.49
Preop mGPS 0 1 2	 61 (63) 17 (17) 19 (19)	 261 (65) 66 (17) 71 (18)	0.61
Opioids No Yes	 1 (1) 97 (99)	 17 (4) 390 (96)	0.10
Preop Dexamethasone No Yes	 38 (39) 60 (61)	 95 (23) 313 (77)	0.05
POD 2 CRP > 150 mg/L No Yes	47 (51) 45 (49)	217 (54) 171 (44)	0.23
POD 3 CRP > 150 mg/L No Yes	 47 (55) 39 (45)	 222 (58) 163 (42)	0.34
POD 4 CRP > 150 mg/L No Yes	 42(56) 33 (44)	 254 (72) 98 (28)	0.005
Neoadjuvant therapy No Yes	 90 (94) 6 (6)	 339 (84) 66 (16)	0.006
Adjuvant therapy No Yes	 59 (61) 37 (38)	 212 (52) 194 (48)	0.06
Stoma type No Ileostomy	 63 (64) 22 (22)	 245 (60) 96 (24)	0.59

Colostomy	14 (14)	63 (15)	
Any complication No Yes	 65 (66) 33 (34)	 282 (70) 123 (30)	0.30
Infective complication No Yes	 75 (76) 23 (23)	 311 (76) 95 (23)	0.54
Clavien -Dindo grade 0 1-2 3-4 5	 56 (57) 29 (30) 10 (10) 3 (3)	 209 (51) 148 (36) 45 (11) 4 (1)	0.94

Table 7.3: The relationship between general vs general + regional anaesthesia and clinicopathological variables in patients undergoing elective surgery for colon cancer in ERP, (n=309).

Characteristic	**GA, (n= 65)**	**GA + RA, (n= 244)**	**P-value**
Age			0.65
<65	25 (38)	84 (34)	
65-74	22 (34)	90 (37)	
>75	18 (28)	70 (29)	
Sex			0.43
Male	35 (54)	126 (52)	
Female	30 (46)	118 (48)	
BMI			0.29
<20	3 (5)	13 (5)	
20-25	27 (41)	62 (26)	
26-30	14 (21)	87 (37)	
>30	21 (32)	76 (32)	
Smoking			0.60
Never	30 (48)	114 (47)	
Ex	22 (35)	98 (41)	
Current	11 (17)	29 (12)	
ASA grade			0.11
1	4 (6)	19 (8)	
2	28 (43)	116 (49)	
3	27 (41)	91 (39)	
4	6 (9)	9 (4)	
TNM stage			0.14
I	14 (22)	47 (20)	
II	29 (46)	84 (35)	
III	17 (27)	83 (35)	
IV	3 (5)	22 (9)	

Surgical approach Open Laparoscopic	 32 (49) 33 (51)	 159 (65) 85 (35)	0.01
Preop mGPS 0 1 2	 36 (57) 11 (17) 16 (25)	 141 (59) 47 (20) 50 (21)	0.57
Opioids No Yes	 1 (2) 63 (98)	 5 (2) 239 (98)	0.63
Preop Dexamethasone No Yes	 26 (40) 39 (60)	 68 (28) 176 (72)	0.49
POD 2 CRP > 150 mg/L No Yes	 31 (48) 34 (52)	 124 (53) 110 (47)	0.26
POD 3 CRP > 150 mg/L No Yes	 32 (53) 28 (47)	 128 (56) 100 (44)	0.40
POD 4 CRP > 150 mg/L No Yes	 27 (53) 24 (47)	 146 (70) 63 (30)	0.01
Neoadjuvant therapy No Yes	 63 (98) 1 (2)	 231 (95) 11 (5)	0.24
Adjuvant therapy No Yes	 36 (56) 28 (44)	 133 (55) 110 (45)	0.47
Stoma type No Ileostomy Colostomy	 48 (74) 13 (20) 4 (6)	 196 (81) 34 (14) 11 (5)	0.22

Any complication			0.40
No	43 (66)	166 (69)	
Yes	22 (34)	76 (31)	
Infective complication			0.45
No	50 (77)	190 (79)	
Yes	15 (23)	52 (21)	
Clavien -Dindo grade			0.81
0	38 (58)	126 (58)	
1-2	19 (29)	90 (37)	
3-4	5 (8)	23 (9)	
5	3 (5)	3 (1)	

Table 7.4: Binary logistic regression of clinicopathological data associated with low v.s high POD 4 CRP concentrations in patients undergoing elective surgery for colorectal cancer in ERP, (n=507).

Variables	Univariate analysis OR (95% CI)	P-value	Multivariate analysis OR (95% CI)	P-value
Age (<65/65-74/>75)	0.70 (0.50-0.98)	0.043	0.74 (0.55-0.99)	0.045
Sex (male/female)	1.15 (0.95-2.52)	0.074	1.48 (0.94-2.31)	0.085
BMI (<20/20-25/26-30/>30)	1.17 (0.89-1.53)	0.253	_	_
Smoking (never/ex/current)	1.57 (1.13-2.19)	0.006	1.58 (1.18-2.12)	0.002
ASA grade (1/2/3/4)	0.82 (0.56-1.20)	0.311	_	_
Surgical technique (open/laparoscopic)	0.72 (0.39-1.34)	0.310	_	_
TNM stage (I/II/III/IV)	0.93 (0.71-1.21)	0.594	_	_
Opioids (no/yes)	1.12 (0.35-3.60)	0.842	_	_
Tumour site (colon/rectum)	0.89 (0.74-1.07)	0.221	_	_
Preop mGPS (0/1/2)	1.55 (1.15-2.10)	0.004	1.41 (1.08-1.84)	0.012
GA alone /GA+ RA (no/yes)	0.58 (0.31-1.07)	0.086	0.56 (0.32-0.97)	0.039
Preop Dexamethasone (no/yes)	0.70 (0.47-1.03)	0.072	0.68 (0.50-0.92)	0.014

8. The relationship between pre-operative medications, the type of anaesthesia and post-operative sequelae in patients undergoing surgery for colorectal cancer.

8.1 Introduction

CRC is one of the most common types of carcinomas. In 2018, it has been estimated that each year around 1.8 million patients are diagnosed with CRC worldwide (Bray et al., 2018).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medications worldwide. In the published literature, some epidemiological, preclinical and clinical studies have supported the chemo preventive effect of NSAIDs and their associations with a reduction of cancer risk in some types of cancer among them colorectal cancer (Wong, 2019). However, other studies have demonstrated no association between NSAID use and cancer.

Approximately 20%- 40% of patients with resectable colorectal cancer have an elevated CRP concentration prior to surgery, indicating a preoperative systemic inflammatory response and is associated with poor prognosis (Park et al., 2016, Park et al., 2017). It has been identified that aspirin and statins by their anti-inflammatory effects, may help in downregulating the inflammatory response in patients with cancer (Park et al., 2014). In addition, accumulating evidence has shown that some drugs may provide a chemo-preventive effect by reducing the risk of cancer. For example, aspirin and other NSAIDs such as cyclooxygenase-2 inhibitors (COXIBs) have been studied extensively. A case-control study showed that a low dose of aspirin administered continuously for 5 years, or more was associated with a risk reduction of CRC (Katona and Weiss, 2020).

Similarly, statins (lipid lowering agents) have also been shown to reduce colorectal tumour development in mice when administered individually or in combination with NSAIDs, but the epidemiological and clinical studies of statins showed inconsistent results in colorectal neoplasia (Suh et al., 2011, Katona and Weiss, 2020). Another therapeutic anti-hypertensive drug class known as Angiotensin-Converting Enzyme Inhibitors (ACEIs) may also have a chemopreventive effect. It has been reported that long-term use of this drug class may be associated with a reduced incidence of CRC (Makar et al., 2014).

Although the long-term administration of previously mentioned medications (aspirin, statins and ACEIs) have been known for their chemopreventive properties, however, few studies have examined the relationship between preoperative use of aspirin, statins and ACEIs, and anaesthetic method applied. Therefore, the aim of the present study was to examine the effect of those medications on the anaesthetic/ surgical procedures and the post-operative sequelae in patients undergoing surgery for colorectal cancer.

8.2 Patients and Methods

A cohort of 477 patients diagnosed with TNM stage I -IV CRC underwent potentially curative resection between 2015 and 2019 at Glasgow Royal Infirmary were included in the analysis. The data were anonymised, clinicopathological variables were recorded in a prospective database and emergency cases were excluded. A priori, patients were divided into two groups, those who received GA (n= 98) and those who received GA + RA (n= 379). Open or laparoscopic surgery was performed in 289 and 188 patients, respectively. Preoperative administration of aspirin, statins, ACEIs, antibiotics and dexamethasone were identified for all patients.

Tumours were staged according to TNM staging system (tumour, node and metastasis), patient comorbidity was assessed using the American Society of Anaesthesiologists (ASA) grading system while the severity of surgical complications was classified using the Clavien-Dindo scale (Fitz-Henry, 2011b, Dindo et al., 2004a). The preoperative systemic inflammatory response was assessed by the preoperative modified Glasgow Prognostic Score (mGPS), as follows; patients with normal CRP concentration (<10 mg/L) were given a score of 0 ; patients with high CRP concentration (>10 mg/L) were given a score of 1 and patients with high CRP concentration (>10 mg/L) and hypoalbuminaemia (<35 g/L) were given a score of 2 (McMillan, 2013a). The magnitude of the postoperative SIR was measured by the post-operative C-reactive protein (CRP ≤150 or >150 mg/L), on day 2, 3 and 4.

The study was approved by the West of Scotland Research Ethics Committee, Glasgow.

8.2.1 Data analysis

Data was analysed using SPSS version 26.0 for Windows (IBM Corporation, Armonk, NY, USA). The X^2 (Chi-square) statistical method was used to test the statistical significance between the preoperative medications, anaesthetic/ surgical method, and clinico-pathological variables. A p-value of <0.05 was considered statistically significant.

8.3 Results

Overall, 477 patients undergoing surgery for colorectal cancer at Glasgow Royal infirmary hospital between 2015 and 2019 were included from a prospectively maintained database. The majority of patients were younger than 65 years of age (197, 41%), male (263, 55%), overweight or obese (326, 68%), non-smokers (221, 47%) and underwent open surgical resection for colorectal cancer (289, 61%). All patients received GA either alone (n =98) or in combination with regional anaesthesia (n =379). IV dexamethasone was administered at induction of anaesthesia to 347 patients (73%) and preoperative IV antibiotics were administered to 462 patients (97%). Patients using one or more medications were subclassified into two groups: patients who received one medication (99, 49%) including aspirin (12, 5%), statins (68, 31%), ACEIs (19, 20%) and those who received two or more medications (103, 51%). Most patients had a mGPS of 0 prior to surgery (308, 66%). Also, most patients had a CRP <150 mg/L on day 2; (324, 69%), day 3; (284, 60%), and day 4; (313, 67%) following surgery.

