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Article

C-Reactive Protein after Intra- and Extra-Corporeal Anastomosis—Different Values but Same Clinical Outcomes: A Single-Center Experience with Patients Undergoing Laparoscopic Right-Hemicolectomy

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Simple Summary: This retrospective single-centre study aims to investigate the role of C-Reactive Protein (CRP) trajectory as a reliable predictive biomarker of colorectal surgery (CRS) complications in patients underwent laparoscopic right hemicolectomy for colorectal cancer (CRC) with intracorporeal (IA) or extracorporeal anastomosis (EA). Our results included 340 patients and it showed that CRP trajectories were higher in patients with IA, despite superimposable complication rate and clinical outcomes, when compared to EA.

Abstract: Background: C-reactive protein (CRP) is a predictive biomarker of colorectal surgery (CRS) complications but has not been evaluated by comparing patients undergoing CRS with intracorporeal anastomosis (IA) or extracorporeal anastomosis (EA). Therefore, we aimed to describe postoperative CRP values between two groups of patients who underwent laparoscopic right hemicolectomy for right-side colon cancer with IA or EA. **Methods:** We retrospectively reviewed the data of patients affected by right-side colon cancers who underwent laparoscopic right-hemicolectomy with ileo-colic IA or EA between January 2016 and December 2022. **Results:** A total of 340 patients underwent laparoscopic right hemicolectomy. EA was performed in 238 (70%) and IA in 102 (30%) cases. Patients with IA showed significantly higher values of CRP in the second, third and fourth postoperative days (15.2 mg/dL vs 9.5 mg/dL $p < 0.001$; 12.9 mg/dL vs 8.7 mg/dL $p < 0.001$; 8.8 mg/dL vs 5.6 mg/dL $p = 0.006$, respectively). Major complications were similar between the two groups (8.4% vs 5.9%, $p = 0.475$). **Conclusion:** The trajectory of CRP values in IA patients was higher compared with EA patients but was not associated with different clinical outcomes or significantly different complication rates.

Keywords: colorectal cancer; laparoscopy; c-reactive protein; anastomosis; postoperative

1. Introduction

Colorectal cancer (CRC) is the third most common cancer globally and the second leading cause of cancer-related mortality [1–3]. Minimally invasive hemicolectomy for right-side CRC is a commonly performed procedure [4,5]. However, despite the introduction of different surgical techniques and enhanced recovery protocols, morbidity remains considerable [6,7]. The anastomotic leak (AL) rate in colorectal surgery (CRS) ranges between 3% and 17%, depending on the anastomosis location, and it is associated with higher morbidity, mortality, costs and worse oncological outcomes, particularly in terms of local recurrence [8–11].

Studies have investigated reliable predictive biomarkers for colorectal complications [12–17]. However, no biomarkers are considered completely reliable and error-free when making early-stage

diagnoses or when complications are present. Therefore, different clinical studies are searching for ways to diagnose ALs and other complications before clinical symptoms appear [13,18].

C-reactive protein (CRP) has been reported to be an important predictor of septic complications and ALs after an elective colorectal resection [19]. ALs can typically be ruled out when CRP is below a certain level, depending on the postoperative day (POD). However, the best response to elevated CRP values is not well defined. Some physicians remeasure CRP levels in the following days [15,20], while some centres perform computed tomography in patients with CRP levels >15 mg/dL on POD 2 or 3 [12].

Recent studies have suggested that the rate of change, i.e., the trajectory, of CRP levels may be more useful than a cut-off point [15,21]. However, CRP trajectory testing via comparing patients undergoing CRS with intracorporeal (IA) or extracorporeal anastomosis (EA) has not yet been evaluated. Therefore, we aimed to describe the postoperative CRP values between two groups of patients who underwent a laparoscopic right hemicolectomy for right-side colon cancer with IA or EA.

2. Material and Methods

We reviewed 340 consecutive patients who underwent a laparoscopic right-hemicolectomy with ileo-colic IA or EA between January 2016 and December 2022 at Fondazione IRCCS San Gerardo dei Tintori Hospital (Monza, Italy). All data were obtained from a prospectively maintained database and analysed retrospectively. All patients signed an informed consent form for the anonymous use of clinical data. We collected baseline characteristics and a co-morbidity index according to the Charlson Comorbidity Index (CCI), operative time (minutes), type of suture, anastomosis (IA or EA) and postoperative data [22]. Until 31 January 2020, patients received EA. After this date, we systematically introduced IA. The first 20 IA cases were dropped from the study as they were considered to be within the learning curve [23]. Postoperative complications according to the Clavien-Dindo classification (CD), including gastrointestinal bleeding, reoperation and hospital stay duration were collected and analysed [24]. Major complications were defined as when the CD score was $\geq$ IIIa. CRP levels (mg/dL) were measured and collected at PODs 1, 2, 3 and 4.

