COLORECTAL SURGERY

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Evaluation of the inflammatory profile following uncomplicated elective colectomy

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Abstract

Background: Attenuation of the inflammatory response in patients undergoing colectomy with modern perioperative care and laparoscopic surgery has been a focus of research in recent years. Despite reported benefits, significant heterogeneity remains with studies including patients undergoing both rectal and colon surgery and including surgery with postoperative complications. Therefore, the aim of the study was to evaluate the inflammatory response in patients undergoing elective colectomy without complications, specifically comparing open and laparoscopic approaches.

Methods: A multicenter prospective study was conducted across four public hospitals in Auckland and Christchurch, New Zealand. Consecutive adults undergoing elective colectomy were included over a 3-year period. Perioperative blood samples were collected and analysed for the following inflammatory markers: IL-6, IL-1β, TNFα, IL-10, CRP, leucocyte and neutrophil count. Statistical analysis was performed using SPSS statistical software.

Results: A total of 168 colectomy patients without complications were included in the analysis. Patients that underwent laparoscopy had significantly reduced IL-6, neutrophils and CRP on postoperative day (POD) 1 ($p < 0.05$) compared to an open approach. IL-10 and TNFα were significantly reduced on POD 2 ($p < 0.05$) in laparoscopic patients. Patients with a Body Mass Index (BMI) greater than 30 kg/m^2 had significantly higher levels of CRP regardless of operative approach. Statins altered both preoperative and postoperative inflammatory markers.

Conclusion: The postoperative inflammatory response is influenced by surgical approach, perioperative medications, and patient factors. These findings have important implications in the utility of biomarkers in the diagnosis of postoperative surgical complications, in particular in the early diagnosis of anastomotic leak.

Introduction

The human body secretes a multitude of inflammatory biomarkers both locally, in the abdominal cavity, and into the systemic circulation after major abdominal surgery. Several biomarkers have been identified as potential surrogate markers for the magnitude of the inflammatory response. Derangements of these biomarkers have been the subject of recent studies, due to their ability to reflect potential intra-abdominal complications.[1]

Pro-inflammatory biomarkers such as tumour necrosis factor (TNFα), Interleukin (IL)-1β and IL-6 play a critical role in promoting immunomodulatory effects of receptor cells (including leucocytes) and downstream inflammatory biomarkers such as C-reactive protein (CRP). Anti-inflammatory cytokines, such as IL-10, play a significant role in buffering this pro-inflammatory

effect to prevent unintentional injury as a result of the inflammatory response. A careful balance of this inflammatory response is therefore required for optimal healing following surgery.[2,3]

Several randomized studies have evaluated CRP and IL-6 following colorectal surgery, however these have often been limited to small numbers, have included both colonic and rectal cases, often did not exclude patients with anastomotic leak or other complications and commonly were not conducted in a modern perioperative care environment.[4,5]

Therefore, the aim of the study was to evaluate the inflammatory response in patients undergoing elective colectomy without postoperative complications, specifically comparing open and laparoscopic approaches in a modern perioperative care environment.