The relationship between clinicopathological characteristics of all 477 patients including anaesthetic technique and pre-operative medication use (no preoperative medication/any preoperative medication) is shown in Table 8.1. There was no significant association between pre-operative medications and anaesthesia but there were significant associations between surgical technique (p-value <0.05), age (p-value <0.001), sex (p-value <0.05), BMI (p-value <0.05), ASA grade (p-value <0.001), TNM stage (p-value <0.001), Tumour site (p-value <0.001), neoadjuvant therapy (p-value <0.001), and adjuvant therapy (p-value <0.001).

Subgroup analysis of 202 patients who received a minimum of one preoperative medication is shown in Table 8.2. These patients were grouped into those who received one medication (49%) and those who received two or more medications (51%). Table 8.2 shows the relationship between clinicopathological characteristics including anaesthetic technique and number of preoperative medications. There was no significant association between pre-operative medications and anaesthesia. Also, there were significant associations between pre-operative medications, ASA grade (p-value =0.005) and POD 4 CRP (p-value <0.05) in patients undergoing surgery for colorectal cancer.

8.4 Discussion

In the present prospective cohort study of patients undergoing surgery for colorectal cancer pre-operative administration of agents such as aspirin, statins and ACEIs, although associated with measures of comorbidity, were not associated with the type of anaesthesia, whether general or general and regional anaesthesia. Therefore, it would appear that such pre-operative medications have little influence on the type of anaesthesia given to patients undergoing surgery for colorectal cancer.

There is now good evidence that agents such as aspirin, statins and ACEIs have a protective effect on the development of colorectal cancer (Gottschall et al., 2018), and it has been postulated that this occurs through an anti-inflammatory effect (Mansouri et al., 2013, Song and Giovannucci, 2014, Drew et al., 2016). However, in the present study it is most likely that such agents were given to treat cardiovascular disease rather than any chemoprotective or anti-inflammatory effect. Indeed, where such medication was given and where more than one of the above medications were given, these patients had greater comorbidity. Therefore, it was of interest that, in the latter group and despite greater comorbidity, those patients had lower POD 4 CRP levels.

Elective surgery and some anaesthetic agents are recognised to induce the activation of hypothalamic pituitary adrenal (HPA) axis and sympathetic nervous system (SNS) leading to suppression of cellular immunity, release of catecholamines and prostaglandin E_2. These, in turn, increase the proinflammatory cytokines such as IL-6 and IL-8, vascular endothelial growth factor (VEGF); and transforming growth factor beta (TGF-β) which promote angiogenesis and therefore may promote metastases in patients with cancer (Dang et al., 2018, Chen et al., 2019b). Moreover, previous research has suggested that the

choice of anesthetic technique may influence long-term clinical outcomes. For example, clinical studies indicated that for cancer patients, it is preferable to use RA or intravenous anaesthesia compared to inhalational anesthesia and opioids (Iwasaki et al., 2015). Therefore, in patients undergoing surgery for cancer, the combination of several factors including surgical trauma, severe inflammation and impaired host immunity provide an environment which accelerate the development of tumor metastasis during the post-operative period. The results of the present study suggest that the pre-existing medication that the patients receive may also be important in this environment.

Of these pre-existing medications, a systematic review and meta-analysis concluded a dose dependent chemopreventive effect of aspirin range from 75-325 mg/day was considered safe and provided an effective primary prevention for long-term use among individuals with an average risk of CRC (Veettil et al., 2018). Also, statins have been proposed as being clinically useful for their preventive effect on tumor progression via 3-Hydroxy-3-Methylglutaryl-Coenzyme (HMG-CoA) reductase-dependent and independent pathways (Gazzerro et al., 2012). Although a large number of trials have revealed the association between statin use and the incidence of CRC, relatively few studies have investigated their effect on survival (Voorneveld et al., 2017). Finally, there is some evidence that long-term use of ACEIs are associated with a lower incidence of cancer as angiotensin II may have a role in carcinogenesis, the regulation of angiogenesis, cell proliferation and inflammation (Katarzyna et al., 2013). Indeed, a protective association has been reported between the treatment with ACEIs and angiotensin receptor blockers (ARBs) and the incidence of some cancer types (Rosenthal and Gavras, 2019). However, to date the clinical efficacy of giving such agents to patients undergoing surgery for colorectal cancer has not been tested (Reitz et al., 2020). The present results provide some preliminary findings and further work is required.

There are some limitations of this study. It was a single centre and there are some potential confounding factors that may have not been examined or adjusted for.

In summary, the pre-operative administration of aspirin, statins and ACEIs were not associated with anaesthetic technique in patients undergoing elective surgery for colorectal cancer. However, there was a significant association between pre-operative medications and measures of patient comorbidity (age, obesity and ASA grade).

8.5 Tables and Footnotes

Table 8.1: The relationship between the administration of pre-operative medications vs no pre-operative medications, type of anaesthesia, and clinico-pathological characteristics in patients undergoing surgery for colorectal cancer from 2015- 2019, (n = 477).

Characteristics	**All, *n* (%)**	**No pre-operative medication, *n* = 273 (58%)**	**Pre-operative medication, *n* = 202 (42%)**	***P*-value**
Age <65 65-74 >75)	 197 (41) 159 (33) 121 (25)	 157 (58) 71 (26) 45 (16)	 39 (19) 87 (43) 276 (38)	<0.001
Sex Male female	 263 (55) 214 (45)	 135 (49) 138 (51)	 127 (63) 75 (37)	0.002
BMI Underweight (<20) Normal (20-25) Overweight (26-30) Obese (>30)	 13 (3) 138 (29) 178 (37) 148 (31)	 9 (3) 90 (33) 101 (37) 73 (27)	 4 (2) 48 (24) 76 (38) 74 (36)	0.005
Smoking Never Ex Current	 221 (47) 176 (37) 75 (16)	 131 (48) 96 (36) 43 (16)	 89 (45) 79 (39) 32 (16)	0.54
ASA grade 1	 44 (9)	 41 (16)	 2 (1)	<0.001

2 3 4	235 (51) 167 (36) 16 (3)	151 (57) 68 (26) 4 (1)	83 (42) 99 (51) 12 (6)	
TNM stage I II III IV	 98 (21) 163 (35) 164 (35) 31 (7)	 46 (17) 90 (35) 111 (43) 13 (5)	 52 (27) 72 (37) 52 (27) 18 (9)	0.05
Tumour site Colon Rectum	 287 (60) 188 (40)	 144 (53) 128 (47)	 141 (70) 60 (30)	<0.001
Surgical technique Open Laparoscopic	 289 (61) 188 (39)	 177 (65) 96 (35)	 112 (55) 90 (45)	0.02
Anaesthetic technique GA GA+RA	 98 (20) 379 (80)	 55 (20) 218 (80)	 42 (21) 160 (79)	0.47
Preop mGPS 0 1 2	 308 (66) 71 (15) 86 (18)	 16 (63) 46 (17) 55 (20)	 137 (71) 25 (13) 31 (16)	0.08
Opioids No Yes	 18 (4) 457 (96)	 11 (4) 260 (96)	 7 (3) 195 (97)	0.46
Neoadjuvant therapy No Yes	 402 (85) 72 (15)	 215 (79) 56 (21)	 185 (92) 16 (8)	<0.001

Adjuvant therapy No Yes	 259 (54) 216 (45)	 131 (48) 141 (52)	 126 (63) 75 (37)	0.001
Preoperative dexamethasone No Yes	 129 (27) 347 (73)	 62 (23) 211 (77)	 67 (33) 134 (67)	0.25
POD 2 CRP > 150 mg/L No Yes	 324 (69) 149 (31)	 191 (71) 80 (29)	 133 (67) 67 (33)	0.20
POD 3 CRP > 150 mg/L No Yes	 284 (60) 189 (40)	 161 (60) 109 (40)	 122 (61) 79 (39)	0.44
POD 4 CRP > 150 mg/L No Yes	 313 (67) 156 (33)	 173 (65) 95 (35)	 139 (70) 60 (30)	0.13
Any complication No Yes	 323 (68) 151 (32)	 188 (69) 83 (31)	 134 (67) 67 (33)	0.30
Infective complications No Yes	 361 (76) 114 (24)	 207 (76) 65 (24)	 152 (76) 49 (24)	0.49

Clavien-Dindo grade 0 1-2 3-4 5	 254 (54) 163 (34) 51 (11) 7 (2)	 143 (53) 100 (37) 26 (10) 3 (1)	 110 (55) 63 (31) 25 (12) 3 (1)	0.59

Table 8.2: The relationship between pre-operative medications, type of anaesthesia, and clinicopathological characteristics in patients undergoing surgery for colorectal cancer from 2015- 2019, (n = 202).

Characteristics	**One medication, *n* = 99 (49%)**	**Two or more medications, *n*= 103 (51%)**	***P*-value**
Age <65 65-74 >75)	 21 (21) 43 (44) 35 (35)	 18 (17) 44 (43) 41 (40)	<0.42
Sex Male female	 58 (59) 41 (41)	 69 (67) 34 (33)	0.13
BMI Underweight (<20) Normal (20-25) Overweight (26-30) Obese (>30)	 0 (0) 27 (27) 37 (38) 35 (35)	 3 (3) 21 (20) 39 (38) 40 (39)	0.69
Smoking Never Ex Current	 48 (49) 34 (35) 15 (16)	 41 (40) 46 (45) 16 (15)	0.33
ASA grade 1 2 3 4	 2 (2) 48 (51) 42 (44) 3 (3)	 0 (0) 36 (36) 56 (55) 9 (9)	0.005

TNM stage I II III IV	 27 (29) 31 (33) 25 (26) 11 (12)	 25 (25) 42 (42) 26 (26) 7 (7)	0.79
Tumour site Colon Rectum	 69 (70) 30 (30)	 72 (71) 30 (29)	0.69
Surgical technique Open Laparoscopic	 54 (55) 45 (45)	 57 (55) 46 (45)	0.51
Anaesthetic technique GA GA + RA	 24 (24) 75 (76)	 19 (18) 84 (82)	0.20
Preop mGPS 0 1 2	 72 (77) 8 (8) 14 (15)	 85 (66) 17 (17) 17 (17)	0.22
Opioids No Yes	 3 (3) 96 (97)	 4 (4) 99 (96)	0.52
Neoadjuvant therapy No Yes	 89 (91) 9 (9)	 96 (93) 7 (7)	0.35

Adjuvant therapy No Yes	 62 (63) 36 (37)	 65 (63) 38 (37)	0.54
Preoperative dexamethasone No Yes	 33 (34) 65 (66)	 33 (32) 70 (68)	0.93
POD 2 CRP > 150 mg/L No Yes	 68 (69) 30 (31)	 65 (64) 37 (36)	0.24
POD 3 CRP > 150 mg/L No Yes	 60 (61) 39 (39)	 62 (61) 40 (39)	0.54
POD 4 CRP > 150 mg/L No Yes	 63 (64) 36 (36)	 76 (76) 24 (24)	0.04
Any complication No Yes	 64 (65) 35 (35)	 70 (69) 32 (31)	0.32
Infective complications No Yes	 70 (71) 29 (29)	 82 (80) 20 (20)	0.07
Clavien-Dindo grade 0 1-2 3-4 5	 53 (53) 31 (31) 14 (14) 1 (1)	 57 (56) 32 (31) 11 (11) 2 (2)	0.73

9. The relationship between nutritional status, anaesthetic approach, and peri-operative characteristics of patients undergoing surgery for colorectal cancer.