2.1. Surgical Technique

For the IAs, we established intestinal continuity using a side-to-side isoperistaltic suturing technique. The arms of the linear vascular cutting stapler (Echelon™/Echelon™ Flex Endopath, Johnson and Johnson/Ethicon or EndoGIA™/EndoGIA™ Ultra, Medtronic/Covidien or SIGNIA™, Medtronic/Covidien) were inserted and fired through transverse incisions on the antimesenteric side of the terminal ileum and transverse colon. The enterotomy site was closed using a double layer of barbed suture (Filbloc®, Assut Europe S.p.A or V-Loc™, Medtronic). For the EAs, we established intestinal continuity using a manual side-to-side isoperistaltic suturing technique with a double layer of 3/0 polyglactin (Vicryl™, Ethicon) or mechanically using a stapler technique, similar to the IA procedure.

2.2. Perioperative Management

All patients were treated according to the Enhanced Recovery After Surgery (ERAS) protocol for CRS [7,25,26]. No patient received mechanical bowel preparation [7,27,28]. All patients received intravenous antibiotic prophylaxis with 2 g of cefoxitin and 500 mg of metronidazole within 60 minutes before starting surgery. In cases of allergy, 500 mg of azithromycin was administered intravenously. At the end of each surgery, we verified the vascularisation of the anastomosis with indocyanine green [29]. Both groups followed the key points of the postoperative ERAS protocol, i.e., all patients were given oral liquid nutrition on the first POD, urinary catheters were almost always removed on the first POD, the nasogastric tube was removed at the end of the surgical procedure and patients were encouraged to initiate mobilisation from the first POD [7].

2.3. Statistical Analysis

Descriptive statistics are reported as percentages and means or medians with 25–75 interquartile ranges (IQRs) and minimum-maximum ranges. Differences between means were compared using the Mann-Whitney U test. The chi-square test and two-by-two cross tables were used to compare categorical data. Differences were statistically significant when p-values were <0.05. Statistical analyses were carried out using IBM SPSS Statistics for Macintosh, Version 27 (IBM Corp, Armonk, NY, USA).

3. Results

During the study period, 340 patients underwent laparoscopic right hemicolectomy for right-side colon cancer. IA was performed in 102 (30%) patients. Baseline patient characteristics are listed in Table 1. In total, 173 (50.9 %) patients were male, with 120 (50.4%) in the EA and 53 (52%) in the IA groups (p=0.795). Median age was the same: 73 years in both the EA and IA groups (p=0.348). No differences in patient comorbidities were found. The CCI distribution was similar in the two groups: 5 vs 6 in the EA and IA groups, respectively (p=0.522).

Table 1. Baseline characteristics.

CHARACTERISTICS	Overall	EA	IA	p-value
n (%)	340 (100)	238 (70)	102 (30)	
Median age, years (IQR)	73 (64-80)	73 (63-79)	73 (65-81)	0.348
Sex, Male, n (%)	173 (50.9)	120 (50.4)	53 (52)	0.795
Previous surgery, n (%)	107 (31.5)	63 (26.5)	44 (43.1)	0.333
Diabetes mellitus, n (%)	49 (14.4)	35 (14.7)	14 (13.7)	0.031
CKD, n (%)	24 (7.1)	16 (6.7)	8 (7.8)	0.232
Arterial Hypertension, n (%)	122 (35.9)	59 (24.8)	63 (61.8)	0.600
COPD, n (%)	16 (4.7)	8 (3.4)	8 (7.8)	0.702
Charlson Comorbidity Index, median (IQR)	5 (4-7)	5 (4-7)	6 (5-7)	0.522

CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; IQR: Interquartile range; IA: intracorporeal anastomosis; EA: extracorporeal anastomosis.

Operative characteristics are listed in Table 2. Manual sutures were used only in the EA group, whereas mechanical sutures were used in all IA patients and 40 (16.8%) EA patients. The median operative time was similar in both groups (172.5 minutes in the EA group vs 188 minutes in the IA group, p=0.059). Abdominal drainage was necessary for 141 (59.2%) EA patients and 27 (26.5%) IA patients (p<0.001). The number of lymph nodes harvested was similar between the two groups (20 in the EA group vs 19 in the IA group, p=0.523).