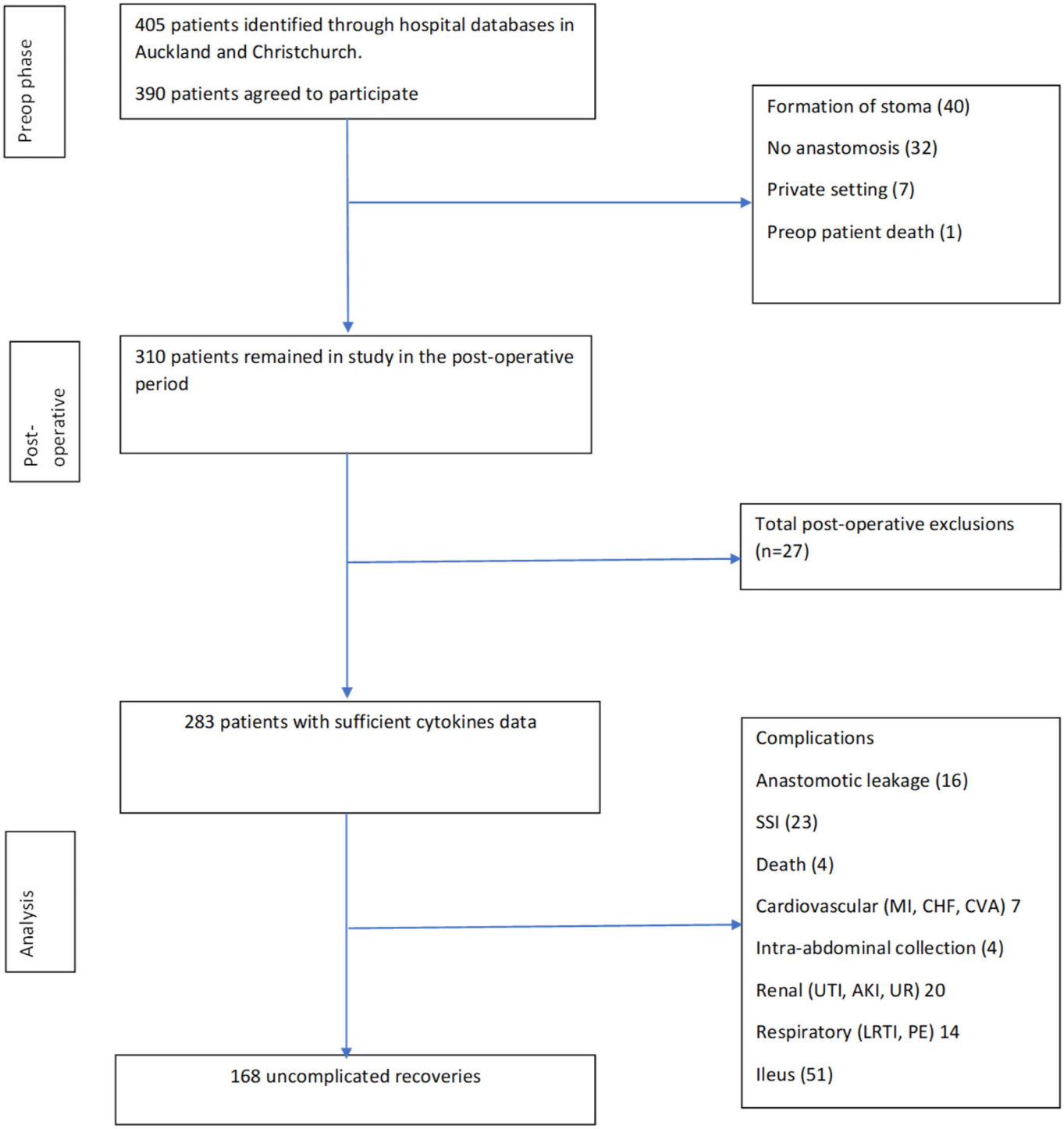

Fig. 1. Patient flow with exclusions.

Methods

Patient selection

Eligible adult (>16 years) patients admitted electively to four public teaching hospitals across Auckland and Christchurch, New Zealand were considered for the study. This study is reported according to the STROBE statement.[6] Consecutive eligible patients were initially approached at preadmission clinics. Exclusion criteria were as follows: patients undergoing surgery with no bowel-to-bowel anastomosis, age less than 16 years, patient refusal and rectal surgery (defined as <15 cm from anal verge), stoma formation, and conversion to open (laparotomy) surgery. Patients that suffered a postoperative complication were excluded from analysis. The study was approved by the New Zealand Health and Disability Ethics Committee (14/NTB/173), with locality approval provided for each centre prior to enrolment.

Perioperative care

In all enrolled patients, hospital-specific enhanced recovery protocols were followed unless specified by the attending surgeon. All operation details such as anaesthetic induction agents and pneumoperitoneum insufflation pressures, were left to attending surgeon or anaesthetic team.