9.1 Introduction

CRC is classified as the third most commonly diagnosed cancer and the fourth most common cause of cancer death in worldwide (Ferlay et al., 2015). In addition to tumour stage, the progression and prognosis of disease are based on the nutritional status and inflammatory factors of the host (Bai and Feng, 2019).

In early-stage disease surgery is the primary modality of cure and therefore the interaction between nutritional, inflammatory, surgical, and anaesthetic factors are of considerable interest. Among patients undergoing colorectal resection, nutritional status is recognised to be an important factor for post-operative complications (Reber et al., 2019, Maurício et al., 2018). In the UK and Europe the Malnutrition Universal Screening Tool (MUST) has been widely adopted as a nutritional risk screening tool in hospitals as recommended by the European Society for Clinical Nutrition and Metabolism (Kondrup et al., 2003). Also, there has been an explosion of recent interest in the use of computed tomography (CT) to quantify muscle and adipose tissue. Such measures have also been associated with clinical outcomes in patients undergoing surgery for CRC. For example, the presence of visceral obesity and sarcopenia have been reported to be associated postoperative complications (Almasaudi et al., 2019, Okugawa et al., 2019). Also, visceral obesity (Okamura et al., 2018) and sarcopenia (Abbass et al., 2019, Abbass et al., 2020, Richards et al., 2012) have been reported to be associated with the presence of a systemic inflammatory response.

However, how these nutritional and inflammatory factors interact with anaesthetic and surgical practice is, to our knowledge, not known. Therefore, the aim of the present study was to examine the relationship between nutritional status (MUST, CT derived body composition), anaesthesia and surgical practice and perioperative characteristics such as the

magnitude of the postoperative SIR and complications of patients undergoing resection for CRC.

9.2 Patients and Methods

9.2.1 Patients

505 consecutive patients who underwent potentially curative resection for CRC between 2015 and 2019 at Glasgow Royal Infirmary hospital were identified from a prospectively maintained database. Anaesthetic technique was categorised into GA or GA + RA. Preoperative CT scans and BMI for those patients were identified and patients were excluded due to the lack of CT scans (n=13) and incomplete MUST information (n=15). A total of 477 patients (male: 263; female: 214) undergoing surgery for CRC were included in the analysis.

BMI of each patient was classified into; underweight (BMI < 18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), and obese (BMI ≥ 30). All tumours were staged according to TNM staging system (tumour, node and metastasis). Patient comorbidity was assessed by using the American Society of Anaesthesiologists (ASA) grading system and the severity of surgical complications were classified using the Clavien-Dindo scale (Fitz-Henry, 2011a, Dindo et al., 2004b). The preoperative modified Glasgow Prognostic Score (mGPS), was used to assess the preoperative systemic inflammatory response as follows; patients with normal CRP concentration (<10 mg/L) were scored as zero; patients with high CRP concentration (>10 mg/L) scored as one and patients with high CRP concentration (>10 mg/L) and hypoalbuminaemia (<35 g/L) scored as two (McMillan, 2013b). The magnitude of the postoperative SIR was measured by the post-operative C-reactive protein (CRP ≤150 or >150 mg/L), on the second, third and fourth postoperative days (Watt et al., 2017).

The study was approved by the West of Scotland Research Ethics Committee, Glasgow.

9.2.2 Methods

MUST was used to identify those patients who were at nutritional risk. This was performed before surgery by a nurse and calculated the overall risk of malnutrition. The overall risk of malnutrition was determined using three independent criteria including current weight status using BMI (kg/m^2), unintentional weight loss in the previous 3-6 months and an acute disease effect that has induced a phase of nil food consumption for more than 5 days (Figure 1). Each parameter can be rated as 0, 1, or 2. Overall risk for malnutrition is established as low (score = 0), medium (score = 1), or high (score > 2).

Preoperative CT scan was used to measure the body composition and was obtained at the level of the third lumbar vertebra as previously described by Richards et al. (Richards et al., 2012). All scans were taken in the three months prior to surgery. Each image was analysed using a free-ware program (NIH Image J version 1.47, http://rsbweb.nih.gov/ij/) shown to provide reliable measurements (Feliciano et al., 2017). Region of interest (ROI) measurements were made of visceral fat (VFA), subcutaneous fat (SFA), and skeletal muscle areas (SMA) (cm^2) using standard Hounsfield Unit (HU) ranges (adipose tissue -190 to -30, and skeletal muscle -29 to +150). These were then normalised for $height^2$ to create indices; total fat index (TFI, cm^2/m^2), visceral fat index (VFI, cm^2/m^2), subcutaneous fat index (SFI, cm^2/m^2), and skeletal muscle index (SMI, cm^2/m^2). Visceral obesity was defined as VFA >160 cm^2 for male and > 80 cm^2 for female. High subcutaneous fat index was defined as > 50 cm^2/m^2 in male and > 42 cm^2/m^2 in female (Dolan et al., 2019). Skeletal muscle radiodensity (SMD, HU) was measured from the same region of interest used to calculate SMI, as its mean HU. A low SMI was defined as described by Dolan et al. as SMI < 45 cm^2/m^2 if BMI < 25 kg/m^2 or SMI < 53 cm^2/m^2 if BMI ≥ 25 kg/m^2 in male patients. In female patients, SMI < 39 cm^2/m^2 if BMI < 25 kg/m^2 or SMI < 41 cm^2/m^2 if BMI ≥ 25 kg/m^2. A low SMD was also defined by Dolan et al. as SMD < 34.1 HU in male and < 34.4 HU in female. These measurements were carried out by two individuals (A. A. and T. A.),

and inter-rater reliability was assessed in a sample of 30 patient images using inter-class correlation coefficients (ICCCs) (SMA ICCC = 0.997; SMD ICCC = 0.998), (TFA ICCC = 1.000; SFA ICCC = 1.000; and VFA ICCC = 0.999). The investigators were blind to all the clinicopathological data of patients.

9.2.3 Data analysis

Data were analysed using SPSS version 26.0 for windows (IBM Corporation, Armonk, NY, USA). The frequency and summary statistics were reported. The X^2 (Chi-square) statistical method was used to test the statistical significance between markers of nutritional status and anaesthetic technique and clinicopathological variables. Due to multiple comparisons, a p-value of <0.01 was considered statistically significant.

9.3 Results

9.3.1 Patients Characteristics

The majority of patients were older than 65 years of age (59%), male (55%), overweight or obese (68%), were current or ex-smokers (53%), low ASA (60%), TNM stage I/II (56%), colon cancer (60%), underwent open surgery (61%) and had general plus regional anaesthesia (80%). The majority of patients had a low nutrition risk measured by MUST score = 0, (83%), had CT defined visceral obesity (71%), subcutaneous obesity (76%), low skeletal muscle index (SMI, 54%), low skeletal muscle density (SMD, 63%), had a normal preoperative mGPS (55%), received opioids (95%) and received dexamethasone (73%, Table 9.1).

9.3.2 Nutritional status, anaesthesia and clinicopathological characteristics (Table 9.1)

A high MUST was significantly associated with older age (p-value <0.05), low BMI (p-value <0.001), smoking (p-value <0.05), high ASA grade (p-value <0.05), open surgery (p-value =0.003), body composition measures including CT defined sarcopenia (p-value <0.001), CT defined myosteatosis (p-value =0.05), CT defined visceral obesity (p-value <0.001) and CT defined subcutaneous adiposity (p-value <0.001), high preoperative mGPS (p-value <0.001), preoperative dexamethasone administration (p-value <0.05) and high postoperative CRP on day 3 (p-value <0.05). However, there was no significant association between MUST and anaesthetic approach (p-value =0.47) or with anaesthesia with any measure of CT scan body composition including VO (p-value =0.83) and SFI (p-value =0.19) and SMI (p-*value* =0.57).

9.3.3 Skeletal muscle index, anaesthesia, and clinicopathological characteristics (Table 9.2)

Table 9.2 shows the relationship between skeletal muscle index, anaesthesia, and clinicopathological characteristics in patients undergoing surgery for colorectal cancer. There were no significant associations between CT defined sarcopenia and anaesthesia (*p*-value =0.57). Also, there were significant associations between SMI, age (*p*-value <0.001), sex (*p*-value <0.05), BMI (*p*-value <0.001), ASA grade (*p*-value <0.05), MUST score (*p*-value <0.001), skeletal muscle density (*p*-value <0.001), subcutaneous adiposity (*p*-value <0.05), and preoperative mGPS (*p*-value <0.05) in patients undergoing surgery for colorectal cancer.

9.3.4 Visceral obesity, anaesthesia, and clinicopathological characteristics

Table 9.3 shows the relationship between visceral obesity, anaesthesia, and clinicopathological characteristics of patients undergoing surgery for colorectal cancer. There was no significant association between body composition measure including CT defined visceral obesity and anaesthesia (*p*-value =0.83). There were significant associations between visceral obesity, BMI (*p*-value <0.001), MUST score (*p*-value <0.001), skeletal muscle index (p-value <0.05), skeletal muscle density (*p*-value <0.001), visceral obesity (*p*-value <0.001), preoperative mGPS (*p*-value <0.05), opioids (*p*-value <0.05), neoadjuvant chemotherapy (*p*-value <0.05), postoperative CRP on day 2 (p-value <0.05) and infective complications (p-value <0.05) in patients undergoing surgery for colorectal cancer.

9.3.5 Subcutaneous obesity, anaesthesia, and clinicopathological characteristics

Table 9.4 shows the relationship between subcutaneous fat index, anaesthesia, and clinicopathological characteristics in patients undergoing surgery for colorectal cancer. There was no significant association between body composition measure including CT defined subcutaneous obesity and anaesthesia (*p*-value =0.19). There were significant

associations between subcutaneous obesity, sex (p-value <0.001), BMI (p-value <0.001), smoking (p-value <0.05), MUST score (p-value <0.001), skeletal muscle density (p-value <0.001), visceral obesity (p-value <0.001), preoperative mGPS (p-value <0.05), neoadjuvant chemotherapy (p-value <0.05), stoma type (p-value <0.05) and POD 4 CRP (p-value <0.05) in patients undergoing surgery for colorectal cancer.

9.4 Discussion

In the present study, despite the importance of nutritional risk factors (and their inter-relationships) in determining short and long-term outcomes following surgery for colorectal cancer, there was no significant association between nutritional status and anaesthetic approach, however, there was a significant association between nutritional risk and surgical method. Obese patients underwent for laparoscopic surgery while those with normal BMI underwent for open surgery.

Logistic regression model was not applied in our study because the results of this work did not show any relationship between nutritional risk, CT based body composition and anaesthesia. These results would suggest, that even within an enhanced recovery programme, the anaesthetic approach is not tailored to the patient's nutritional status per se and that other factors, such as surgical approach are likely to exert a greater influence on practice.

The results of the present study show that nutritional status measures were consistently associated with the SIR. These observations are consistent with observations made in a variety of common solid tumours (Abbass et al., 2019).

An enhanced recovery after surgery (ERAS) is a pathway designed to use components of treatment to reduce the surgical stress response and thus reduce post-operative complications and accelerate the post-operative recovery. Indeed, it has been reported that ERAS protocols reduce the morbidity rate, improve the recovery, and shorten the length of hospital stay in patients undergoing surgery for colorectal cancer (Pedziwiatr et al., 2018, Gustafsson et al., 2019). However, the evidence base for the components of such a pathway has been questioned (Watt et al., 2015d).

In terms of anaesthesia, within an ERAS pathway, recommendations include; avoidance of long-acting pre-medicant drugs, minimisation of pre-operative fasting, proactive treatment of post-operative nausea and vomiting, and use of multi-modal analgesia. There is currently

no agreed optimal anaesthetic, with recommendations focusing on the avoidance of overly deep levels of general anaesthesia whichever technique is used. Whilst, there is some evidence that anaesthetic approach may moderate the post-operative systemic inflammatory response (Alhayyan et al., 2020a, Alhayyan et al., 2020b), this remains poorly defined and further work in patients receiving anaesthetics with anti-inflammatory effects, such as TIVA will be useful in teasing out such relationships (Roh et al., 2019).

Traditionally, in major cancer surgery, analgesic regimens mainly rely on opioids to obtain effective analgesia, but this can cause undesirable side effects and delay recovery (Dunkman and Manning, 2018). Within an ERAS pathway it is desirable to minimise the use of opioids and promote the use of multimodal analgesia to optimize recovery to normal functioning (Gustafsson et al., 2019). It was of interest that in the present study where all patients were enrolled in an ERAS protocol, only few patients received propofol for the maintenance of anaesthesia and most patients received opioids and inhalational anaesthesia. Therefore, it would appear that within our ERAS protocol that both anaesthesia and analgesia were suboptimal, and this would have hampered our ability to detect an effect on the post-operative systemic inflammatory response.

Some limitations should be acknowledged in the present study including, its retrospective nature, at a single centre, with only those patients with an available CT scans and with MUST scores were included in the analysis. However, compared with other studies in the field, the patient cohort was relatively large with detailed clinicopathological characteristics.

In summary, the present study shows that in patients undergoing elective surgery for colorectal cancer within an ERAS pathway, the anaesthetic method was not associated with measures of nutritional status or the SIR. Further studies examining such relationships in patients receiving multi-modal anaesthesia and analgesia are warranted.

9.5 Figures and Legends

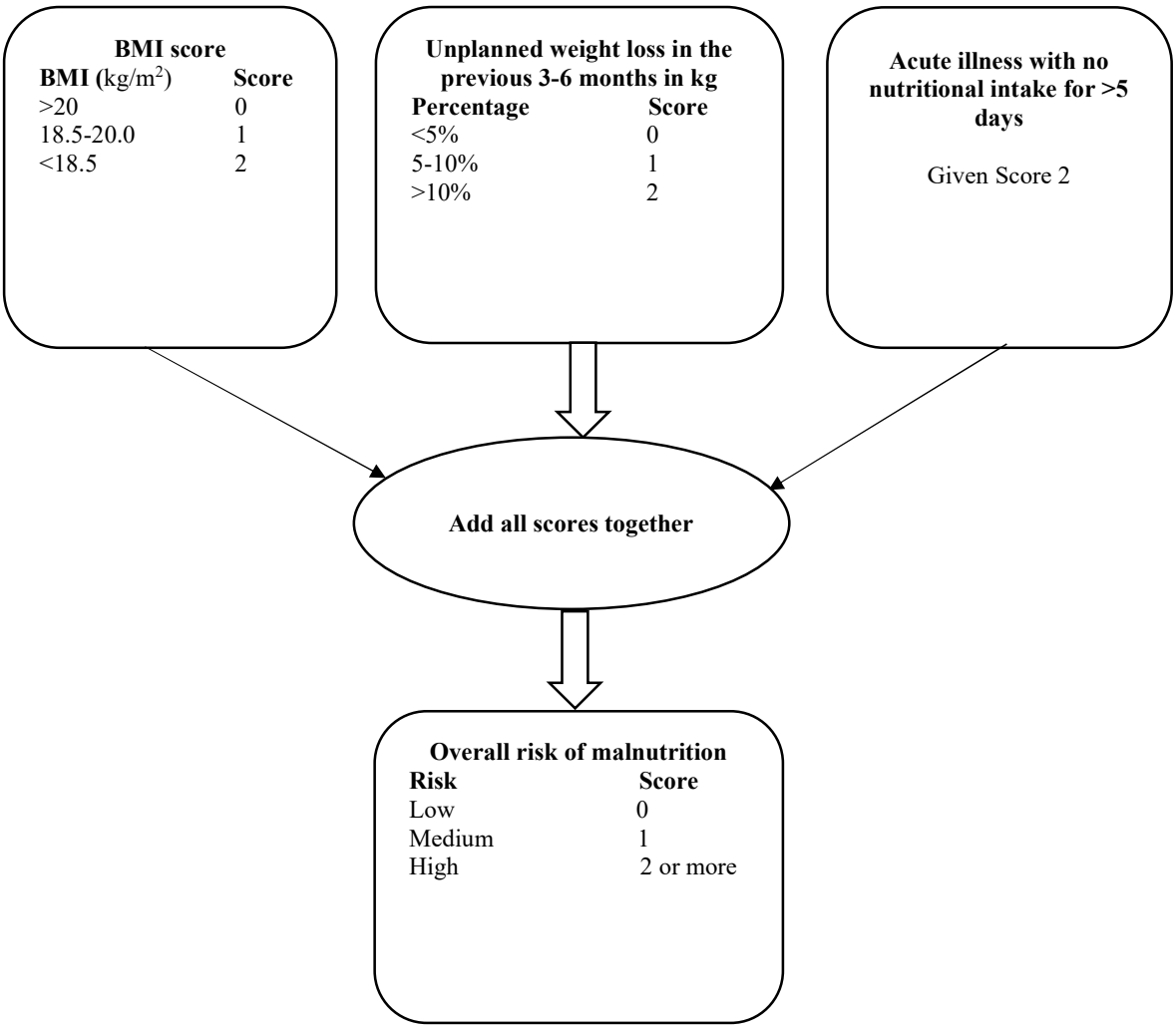


Figure 9.1: Malnutrition Universal screening tool (Elia and BAPEN, 2003).

9.6 Tables and Footnotes

Table 9.1: The relationship between nutritional risk, anaesthesia, and clinicopathological characteristics in patients undergoing surgery for colorectal cancer, (*n* = 477).

Characteristics	All, *n* (%)	Low risk, *n* = 396 (83%)	Medium to high risk, *n* = 80 (17%)	*P*-value
Age				0.02
<65	197 (43)	169 (43)	28 (35)	
65-74	159 (33)	136 (34)	23 (28)	
>75)	121 (25)	91 (23)	30 (37)	
Sex				0.37
Male	263 (55)	222 (56)	41 (51)	
female	214 (45)	174 (44)	40 (49)	
BMI				<0.001
Underweight (<20)	12 (3)	3 (1)	10 (12)	
Normal (20-25)	138 (29)	97 (24)	41 (51)	
Overweight (26-30)	178 (37)	155 (39)	23 (28)	
Obese (>30)	148 (31)	141 (36)	7 (9)	
Smoking				0.01
Never	221 (47)	190 (48)	31 (38)	
Ex	176 (37)	147 (38)	29 (36)	
Current	75 (16)	54 (14)	21 (26)	
ASA grade				0.02
1	44 (10)	39 (10)	5 (6)	
2	235 (51)	201 (52)	34 (44)	
3	167 (36)	133 (35)	34 (44)	
4	16 (3)	11 (3)	5 (6)	

TNM stage I II III IV	 98 (21) 163 (35) 164 (35) 31 (9)	 87 (22) 123 (31) 144 (37) 26 (10)	 11 (14) 40 (52) 20 (26) 5 (8)	0.93
Tumour site Colon Rectum	 287 (60) 188 (40)	 230 (58) 165 (42)	 57 (71) 23 (29)	0.07
Surgical technique Open Laparoscopic	 289 (61) 188 (39)	 228 (58) 168 (42)	 61 (75) 20 (25)	0.003
Anaesthetic approach GA GA+RA	 98 (20) 379 (80)	 79 (20) 317 (80)	 19 (23) 62 (77)	0.47
Visceral obesity combined sex No Yes	 137 (29) 340 (71)	 91 (23) 305 (77)	 46 (57) 35 (43)	<0.001
Subcutaneous adiposity No Yes	 113 (24) 361 (76)	 76 (19) 318 (81)	 37 (46) 43 (54)	<0.001
Sarcopenia Dolan-combined sex No Yes	 221 (46) 255 (54)	 200 (50) 196 (50)	 22 (36) 58 (64)	<0.001
Myosteatosis Dolan-combined sex No Yes	 178 (37) 299 (63)	 140 (35) 256 (65)	 37 (47) 43 (53)	0.05
Preop mGPS				<0.001

0 1 2	308 (67) 71 (15) 86 (18)	272 (71) 56 (14) 57 (15)	36 (45) 15 (19) 29 (36)	
Opioids No Yes	 18 (4) 457 (96)	 17 (4) 377 (96)	 1 (1) 80 (99)	0.18
Neoadjuvant therapy No Yes	 402 (85) 72 (15)	 337 (85) 57 (15)	 65 (81) 15 (19)	0.33
Adjuvant therapy No Yes	 259 (55) 216 (45)	 212 (54) 182 (46)	 47 (58) 34 (42)	0.48
Preoperative dexamethasone No Yes	 129 (27) 347 (73)	 102 (26) 293 (74)	 27 (33) 54 (67)	0.01
POD 2 CRP > 150 mg/L No Yes	 324 (69) 149 (31)	 275 (70) 117 (30)	 48 (61) 32 (39)	0.08
POD 3 CRP > 150 mg/L No Yes	 284 (60) 189 (40)	 242 (60) 148 (40)	 40 (49) 40 (51)	0.03
POD 4 CRP > 150 mg/L No Yes	 313 (67) 156 (33)	 264 (68) 125 (32)	 49 (61) 31 (39)	0.25
Stoma type No	 283 (60)	 235 (60)	 48 (60)	0.93

Ileostomy Colostomy	111 (23) 79 (17)	93 (24) 65 (16)	18 (22) 14 (18)	
Any complication No Yes	 323 (68) 151 (32)	 273 (69) 120 (31)	 50 (62) 31 (38)	0.17
Infective complications No Yes	 361 (76) 114 (24)	 304 (77) 90 (23)	 57 (70) 24 (30)	0.19
Clavien-Dindo grade 0 1-2 3-4 5	 254 (54) 163 (34) 51 (11) 7 (1)	 216 (55) 127 (30) 46 (14) 7 (1)	 38 (47) 36 (44) 5 (7) 1 (2)	0.89

Table 9.2: The relationship between body composition, in particular skeletal muscle index, anaesthesia, and clinicopathological characteristics in patients undergoing surgery for colorectal cancer, (n = 476).