Main outcome and blood tests

The following inflammatory parameters and biomarkers were measured from preoperative to POD 5: WCC ($\times 10^9$/L), neutrophils ($\times 10^9$/L), CRP (mg/L), IL-1β (pg/mL), IL-6 (pg/mL), IL-10 (pg/mL) and TNFα (pg/mL).

Full blood count (including WCC and Neutrophils), and CRP were analysed at each hospital site. EDTA (ethylenediaminetetraacetic acid) tube samples were centrifuged at $\times 1000g$, with supernatant removed, aliquoted and stored at <80°C for cytokine analysis. Samples were analysed in duplicate using a commercially available immunoassay kit, Millipore® Milliplex (Merck, Millkpore Corporation, Billerica, MA, USA).

Statistical analysis

Statistical analysis was performed using the Statistical package for the Social Sciences (SPSS ver. 25 Inc., Chicago, IL) software. Means, percentages and standard deviations were calculated and are shown where appropriate. Comparison of categorical variables were performed using Chi-square and Fisher's exact test. Normality was assessed using the Shapiro–Wilks test. The student *t* test was used for parametric variables, and Mann–Whitney *U* for non-parametric variables. Significance of differences were tested by analysis of variances (One-way ANOVA). Statistically significant differences were defined as $p < 0.05$. Multiple regression analysis performed where multiple factors predicted inflammatory response.

Table 1 Other complications

Other complication	*n* (%)
SSI	23 (9.2)
Death	4 (1.6)
Cardiovascular (MI, CHF and CVA)	7 (2.8)
Intra-abdominal collection	4 (1.6)
Renal (UTI,AKI and UR)	20 (8)
Respiratory (LRTI and PE)	14 (5.6)
Ileus	51 (20.3)

Abbreviations: AKI, acute kidney injury; CCF, congestive heart failure; CVA, cerebral vascular accident; MI, myocardial infarction; LRTI, lower respiratory tract infection; PE, pulmonary embolism; SSI, Surgical site infection; UTI, urinary tract infection, UR, urinary retention.

Results

A total of 405 patients undergoing colectomy were identified over 3 years across four public hospitals in Auckland and Christchurch,

Table 2 Baseline summary of included patients (*) denotes direct comparison between open and laparoscopic group showing a statistically significant result ($p < 0.05$)

Baseline variables	Open ($n = 53$)	Laparoscopy ($n = 115$)	*p*-value
Demographics			
Age (Median, years, IQR)	71 (21)	66 (25)	0.397
BMI (median, IQR)	29 (6.9)	27 (6.9)	0.048*
Obese *n* (% with >30 BMI)	25 (47.4)	31 (27.3)	0.025*
Gender male *n* (%)	28 (53)	57 (50)	0.602
Previous abdominal surgery *n* (%)	25 (46.5)	33 (28.4)	0.038*
Primary cancer diagnosis *n* (%)	8 (15.4)	11 (9.7)	1.00
Comorbidity *n* (%)			
Current smoker (%)	5 (9.8)	6 (5.4)	0.294
Hypertension (%)	26 (50)	60 (53.1)	0.711
Respiratory disease (%)	9 (17.3)	21 (18.6)	0.843
Dyslipidaemia (%)	12 (23.1)	17 (15)	0.208
Liver disease (%)	1 (1.9)	1 (0.9)	0.571
Type 2 Diabetes mellitus (%)	12 (23.1)	8 (7.1)	0.003*
Cardiovascular disease (% approach)	10 (19.2)	33 (29.2)	0.175
Renal disease (%)	5 (9.6)	8 (7.1)	0.574
Preoperative medications			
Statins	18 (39.1)	33 (30)	0.284
Steroids	2 (4.3)	0	0.028*
Anticoagulation	4 (8.7)	16 (14.7)	0.310
Operative details			
ASA (%)			0.693
1	2 (3.8)	7 (6.1)	
2	35 (66)	70 (60.9)	
3	16 (30)	36 (31.3)	
4	0	2 (1.7)	
Time in OT (median in minutes, IQR)	157.50 (65)	180.00 (85)	0.107
Type of surgery *n* (%)	Open	Laparoscopic	
High anterior resection	12 (22.6)	50 (43.5)	0.092*
Left hemicolectomy	3 (5.7)	4 (3.5)	0.51
Right hemicolectomy	30 (56.6)	58 (50.4)	0.46
Reversal of Hartmann	5 (9.4)	2 (1.7)	0.020*
Sub/total colectomy	3 (5.7)	1 (0.9)	0.058
Length of stay			
Median (IQR)	6 (2)	5 (2)	0.052
Preoperative			
Pre-operative albumin (mean, g/L, SD)	35.9 ± 4.06	37.4 ± 3.39	0.059
Total protein levels (Mean, g/L, SD)	70.5 ± 5.98	72.3 ± 5.4	0.149

Table 3 Summary of measured inflammatory biomarkers

Biomarker	Preop	POD 1	POD 2	POD 3	POD 4	POD 5
CRP (mg/L)						
Open	14.7*	90.8*	138.6*	137.3*	101.2*	89.4
Lap	6.4*	70*	88.4*	85.2*	72.2*	76.8
Leucocyte ($\times 10^9$ /L)						
Open	7.9	11.8*	10.5	8.7	7.5	6.9
Lap	7.3	10.8*	9.5	8.1	7.5	7.7
Neutrophils (($\times 10^9$ /L)						
Open	5.1	9.5*	8.2*	6.6*	5.3	4.5*
Lap	4.9	8.3*	7*	5.7*	5.1	5.4*
IL-10 (pg/mL)						
Open	26.2	26.2	21.9	24.6	20	18.5
Lap	21.9	21	17.9	20.9	31.6	35
IL-6 (pg/mL)						
Open	12.8	48*	34.6*	30.2*	18.3	17.8
Lap	10.8	29.2*	19.7*	19.1*	16.3	15
IL-1β (pg/mL)						
Open	8.2	5.9	6.4	6.4	6.2	5.2
Lap	6.4	4.3	4.6	5	8.2	6.6
TNFα (pg/mL)						
Open	32.4	28	30.8	33.6	29.2	28.6
Lap	28.2	26.6	25.4	27.3	36.1	31

Note: Displayed as mean. (*) denotes a statistically significant result. Lap: Laparoscopic group; pg.: Picogram; POD: Post-operative day.

Abbreviations: Lap, laparoscopic approach; IL, interleukin; Open, open approach; Preop, preoperative day/before surgery; POD, postoperative day; TNF, tumour necrosis factor.