Skeletal muscle index (SMI), SMI < 45 cm^2/m^2 if BMI < 25 kg/m^2 and SMI < 53 cm^2/m^2 if BMI ≥ 25 kg/m^2 in male patients. In female patients, SMI < 39 cm^2/m^2 if BMI < 25 kg/m^2 and SMI < 41 cm^2/m^2 if BMI ≥ 25 kg/m^2			
Characteristics	**Not sarcopenic, *n* = 221 (46%)**	**Sarcopenic, *n* = 255 (54%)**	***P*-value**
Age			<0.001
<65	111 (50)	86 (34)	
65-74	72 (33)	86 (34)	
>75)	38 (17)	83 (32)	
Sex			0.02
Male	110 (50)	153 (60)	
female	111 (50)	102 (40)	
BMI			<0.001
Underweight (<20)	2 (1)	11 (5)	
Normal (20-25)	53 (24)	84 (33)	
Overweight (26-30)	68 (31)	110 (43)	
Obese (>30)	98 (44)	50 (19)	
Smoking			0.60
Never	101 (46)	119 (47)	
Ex	79 (36)	97 (38)	
Current	38 (18)	37 (15)	
ASA grade			0.003
1	26 (12)	18 (8)	
2	116 (54)	119 (48)	
3	69 (32)	97 (39)	
4	3 (2)	13 (5)	
TNM stage			0.20
I	56 (27)	42 (17)	

II III IV	58 (28) 82 (38) 12 (7)	105 (43) 82 (32) 19 (8)	
Tumour site Colon Rectum	 132 (60) 88 (40)	 154 (61) 100 (39)	0.70
Surgical technique Open Laparoscopic	 135 (61) 86 (39)	 153 (60) 102 (40)	0.80
Anaesthetic approach GA GA+RA	 43 (20) 178 (80)	 55 (22) 200 (78)	0.57
MUST score Low risk Medium risk High risk	 200 (90) 14 (6) 7 (4)	 196 (77) 30 (12) 29 (11)	<0.001
Myosteatosis Dolan-combined sex No Yes	 103 (47) 118 (53)	 74 (29) 181 (71)	<0.001
Visceral obesity combined sex No Yes	 56 (25) 165 (75)	 80 (31) 175 (69)	0.14
Subcutaneous adiposity No Yes	 41(19) 178 (81)	 72 (28) 183 (72)	0.01

Preop mGPS 0 1 2	 155 (73) 26 (12) 33 (15)	 152 (61) 45 (18) 53 (21)	0.01
Opioids No Yes	 11 (5) 208 (95)	 7 (3) 248 (97)	0.19
Neoadjuvant therapy No Yes	 119 (54) 101 (46)	 139 (55) 115 (45)	0.34
Adjuvant therapy No Yes	 212 (54) 182 (46)	 27 (60) 18 (40)	0.89
Preoperative dexamethasone No Yes	 60 (27) 160 (73)	 68 (27) 187 (73)	0.75
POD 2 CRP > 150 mg/L No Yes	 160 (72) 61 (28)	 164 (65) 87 (35)	0.09
POD 3 CRP > 150 mg/L No Yes	 141 (64) 80 (36)	 143 (57) 108 (43)	0.13
POD 4 CRP > 150 mg/L No Yes	 147 (67)	 165 (66) 84 (34)	0.84

	72 (33)		
Stoma type No Ileostomy Colostomy	 140 (64) 44 (20) 36 (16)	 142 (56) 67 (26) 43 (18)	0.25
Any complication No Yes	 156 (71) 63 (29)	 166 (65) 88 (35)	0.17
Infective complications No Yes	 169 (77) 50 (23)	 191 (75) 64 (25)	0.56
Clavien-Dindo grade 0 1-2 3-4 5	 216 (54) 127 (31) 46 (14) 7 (1)	 23 (51) 18 (41) 2 (4) 2 (4)	0.99

Table 9.3: The relationship between visceral obesity, anaesthesia, and clinicopathological characteristics in patients undergoing surgery for colorectal cancer, (n = 477).

Visceral obesity (VO), VFA >160 cm^2 for male and >80 cm^2 for female			
Characteristics	**No, *n* = 137 (29%)**	**Yes, *n* = 340 (71%)**	***P*-value**
Age			0.68
<65	62 (45)	135 (40)	
65-74	38 (28)	121 (36)	
>75)	37 (27)	84 (24)	
Sex			0.12
Male	68 (50)	195 (57)	
female	69 (50)	145 (43)	
BMI			<0.001
Underweight (<20)	13 (10)	0 (0)	
Normal (20-25)	87 (64)	51 (14)	
Overweight (26-30)	35 (25)	143 (43)	
Obese (>30)	2 (1)	146 (43)	
Smoking			0.48
Never	68 (50)	153 (45)	
Ex	37 (27)	139 (41)	
Current	31 (23)	44 (14)	
ASA grade			0.95
1	15 (12)	29 (9)	
2	63 (49)	172 (52)	
3	45 (34)	122 (37)	
4	7 (5)	9 (2)	
TNM stage			0.29
I	19 (14)	79 (24)	
II	57 (43)	106 (33)	

III	49 (38)	115 (35)	
IV	7 (5)	24 (8)	
Tumour site			0.86
Colon	230 (60)	33 (25)	
Rectum	53 (40)	135 (75)	
Surgical technique			0.21
Open	89 (65)	200 (59)	
Laparoscopic	48 (35)	140 (41)	
Anaesthetic approach			0.83
GA	29 (21)	69 (20)	
GA+RA	108 (79)	271 (80)	
MUST score			<0.001
Low risk	91 (67)	305 (90)	
Medium risk	24 (18)	21 (6)	
High risk	21 (15)	14 (4)	
Sarcopenia Dolan-combined sex			0.01
No	41 (36)	178 (49)	
Yes	72 (64)	183 (51)	
Myosteatosis Dolan-combined sex			<0.001
No	68 (60)	108 (30)	
Yes	45 (40)	253 (70)	
Subcutaneous adiposity			<0.001
No	74 (54)	32 (11)	
Yes	62 (46)	299 (89)	
Preop mGPS			0.02
0	80 (60)	228 (70)	
1	24 (17)	47 (14)	
2	32 (23)	54 (16)	

Opioids No Yes	 9 (6) 128 (94)	 9 (3) 329 (97)	0.04
Neoadjuvant therapy No Yes	 107 (79) 28 (21)	 295 (87) 44 (13)	0.03
Adjuvant therapy No Yes	 75 (55) 61 (45)	 184 (54) 155 (46)	0.86
Preoperative dexamethasone No Yes	 32 (23) 105 (77)	 97 (28) 242 (72)	0.96
POD 2 CRP > 150 mg/L No Yes	 104 (76) 33 (24)	 220 (65) 116 (35)	0.02
POD 3 CRP > 150 mg/L No Yes	 90 (66) 47 (34)	 194 (58) 142 (42)	0.10
POD 4 CRP > 150 mg/L No Yes	 95 (70) 40 (30)	 218 (65) 116 (35)	0.28
Stoma type No Ileostomy	 78 (58) 33 (25)	 205 (60) 78 (23)	0.70

Colostomy	23 (17)	56 (17)	
Any complication No Yes	 100 (73) 37 (27)	 223 (66) 114 (34)	0.14
Infective complications No Yes	 113 (82) 24 (18)	 248 (73) 90 (27)	0.03
Clavien-Dindo grade 0 1-2 3-4 5	 77 (56) 49 (36) 9 (7) 2 (1)	 177 (50) 114 (41) 42 (8) 5 (1)	0.14

Table 9.4: The relationship between subcutaneous fat index, anaesthesia, and clinicopathological characteristics in patients undergoing elective surgery for colorectal cancer, (n = 474).

Subcutaneous Fat Index (SFI), > 50 cm^2/m^2 in male and ≥ 42 cm^2/m^2 in female

Characteristics	No, *n* = 113 (24%)	Yes, *n* = 361 (76%)	*P*-value
Age			0.77
<65	50 (44)	146 (40)	
65-74	38 (30)	124 (35)	
>75)	30 (26)	91 (25)	
Sex			<0.001
Male	85(75)	177 (49)	
female	28 (25)	184 (51)	
BMI			<0.001
Underweight (<20)	12 (10)	1 (1)	
Normal (20-25)	61 (54)	7 (7)	
Overweight (26-30)	38 (34)	139 (41)	
Obese (>30)	2 (2)	145 (51)	
Smoking			0.01
Never	44 (39)	175 (49)	
Ex	43 (38)	132 (37)	
Current	26 (23)	49 (14)	
ASA grade			0.28
1	8 (7)	36 (10)	
2	55 (51)	178 (51)	
3	39 (36)	127 (36)	
4	6 (6)	10 (3)	
TNM stage			0.31
I	18 (17)	80 (23)	
II	42 (39)	121 (35)	
III	39 (37)	123 (36)	
IV	8 (7)	23 (6)	

Tumour site Colon Rectum	 67 (60) 45 (40)	 219 (61) 141 (39)	0.94
Surgical technique Open Laparoscopic	 69 (61) 44 (39)	 219 (61) 142 (39)	0.51
Anaesthetic approach GA GA+RA	 28 (25) 85 (75)	 69 (19) 292 (81)	0.19
MUST score Low risk Medium risk High risk	 76 (67) 17 (15) 20 (18)	 318 (88) 27 (8) 16 (4)	<0.001
Sarcopenia Dolan-combined sex No Yes	 56 (41) 80 (59)	 165 (48) 175 (52)	0.14
Myosteatosis Dolan-combined sex No Yes	 68 (60) 45 (40)	 108 (30) 253 (70)	<0.001
Visceral obesity No Yes	 74 (64) 39 (36)	 62 (17) 299 (83)	<0.001
Preop mGPS 0 1 2	 64 (57) 19 (17) 30 (26)	 241 (69) 52 (15) 56 (16)	0.007
Opioids No	 6 (5)	 12 (3)	0.34

Yes	107 (95)	347 (97)	
Neoadjuvant therapy No Yes	 87 (78) 24 (22)	 312 (87) 48 (13)	0.02
Adjuvant therapy No Yes	 59 (53) 53 (47)	 199 (55) 161 (45)	0.35
Preoperative dexamethasone No Yes	 31 (27) 82 (73)	 96 (27) 264 (73)	0.94
POD 2 CRP > 150 mg/L No Yes	 81 (72) 31 (28)	 241 (67) 117 (33)	0.32
POD 3 CRP > 150 mg/L No Yes	 74 (67) 37 (33)	 208 (58) 151 (42)	0.10
POD 4 CRP > 150 mg/L No Yes	 83 (75) 27 (25)	 227 (64) 129 (36)	0.02
Stoma type No Ileostomy Colostomy	 57 (51) 31 (28) 23 (21)	 224 (62) 80 (23) 55 (15)	0.04

Any complication No Yes	 78 (69) 35 (31)	 242 (68) 116 (32)	0.77
Infective complications No Yes	 91 (80) 22 (20)	 268 (75) 91 (25)	0.20
Clavien-Dindo grade 0 1-2 3-4 5	 59 (52) 42 (37) 10 (9) 2 (2)	 193 (55) 120 (33) 41 (11) 5 (1)	0.85

10. The relationship between opioid administration, type of anaesthesia and clinicopathological characteristics in patients undergoing surgery for colorectal cancer.