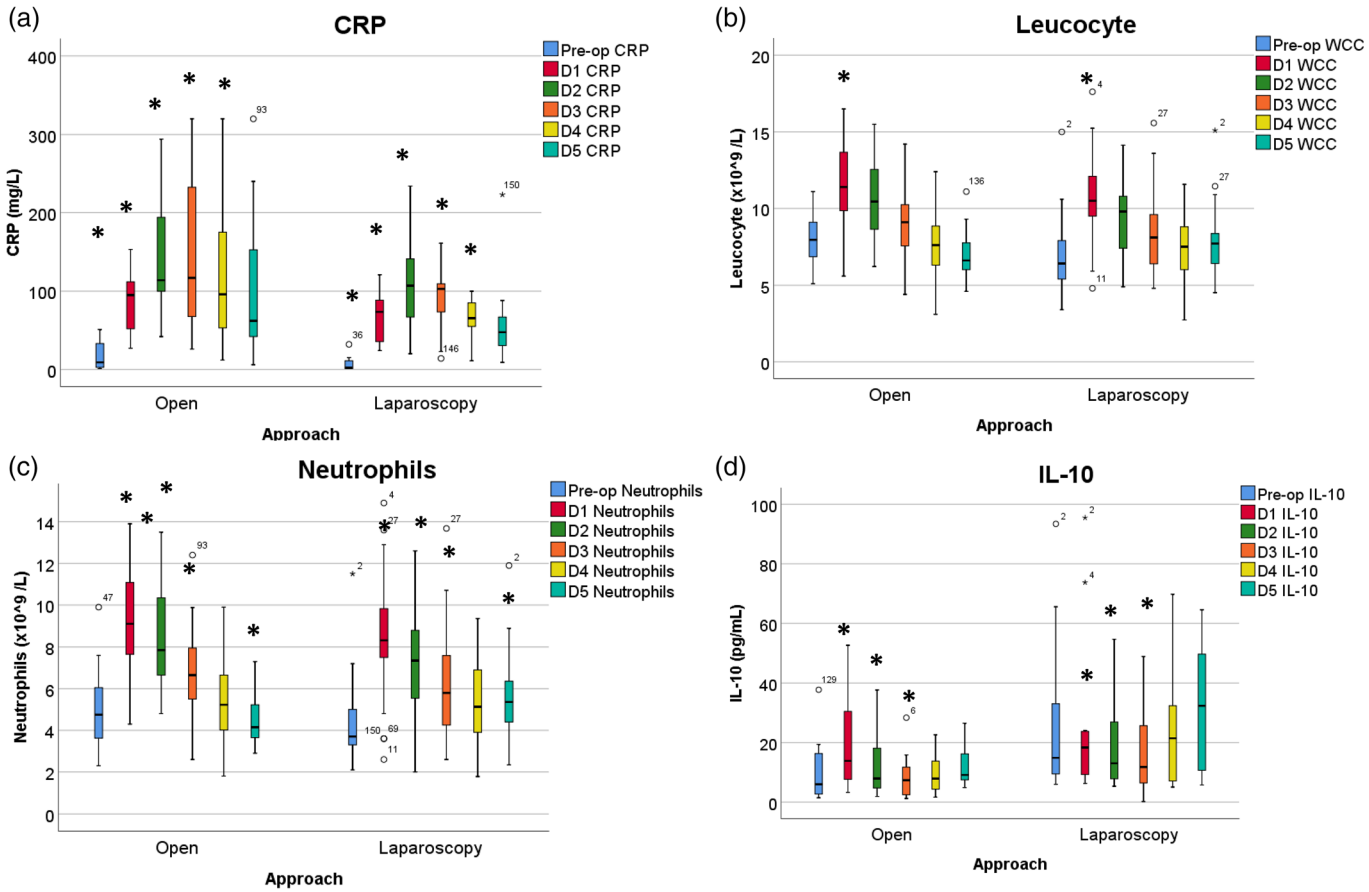

Fig. 2. Boxplot of measured inflammatory biomarkers. (a) CRP, (b) leucocyte, (c) neutrophils and (d) IL-10. (*) denotes a statistically significant result. Lap: laparoscopic group; pg.: picogram; POD: post-operative day.

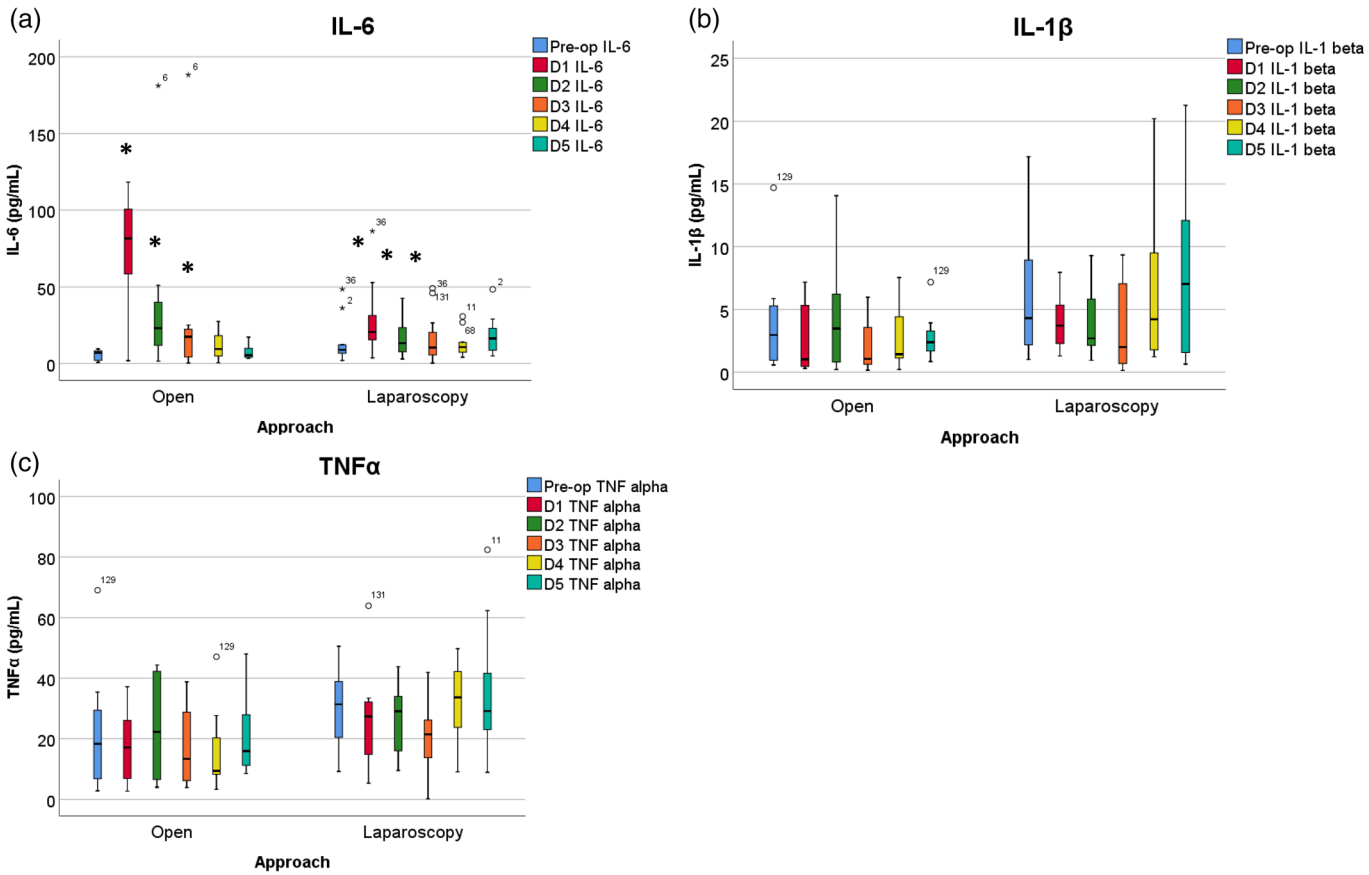

Fig. 3. Boxplot of measured inflammatory biomarkers. (a) IL-6, (b) IL-1β and (c) TNF-α. (*) denotes a statistically significant result. Lap: laparoscopic group; pg.: picogram; POD: post-operative day.

New Zealand. Patient flow including exclusions are shown in Figure 1. Overall, 168 patients (59.4%) did not have any reported perioperative complications. Seven patients were excluded due to having their operation moved to a private hospital, with 27 patients excluded post-surgery due to either withdrawal of consent or incomplete data and blood samples collection. These are listed in Table 1.

Baseline characteristics

Baseline characteristics are shown in Table 2. The majority of patients included in this study underwent a laparoscopic colectomy. The indications for surgery were for colonic cancer in the majority >95% of cases. Patients in the open group had significantly higher BMI than patients in the laparoscopic group ($p < 0.05$). Patients that underwent an open colonic resection were significantly more obese and had undergone previous abdominal surgery more frequently ($p < 0.05$).