10.1 Introduction

In developed countries, CRC is the fourth leading cause of cancer death (Torre et al., 2015). Until now, the treatment is mainly based on surgery by removing the cancer tissue and by using chemo/ radiotherapy (Mishra et al., 2013). Since surgery results in a whole-body stress response, patient and surgery associated factors are likely to be important in determining the impact on the immune system and outcome of surgery (Wall et al., 2019b).

Enhanced recovery protocols have examined the benefit of using RA in reducing the stress response from surgery, minimising opioid use and promoting early mobilisation following surgery, however due to the lack of objective end-points their effects on enhancing recovery is not clear (Watt et al., 2015d). In particular, it would appear that in patients who received epidural anaesthesia, although pain was better controlled, the effect on the magnitude of the post-operative systemic inflammatory response was not clear (Chen et al., 2015, Siekmann et al., 2017b, Kehlet, 2020, Alhayyan et al., 2020a).

Chapter 6 has examined the effect of anaesthesia on the postoperative CRP concentrations as a marker of the postoperative SIR in colon cancer patients and reported that the anaesthetic method may influence the postoperative CRP. In particular, in those patients undergoing open surgery for colon cancer CRP on post-operative day 2 was lower and therefore, there is some evidence that regional anaesthesia may affect the postoperative SIR (Alhayyan et al., 2020b).

Opioids have been used for a long time as an effective treatment for post-operative pain in patients undergoing surgery for cancer. They exert the analgesic effect through binding to

opioid receptors in the central nervous system. However, they may produce a pro-inflammatory effect by interacting with opioid receptors on the membranes of immune cells and increase pro-inflammatory cytokine production (Rogers and Peterson, 2003, Reece, 2012, Chopan and Littenberg, 2015). Therefore, the aim of the present study was to examine the relationship between opioid administration, anaesthetic approach and clinicopathological variables in patients undergoing elective surgery for colorectal cancer.

10.2 Patients and Methods

The present study utilised a prospective proforma including clinicopathological data, all the anaesthetic technique or agents and all the medications administered before and after induction of anaesthesia such as neuromuscular blockers, steroids, antibiotics, and benzodiazepines in patients who underwent elective surgery for colorectal cancer.

519 consecutive patients who underwent elective open (n= 289) or laparoscopic surgery (n= 188) for colorectal cancer from 2015 – 2019 within an ERAS pathway were identified from a prospectively maintained database at single centre. Of these only 477 patients had documented anaesthetic records. Patients either received general anaesthesia (n= 98) or general + regional anaesthesia (n= 379). Some patients received opioid analgesia postoperatively (n= 278) while 187 did not receive morphine after surgery, but they received other type of opioids.

The study was approved by the West of Scotland Research Ethics Committee, Glasgow. Data were anonymised and all emergency cases were excluded from the study.

In addition, the CRP level (CRP ≤150 or >150 mg/L) was measured on day 2-4 after surgery which reflects the magnitude of the postoperative systemic inflammatory response. TNM staging system (tumour, node and metastasis) was used for tumour stage, the comorbidity of patients was assessed by using the American Society of Anaesthesiologists (ASA) grading system and the severity of surgical complications was classified using the Clavien-Dindo scale (Fitz-Henry, 2011b, Dindo et al., 2004a).

10.2.1 Data analysis

Data were analysed using SPSS version 27.0 for windows (IBM Corporation, Armonk, NY, USA). For the statistical analysis, the X^2 (Chi-square) was used to test the statistical significance between the opioid administration, anaesthetic method and clinicopathological variables with a p-value of <0.05 considered statistically significant. Moreover, binary logistic regression model was used to examine the relationship between the opioid administration, anaesthesia and clinicopathological variables with the calculation of odds ratio (OR) and 95% confidence interval (CI). On univariate analysis, all the clinicopathological variables with a p-value <0.10 were included into a multivariate analysis using a backward conditional model to identify independently significant variables.

10.3 Results

The majority of patients were <65 years old (42%), male (55%), overweight (37%) or obese (31%), non-smokers (47%), underwent open surgery (61%) and received general + regional anaesthetic technique (80%). Preoperative IV dexamethasone was administered to 347 patients (73%). Morphine was administered postoperatively for 278 (60 %) patients (Table 10.1).

Table 10.1 shows the relationship between patients who received morphine versus patients who did not receive morphine, anaesthesia and clinicopathological characteristics in patients undergoing elective surgery for colorectal cancer. There was a significant association between opioids administered v.s no opioids administered, anaesthetic technique ($p<0.001$), and surgical technique ($p<0.01$).

Table 10.2 shows the relationship between opioid administration and clinicopathological data of patients undergoing elective surgery for colorectal cancer. There was a significant association between opioids administered, age ($p<0.05$), sex ($p\leq0.01$), BMI ($p<0.01$), ASA grade ($p<0.01$), anaesthesia ($p<0.001$), POD 2, POD 3 and POD4 CRP >150 mg/L (all $p<0.01$). There was a significant association between opioids administered and any complication ($p<0.01$) and infective complications ($p<0.05$).

Table 10.3 shows the binary logistic regression of clinicopathological data associated with low versus high dose of morphine in patients undergoing elective surgery for colorectal cancer. On univariate analysis, morphine administration was significantly associated with sex ($p<0.05$), BMI ($p<0.01$), ASA grade ($p<0.001$), anaesthetic technique ($p<0.001$) and a lower POD 2 CRP (≤150/>150 mg/L, $p<0.001$). On multivariate analysis, morphine administration was independently associated with sex (OR 1.97; CI 1.12-3.45; p=0.018), BMI (OR 1.66; CI 1.18-2.33; p=0.003), ASA grade (OR 0.46; CI 0.30-0.71; p=0.001),

anaesthetic technique, (OR 0.32; CI 0.17-0.59; p<0.001) and a lower POD 2 CRP (OR 3.33; CI 1.86-5.97; p<0.001).

Table 10.4 shows binary logistic regression of clinicopathological data associated with low versus high dose of morphine in male patients undergoing elective surgery for colorectal cancer. On univariate analysis, morphine administration was significantly associated with ASA grade (p<0.01), and anaesthetic technique (p<0.05). On multivariate analysis, morphine administration was independently associated with ASA grade (OR 0.37; CI 0.20-0.69; p=0.001), and anaesthetic technique (OR 0.37; CI 0.17-0.68; p=0.009).

Table 10.5 shows opioid equivalency doses for different opioid drugs, for both oral and parenteral routes of administration. This was used when referring the doses of different opioids that are estimated to give the same pain relief. The calculation of equi analgesic dose is used to choose the appropriate initial dose when changing the route of administration or one type of opioid to another.

10.4 Discussion

The results of the present study showed that morphine administration was associated with both patient factors and factors associated with the anaesthetic technique. In particular, male sex, obesity and the magnitude of the systemic inflammatory response were independently associated with greater morphine administration whereas comorbidity and regional anaesthesia were independently associated with lesser morphine administration. When these factors were examined in male patients (n=70), only opioid administration was independently associated ASA grade and anaesthetic technique. In addition, the number of male patients were more than female. Taken together these results show the relative importance of the drivers of opioid administration in patients undergoing surgery for colorectal cancer within an enhanced recovery protocol.

Of the above factors the use of a regional anaesthetic appeared to have the greatest association with lower opioid administration. Given that there is increasing concern about the detrimental effects of the use of opioids in cancer surgery (Wall et al., 2019b), there is a need to consider further anaesthetic and analgesic approaches that spare opioid administration. For example, the use of other multi-modal analgesic drugs such as NSAIDS, paracetamol, clonidine, magnesium, and intravenous lignocaine (Wall et al., 2019b) and by utilising RA techniques where possible.

Of the above factors the magnitude of the post-operative systemic inflammatory response appeared to have the greatest association with higher opioid administration. Given that there is now evidence that magnitude of the post-operative systemic inflammatory response is associated with post-operative infective complications and poorer long term survival (Watt et al., 2017a, McSorley et al., 2016b), and that, in the advanced cancer patient, systemic inflammation is associated with pain (Laird et al., 2013, Boland et al., 2020). There is a need to reduce the magnitude of the surgery induced systemic

inflammatory response. For example, minimally invasive surgery reduces the magnitude of the post-operative systemic inflammatory response in patients with cancer (Watt et al., 2015d). Therefore, from the above, there may be modifications to anaesthetic and surgical practice that would reduce the requirements for opioids in the post-operative period and reduce the magnitude of the post-operative systemic inflammatory response. It is anticipated that such reductions would improve short term and long-term outcomes in patients undergoing surgery for colorectal cancer.

In the present study, anaesthetic technique was more closely associated with opioid administration than surgical technique. This is perhaps surprising given that the magnitude of the post-operative SIR is different between two surgical approaches, and it may be anticipated that in open surgery with higher operative trauma there may be more requirement for opioids. However, these results may simply reflect the anaesthetist preference for post-operative opioid administration. Further work on the determinants of opioid administration in the post-operative period is required to clearly delineate these relationships.

The CRP profile may be a cause of higher morphine administration since it may reflect the magnitude of surgical injury. Alternatively, it may reflect the pro-inflammatory effect of opioids. Unfortunately, such cross-sectional studies cannot differentiate between a cause or a consequence.

The present retrospective observational cohort study has some limitations. The use of surgical and anaesthetic techniques was variable, and it was a single-centre study. However, this study was carried in a relatively large well documented group of patients undergoing surgery for colorectal cancer. The present study, carried out using data collected from a prospective proforma, examined the association between post-operative opioid administration and patient related and anaesthetic related factors. Although the aim

was broad it has provided a comprehensive data analysis not previously reported in the literature. Similarly, the sequelae of events in the systemic inflammatory response to elective surgery is complex and remains the subject of ongoing investigation, there is a well characterised acute phase protein response by the liver to such tissue injury. Of the liver proteins produced, CRP is prototypical and clinically useful since its concentration in the plasma reflects the magnitude of surgical injury (Watt et al., 2015c). Indeed, plasma CRP concentration thresholds have been used clinically to guide safe discharge after elective colorectal surgery (Singh et al., 2014).

In summary, in patients undergoing elective surgery for colorectal cancer, opioid administration was independently associated with both anaesthetic and operative factors. These may be important in reducing the requirement for opioid administration.

10.5 Tables and Footnotes

Table 10.1: The relationship between the administration of opioids vs non opioids administered, anaesthesia, and clinicopathological characteristics in patients undergoing surgery for colorectal cancer from 2015- 2019, (n = 477).

Characteristics	All, *n* (%)	Patients who did not receive morphine, n =187 (40%)	Patients who received morphine, *n* =278 (60%)	*P*-value
Age				0.96
<65	197 (42)	48 (40)	142 (41)	
65-74	159 (33)	42 (35)	114 (33)	
>75)	121 (25)	30 (25)	89 (26)	
Sex				0.18
Male	263 (55)	71 (59)	159(46)	
female	214 (45)	49 (41)	39 (36)	
BMI				0.93
Underweight (<20)	13 (3)	3 (2)	9 (3)	
Normal (20-25)	138 (29)	60 (32)	77 (28)	
Overweight (26-30)	178 (37)	70 (37)	102 (37)	
Obese (>30)	148 (31)	54 (29)	90 (32)	
Smoking				0.51
Never	221 (47)	52 (44)	163 (48)	
Ex	176 (37)	49 (41)	122 (36)	
Current	75 (16)	18 (15)	56 (16)	
ASA grade				0.54
1	44 (10)	11 (10)	30 (9)	

2	235 (51)	63 (55)	165 (49)	
3	167 (36)	35 (30)	130 (39)	
4	16 (3)	6 (5)	10 (3)	
TNM stage				0.76
I	98 (21)	25 (21)	70 (21)	
II	163 (35)	42 (35)	116 (34)	
III	164 (35)	41 (34)	121 (36)	
IV	31 (7)	9 (8)	21 (6)	
Tumour site				0.55
Colon	287 (60)	69 (58)	210 (61)	
Rectum	188 (40)	51 (42)	133 (39)	
Anaesthetic technique				<0.001
GA	98 (20)	47 (39)	46 (13)	
GA+RA	379 (80)	73 (61)	299 (87)	
Surgical technique				0.002
Open	289 (61)	59 (49)	223 (65)	
Laparoscopic	188 (39)	61 (51)	122 (35)	
Preop mGPS				0.13
0	308 (66)	72 (62)	227 (67)	
1	71 (15)	17 (14)	53 (16)	
2	86 (19)	28 (24)	57 (17)	
Neoadjuvant therapy				0.12
No	402 (85)	106 (88)	285 (83)	
Yes	72 (15)	14 (12)	57 (17)	
Adjuvant therapy				0.10
No	259 (55)	59 (49)	193 (56)	
Yes	216 (45)	61 (51)	150 (44)	

Preoperative dexamethasone No Yes	 129 (27) 347 (73)	 32 (27) 133 (79)	 96 (28) 248 (72)	0.19
POD 2 CRP > 150 mg/L No Yes	 324 (69) 149 (31)	 78 (66) 41 (34)	 237 (69) 106 (31)	0.27
POD 3 CRP > 150 mg/L No Yes	 284 (60) 189 (40)	 73 (62) 45 (38)	 202 (59) 142 (41)	0.31
POD 4 CRP > 150 mg/L No Yes	 313 (67) 156 (33)	 79 (68) 38 (32)	 226 (66) 115 (34)	0.45
Stoma type No Ileostomy Colostomy	 283 (60) 111 (23) 79 (17)	 73 (61) 28 (23) 18 (15)	 201 (59) 80 (23) 61 (18)	0.51
Any complication No Yes	 323 (68) 151 (32)	 81 (68) 39 (32)	 233 (68) 110 (32)	0.50
Infective complications No Yes	 361 (76) 114 (24)	 87 (73) 33 (27)	 263 (77) 80 (23)	0.21
Clavien-Dindo grade 0	 254 (53)	 60 (50)	 187 (54)	0.16

1-2 3-4 5	163 (34) 51 (11) 7 (2)	41 (33) 17 (14) 2 (2)	119 (35) 33 (10) 4 (1)	

Table 10.2: The relationship between opioid administration (morphine equivalent), anaesthesia, and clinicopathological characteristics in patients undergoing surgery for colorectal cancer from 2015- 2019, (*n* = 278).

Characteristics	Morphine < 15 mg, *n* =169 (61%)	Morphine > 15 mg, *n* =109 (39%)	*P*-value
Age			0.02
<65	62 (37)	52 (48)	
65-74	60 (35)	38(35)	
>75)	47 (28)	19 (17)	
Sex			0.01
Male	85 (50)	70 (64)	
female	84 (50)	39 (36)	
BMI			0.003
Underweight (<20)	7 (4)	0 (0)	
Normal (20-25)	57 (34)	27 (25)	
Overweight (26-30)	58 (34)	36 (33)	
Obese (>30)	47 (28)	46 (42)	
Smoking			0.57
Never	79 (48)	49(45)	
Ex	64 (38)	41 (38)	
Current	23 (14)	18 (17)	
ASA grade			0.003
1	10 6)	13 (12)	
2	73 (46)	67 (61)	
3	68 (43)	28 (26)	
4	7 (5)	1 (1)	
TNM stage			0.70
I	41 (27)	25 (23)	
II	53 (32)	44 (41)	

III IV	58 (35) 9 (56)	32 (30) 5 (56)	
Tumour site Colon Rectum	 116 (70) 51 (30)	 75 (70) 33 (30)	0.73
Anaesthetic technique GA GA+RA	 33 (19) 136 (81)	 45 (41) 64 (59)	<0.001
Surgical technique Open Laparoscopic	 89 (53) 80 (47)	 58 (53) 51 (47)	0.51
Preop mGPS 0 1 2	 112 (69) 22 (14) 28 (17)	 70 (65) 21 (19) 17 (16)	0.77
Neoadjuvant therapy No Yes	 148 (89) 18 (11)	 101 (93) 8 (7)	0.22
Adjuvant therapy No Yes	 96 (58) 71 (42)	 61 (56) 48 (44)	0.45
Preoperative dexamethasone No Yes	 35 (21) 133 (79)	 31 (28) 78 (72)	0.41
POD 2 CRP > 150 mg/L No Yes	 128 (77)	 57 (52)	<0.001

	39 (23)	52 (48)	
POD 3 CRP > 150 mg/L No Yes	 113 (68) 54 (32)	 55 (51) 43 (49)	0.004
POD 4 CRP > 150 mg/L No Yes	 119 (72) 47 (28)	 60 (57) 46 (43)	0.008
Stoma type No Ileostomy Colostomy	 117 (70) 37 (22) 14 (8)	 70 (64) 25 (23) 14 (13)	0.22
Any complication No Yes	 126 (75) 41 (25)	 67 (62) 42 (38)	0.01
Infective complications No Yes	 133 (80) 34 (20)	 76 (70) 33 (30)	0.04
Clavien-Dindo grade 0 1-2 3-4 5	 98 (59) 53 (32) 14 (8) 2 (1)	 53 (49) 42 (38) 12 (11) 2 (2)	0.16

Table 10.3: Binary logistic regression of clinicopathological data associated with low vs high dose of morphine in patients undergoing elective surgery for colorectal cancer (n= 278).

Variables	Univariate analysis OR (95% CI)	*P*-value	Multivariate analysis OR (95% CI)	*P*-value
Age (<65/65-74/>75)	0.90 (0.61-1.34)	0.624	_	_
Sex (male/female)	2.03 (1.13-3.63)	0.017	1.97 (1.12-3.45)	0.018
BMI (<20/20-25/26-30/>30)	1.64 (1.14-2.34)	0.006	1.66 (1.18-2.33)	0.003
ASA grade (1/2/3/4)	0.44 (0.27-0.72)	0.001	0.46 (0.30-0.71	0.001
GA alone /GA+ RA (no/yes)	0.33 (0.18-0.63)	0.001	0.32 (0.17-0.59)	<0.001
POD 2 CRP > 150 mg/L (no/yes)	2.60 (1.22-5.54)	0.013	3.33 (1.86-5.97)	<0.001
POD 3 CRP > 150 mg/L (no/yes)	0.97 (0.40-2.34)	0.95	_	_
POD 4 CRP > 150 mg/L (no/yes)	1.39 (0.61-3.18)	0.42	_	_

Table 10.4 Binary logistic regression of clinicopathological data associated with low vs high dose of morphine in male patients undergoing elective surgery for colorectal cancer, (n= 155).

Variables	Univariate analysis OR (95% CI)	*P*-value	Multivariate analysis OR (95% CI)	*P*-value
Age (<65/65-74/>75)	0.90 (0.53-1.54)	0.716	_	_
BMI (<20/20-25/26-30/>30)	1.54 (0.90-2.62)	0.108	_	_
ASA grade (1/2/3/4)	0.39 (0.19-0.77)	0.007	0.37 (0.20-0.66)	0.001
GA alone /GA+ RA (no/yes)	0.34 (0.15-0.77)	0.011	0.37 (0.17-0.78)	0.009
POD 2 CRP > 150 mg/L (no/yes)	0.25 (0.94-6.98)	0.064	_	_
POD 3 CRP > 150 mg/L (no/yes)	0.82 (0.23-2.90)	0.766	_	_
POD 4 CRP > 150 mg/L (no/yes)	2.55 (0.83-7.84)	0.102	_	_

Table 10.5 Morphine equianalgesic table.

Name of opioid	Oral (mg)	Parenteral (mg)
Morphine	30	10
Fentanyl (IV only)	---	0.1 (100 mcg)

11. Conclusions and future work

11.1 Overview of thesis

Colorectal cancer (CRC) contributes to the second leading cause of death in UK (CRUK, 2015). Most patients undergo oncologic surgery as a key component of their treatment. During surgery patients are given anaesthesia (general and/or regional). Surgery activates the hypothalamic pituitary adrenal (HPA) axis and sympathetic nervous system and a phenomenon called surgical stress response occurs resulting in profound effects on both the innate and adaptive cell mediated immune systems. Cancer recurrence risk or tumour dissemination potentially initiated from a stress response caused by surgery and some perioperative therapies such as volatile anaesthesia and analgesic opioids (Behrenbruch et al., 2018).

The impact of anaesthetic techniques is varying on their effects on innate and cellular immunity that may be translated into their influence on long-term outcomes. Previous retrospective and prospective studies have hypothesized that regional anaesthesia on various cancer types may improve cancer related outcomes (Lin et al., 2020). In addition, general anaesthesia whether intravenous or inhalational have also different influence on immunity and stress response. For example, inhalational anaesthesia has been reported to have greater stress response than propofol based TIVA, decrease cell ratios of T1 helper cell/T2 helper cell, impair the activity of NK cell, and induce apoptosis of T lymphocytes. On the other hand, propofol has shown to preserve NK cell function (Chang et al., 2021). Therefore, it is plausible that anaesthesia may modify the surgical stress response (Cusack and Buggy, 2020). However, such an effect has to be investigated in the context of other factors such as the patient characteristics, the type of surgery and a reliable marker of the systemic inflammatory response. A wealth of evidence has shown that CRP reflects the

magnitude of surgical trauma and it can be routinely measured in clinical laboratories (Watt et al., 2015). Therefore, after elective operation, CRP can be used to monitor the magnitude of SIR. For example, open surgery is associated with greater increase in CRP when compared with laparoscopic surgery. Furthermore, it has been identified that cardio-vascular drugs such aspirin, some other nonsteroidal anti-inflammatory including cyclooxygenase-2 inhibitors, and statins may have a benefit in reducing the inflammatory response in cancer survivors (Park et al., 2014).