Inflammatory response

Biomarkers values are shown in Table 3. Figures 2 and 3 show the box-plots of the biomarker profile for open versus laparoscopic groups from pre-operation to POD5. Following surgery, CRP was significantly higher in open colectomy on POD 1–4 as were neutrophil count on POD 1–3 and 5, and IL-6 on POD 1–3. Other inflammatory markers showed no statistically significant differences.

BMI and inflammatory response

CRP levels were significantly elevated in obese patients on POD 2 and POD 4. A multiple regression analysis was performed from BMI and surgical approach. These variables statistically significantly predicted POD 2 ($F(2, 82) = 8.1$, $p < 0.01$, $R^2 = 0.165$), and POD 4 CRP ($F(2, 67) = 7.85$, $p < 0.01$, $R^2 = 0.190$), with an average model fit. Both BMI and approach added statistically significantly to the prediction.

Discussion

This prospective observational study has shown that patients undergoing laparoscopic colectomy without complications have a reduced inflammatory response compared with equivalent open colectomy. CRP, neutrophil count and IL-6 showed significant differences from Preop, to POD 1 to POD 3, and POD 5. BMI also significantly impacted the inflammatory response following colectomy regardless of operative approach.

Results of this prospective study are consistent with similar studies performed in an ERAS environment. It is unclear whether the postoperative care provided by ERAS is the key contributor to this measured benefit seen in laparoscopy patients. A large RCT, the LAFA-study, shows either laparoscopic surgery or ERAS implementation significantly reduced post-

operative hospital stay, with both implementations combined having the greatest effect. Patients treated with open and ERAS protocols or laparoscopic and standard care had a similar postoperative recovery. Although laparoscopy was found to be the only significant independent factor to reduce total hospital stay and morbidity, it appears laparoscopic and ERAS protocols both impact recovery to an equivalent degree.[7]

Interestingly, Stage *et al.*[8] found significantly elevated CRP and IL-6 levels in their laparoscopy group. This result was attributed to perioperative utilization of NSAIDs (non-steroidal ant-inflammatory drugs). Other perioperative medications have been shown to attenuate the inflammatory response following surgery. A recent RCT by Singh *et al.* showed a reduced postoperative inflammatory response with perioperative statin use.[9]

Other patient factors such as BMI and region of gut resection may affect inflammatory responses. Human adipose tissue secretes pro-inflammatory cytokines such as IL-6, likely inducing a pro-inflammatory state in the obese patient. This is evident in a recent study that showed an increase in systemic CRP levels in patients with an elevated BMI.[10] In our study, CRP was significantly elevated in obese patients compared with non-obese patients. Multiple regression analysis further outlines the higher-than-normal inflammatory response after surgery in obese patients regardless of operative approach.

An important limitation of this study is lack of information about use of anaesthetic drugs. Though the exclusion of other complications helped lessen study heterogeneity, perioperative medications including dexamethasone administered by the anaesthetist on induction, utilization of NSAIDs and opioid use may have affected the observed results.

In conclusion, this prospective observational study has shown that the inflammatory response following elective colectomy is affected by surgical approach, BMI, surgical resection and preoperative medications. This has implications for the detection of AL, other surgical complications and long-term oncological outcomes following elective colectomy. In the immediate postoperative period, a normal inflammatory result for an obese patient undergoing an open procedure may well represent a significant complication in a non-obese patient who has undergone a laparoscopic procedure. Evaluating these baseline differences in the presence of post-operative complications may further highlight these differences.

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Author contributions

Bruce Su'a: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; validation; visualization; writing – original draft; writing – review & editing. **Tony Milne:** Data curation; investigation; validation. **Rebekah Jaung:** Data curation; investigation; validation. **James Jin:** Formal analysis; writing – review and editing. **Darren Svirskis:** Conceptualization; methodology; resources; supervision; validation. **Tim Eglinton:** Conceptualization; funding acquisition; resources; supervision; validation. **Ian Bissett:** Conceptualization; resources; supervision. **Andrew Hill:** Conceptualization; funding acquisition; resources; supervision; writing – original draft; writing – review & editing.

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