As a part of anaesthesia, analgesia should be included intra and post-operatively with opioids. Although opioids are considered as the most powerful analgesic drug and effectively used to manage acute cancer surgery pain and chronic cancer related pain. However, the use of opioids may produce undesirable side effects including respiratory depression, constipation, delay recovery of bowel function, post-operative nausea and vomiting, drowsiness, and sweating (Szczepaniak et al., 2020). Additionally, the immune-suppressive effect of opioids has been recognised for a long time. They act on opioid receptors and non-opioid toll-like receptors and produce direct effect on immune cells or indirect effects via sympathetic nervous system and hypothalamic-pituitary-adrenal axis (Boland and Pockley, 2018).

It has been reported that morphine, fentanyl, methadone, remifentanil, and codeine have immunomodulatory effect while oxycodone, hydrocodone, tramadol, and buprenorphine do not (Buggy 2020). Outcome may be influenced by the opioid dose and duration of exposure (Boland and Pockley, 2018).

In recent years, there was a retrospective study focused on the correlation between post-operative CRP and narcotic use. The author investigated, in patients who underwent for laparoscopic major abdominal surgery, there was a positive association between an increase of CRP level, opioid consumption and higher pain score (Choi et al., 2019).

In patients undergoing elective colorectal surgery, ERAS protocol has been implemented and designed to reduce hospital stay, minimize surgical stress response, accelerate recovery, and improve outcomes. The elements include pre-operative oral intake, avoidance of mechanical bowel preparation, early post-operative mobilization, and laparoscopic surgical technique. The use of multimodal analgesic therapy is an integral part of ERAS. This includes opioid-sparing analgesic regimens such as the administration of systemic medications, regional and neuraxial techniques to improve pain while reducing opiate consumption and their side effects with early mobility, early return of GI function and minimizing post-operative morbidity. Patients who have had an open surgery may receive an epidural analgesia whereas TAP blocks may be used for those who have had laparoscopic surgery (Simpson et al., 2019).

The aim of this thesis was to examine the relationship between the perioperative characteristics, perioperative anaesthesia, and the postoperative systemic inflammatory response following surgery for colorectal cancer investigating whether anaesthesia influences the post-operative systemic inflammatory response in particular CRP level on day 2-4 and post-operative complications.

In Chapter 5, a systematic review and meta-analysis of 60 randomised controlled trials was carried out on the effect of general anaesthesia, regional anaesthesia or both combined on the postoperative systemic inflammatory response and post-operative infective complications in patients undergoing surgery with varying severity. The mean or median values of both IL-6 and CRP were taken for each study and the mean value was calculated for each anaesthetic group at sampling points of 12-24 and 24-72 hours for IL-6 and CRP respectively. There was a suggestion that TIVA using propofol was associated with a reduction in the magnitude of the postoperative systemic inflammatory response, in particular CRP but not IL-6, in moderate to major severity of surgery. However, there

were no other specific anaesthetic methods including general, regional, and combined anaesthetics that reduced the magnitude of the post-operative SIR and infective complications. It was concluded that the magnitude of the post-operative SIR and infective complications was not affected by specific anaesthetic techniques, but the limitations should be taken in consideration including small number of sample size in each arm, high level of heterogeneity and most of the included studies had low granularity of data and this may have affected the results of meta-analysis. In addition, the review included a variety of studies with different tumour type, minor, moderate to severe surgery, with different types of anaesthesia and this may have influenced the efficacy of the anaesthetic agent examined.

To establish whether colorectal cancer surgery may be a suitable model a retrospective cohort study was conducted in Chapter 6. This cohort study included only those patients who underwent for colon resection. In this chapter the relationship between anaesthetic technique, clinicopathological characteristics and the magnitude of the postoperative systemic inflammatory response in patients undergoing elective surgery for colon cancer was examined. It was concluded that in patients undergoing surgery for elective colon cancer, the type of anaesthesia varied over time and appeared to influence the magnitude of the postoperative SIR on post-operative day 2 CRP in open surgery but not laparoscopic surgery. Furthermore, potential confounding factors such as pre-operative administration of dexamethasone were identified. In a significant proportion of patients, dexamethasone was given to reduce nausea and vomiting after surgery and appeared to reduce the magnitude of post-operative SIR and post-operative complications. Future work was required to better define this relationship.

Chapter 7 presented a prospective cohort study about the effect of anaesthesia on the magnitude of the postoperative systemic inflammatory response in patients undergoing

elective surgery for colorectal cancer in the context of an enhanced recovery pathway. This study was conducted by using a specific proforma including clinicopathological data, all the anaesthetic technique and/or agents and all the medications administered before and after induction of anaesthesia. It was shown that there was a modest but an independent association between regional anaesthesia (RA) and a lower magnitude of the postoperative SIR. These results were supportive of a role for anaesthetic technique in modulating the postoperative SIR.

Chapters 8- 10 examined other potential confounding factors, using the prospective cohort data, and examined whether the administration of pre-operative medications, the nutritional status and opioids consumption may also influence the type of anaesthesia and the post-operative systemic inflammatory response in patients undergoing surgery for colorectal cancer. Chapter 8 reported that although there was a significant association between pre-operative medications and assessment of patient comorbidity (age, obesity and ASA grade), there was no significant association between pre-operative medications including aspirin, statins and ACE inhibitors and any anaesthetic regimen.

Chapter 9 reported that although there was a significant association between MUST score and CT based body composition and measures of comorbidity and the post-operative systemic inflammatory response, there was no significant association between measures of nutritional status and anaesthetic approach.

Chapter 10 reported that taking into account potential confounding factors, opioid administration was independently associated with both anaesthetic and operative factors. From the results of these thesis, anaesthetic practice is closely linked with type of surgery, open or laparoscopic, rather than the patient characteristics and paradoxically potential pro-inflammatory anaesthesia tends to be given to patients undergoing open surgery (producing the greater systemic inflammatory response). Given the importance of patient characteristics in determining surgical outcome, further work is required to determine the optimal anaesthetic regimen for the patient and surgical approach to be used to resect

colorectal cancer. The role of anaesthesia may become less important if the magnitude of surgical injury could be minimized.

11.2 Future work

In oncological surgery, it has long been postulated that the anaesthetic regimen may through its impact on the immune/ inflammatory response influence cancer recurrence. It is an attractive target since it is readily modifiable. However, detailed evidence has been lacking due to the number of potential confounding factors in such analysis. The present thesis attempted to address some of these limitations.

The advantage of combining optimal general with regional anaesthesia includes early recovery, effective postoperative analgesia with less post-operative nausea and vomiting. In particular, following resection of colorectal cancer, ERAS protocols have been shown to improve recovery by reducing the length of hospital stay and opioid use and is now recommended for such cancer surgery (Gustafsson et al., 2019). The ERAS guidelines for colorectal cancer now recommend pre-operative nutritional care, preventions of nausea and vomiting, antimicrobial prophylaxis, applying minimally invasive techniques such as laparoscopic, using multimodal analgesia including regional analgesic techniques such as epidural analgesia (EA), spinal anaesthesia. transversus abdominis plane (TAP), rectus sheath blocks or continuous wound infiltration (CWI), avoidance of systemic morphine, avoidance of nasogastric tube with early oral feeding (Gustafsson et al., 2019). Recently, preoperative corticosteroids have been incorporated into a fast-track surgery protocol and thereby reduce the postoperative SIR and postoperative complications (McSorley et al., 2017b).

Most data are available from retrospective studies and data from prospective randomized controlled trials are lacking. Further work is required to fully understand the different effect of anaesthetic techniques and/ or agents on the post-operative systemic inflammatory response and long-term outcomes after cancer surgery. It is also important to standardise

anaesthesia together with the surgical insult within a specific group of patients to make the study groups homogenous and capable of teasing out the effect of particular agents.

Recently, it has been reported that amide local anaesthesia with lidocaine and IV anaesthesia with propofol might improve cancer outcomes by improving the immunity and thus leading to reduction in cancer recurrence (Johnson et al., 2018, Freeman et al., 2019).

Several studies have tried to compare the outcomes of cancer surgery with the use of propofol-based TIVA or inhalational anaesthesia. In this regard, propofol has potentially several benefits in cancer patients over other general anaesthetics such as inhalational agents. In RCT that compared between two groups; a group of breast cancer patients who received propofol with postoperative ketorolac analgesia and a group who received sevoflurane with postoperative fentanyl analgesia. The NK cell function was better preserved with a propofol-ketorolac group compared with the sevoflurane group. Most clinical trials have indicated that propofol was associated with better survival outcomes in surgical cancer patients (Li et al., 2018, Xu et al., 2020a). Another RCT with breast cancer patients showed that RA with paravertebral block and propofol did not reduce the recurrence in comparison with GA by using sevoflurane and opioids (Sessler et al., 2019).

A retrospective study by Wu et al. have found that propofol anaesthesia for colon cancer surgery was associated with better survival than volatile anaesthesia (Wu et al., 2018b). The same result was obtained with another tumour type, specifically, those who underwent for open pancreatic cancer surgery (Lai et al., 2020). In other surgical discipline such as plastic surgery, TIVA anaesthesia has been effectively administered for sedation with anaesthesia and adopted to reduce the surgical trauma. Based on this, it would be of interest to do further work with TIVA in colorectal cancer surgery and their effects on multiple factors mainly inflammatory profiles. Although a number of studies have indicated the advantages of the use of TIVA over inhalational anaesthesia, few

anaesthetists in our centre had experience with this technique and the short acting effect of propofol may put off anaesthetists from changing routine clinical practice to maintain anaesthesia in patients with colorectal cancer.

Adjuvant strategies targeting the inflammatory profiles such as neuraxial analgesia, β-blockers, nonsteroidal anti-inflammatory drugs (NSAIDs) may have beneficial effects in patients with major cancer surgery (Sessler and Riedel, 2019). Therapeutically, it is important to target the perioperative period by applying some methods to decrease the inflammatory response to surgery and may therefore minimize the effect of surgical treatments and combining β-adrenergic receptor antagonists and cyclo-oxygenase-2 (COX-2) inhibitors in the perioperative setting. Any confounding factors that may affect the results may need to be adjusted such pre-operative dexamethasone and any other pre-operative medications.

Future work should also focus on the optimization of patients' medically and physically in the preoperative, perioperative, and postoperative period. For example, optimize anaesthesia, patient nutrition status, GI function, and pain control. Furthermore, it is important to optimize and compare between different surgical types including robotic, laparoscopic, and open colorectal surgery and the perioperative stress and immune response after each surgical approach. As an example, it has been reported that robotic colorectal surgery may be an alternative to open or laparoscopic surgery, as a minimally invasive option on colorectal resection. A prospective study found that the inflammatory response was less with robotic colorectal surgery compared with an open approach (Zawadzki et al., 2017). In another prospective study, a surgical stress response was compared between robotic, laparoscopic, and open colorectal surgery and it was lower in both robotic and laparoscopic patients than in open surgical patients (Shibata et al., 2015). Since there was an association between anaesthesia and type of surgery, a point to be

addressed in the future whether the effect of anaesthesia will be quite different or not in patients undergoing robotic colorectal surgery because the requirement for opioids may be less.

In summary, different types of cancer may respond differently to pharmacological intervention and more clinical trials are needed in each cancer types to confirm the role of anaesthesia in outcomes following cancer surgery. Also, there are ongoing clinical trials comparing between TIVA and inhalational anaesthesia in multiple cancer types and the results are awaited.

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