Table 2. Operative outcomes.

OPERATIVE CHARACTERISTICS	TOTAL	EA (n=238)	IA (n=102)	p-value
Operative time, min, median (IQR)	179 (141.5-215)	172.5 (140-210)	188 (150-228)	0.059
Manual sutures, n (%)	198 (58.2)	198 (83.2)	0 (0)	<0.001
Mechanical sutures, n (%)	142 (41.8)	40 (16.8)	102 (100)	<0.001
Abdominal drainage, n (%)	168 (49.4)	141 (59.2)	27 (26.5)	<0.001
Lymph nodes, median (IQR)	20 (15-26)	20 (15-26)	19 (15-25)	0.523

IQR = Interquartile range; IA: intracorporeal anastomosis; EA: extracorporeal anastomosis.

No significant differences in complication rates were found between the two groups (Table 3). Furthermore, the AL rate was similar between the two groups: 12 (5%) patients in the EA group vs 4 (3.9%) in the IA group (p=0.718). Gastrointestinal bleeding occurred in 2 (0.8%) patients in the EA group vs 6 (5.9%) in the IA group (p=0.218). Re-operation was necessary for 19 (8%) patients (10 for AL, 2 for gastrointestinal bleeding, 7 for anastomotic stenosis) in the EA group and for 6 (5.9%) patients in the IA group (3 for AL, 3 for gastrointestinal bleeding), which was not significantly

different (p=0.567). There was no mortality in either group. The median hospital stay duration was 7 (IQR 6–9, p=0.236) days in the two groups.

Table 3. Postoperative outcomes.

POSTOPERATIVE OUTCOMES	Overall	EA (n=238)	IA (n=102)	p-value
Overall morbidity, n (%)	94 (27.6)	75 (31.5)	36 (35.2)	0.464
Major complications, n (%)	26 (7.6)	20 (8.4)	6 (5.9)	0.475
Clavien-Dindo grade				
IIIB, n (%)	15 (4.4)	13 (5.5)	2 (2)	0.167
IVA, n (%)	6 (1.8)	5 (2.1)	1 (1)	0.496
IVB, n (%)	5 (1.5)	2 (0.8)	3 (2.9)	0.127
V, n (%)	0	0	0	
Gastrointestinal bleeding, n (%)	8 (2.3)	2 (0.8)	6 (5.9)	0.218
Anastomotic leak, n (%)	16 (4.6)	12 (5)	4 (3.9)	0.718
Superficial SSI, n (%)	18 (5.3)	12 (5)	6 (5.9)	0.677
Deep SSI, n (%)	12 (3.6)	10 (4.2)	2 (2)	0.338
Reoperation, n (%)	25 (7.3)	19 (8)	6 (5.9)	0.567
LOS, days, median (IQR)	7 (6-9)	7 (6-9)	7 (5-9)	0.236

SSI: Surgical Site Infection; LOS: length of stay; IQR: Interquartile range; IA: intracorporeal anastomosis; EA: extracorporeal anastomosis.

Postoperative CRP values are reported in Table 4. As depicted in Figure 1, CRP values were 9.5 mg/dL for the EA group vs 15.2 mg/dL for the IA group (p<0.001) on POD 2, 8.7 mg/dL in the EA group vs 12.9 mg/dL in the IA group (p<0.001) on POD 3 and 5.6 mg/dL in the EA group vs 8.8 mg/dL in the IA group (p=0.006) on POD 4. Significant differences were also found considering patients without major complications: 8.7 mg/dL in the EA group vs 14.6 mg/dL in the IA group (p<0.001) on POD 2, 8.6 mg/dL in the EA group vs 12.6 mg/dL in the IA group (p<0.001) on POD 3 and 5.3 mg/dL in the EA group vs 8.4 mg/dL in the IA group (p=0.003) on POD 4. However, when we considered only patients with major complications (CD score ≥IIIa), no significant differences in CRP levels were observed postoperatively.

Table 4. CRP (mg/dL) trends.

CRP LEVELS, OVERALL				
POSTOPERATIVE DAY	Overall	EA (n=238)	IA (n=102)	p-value
I median (IQR)	6.2 (4.3-8.4)	6 (4.4-8)	6.7 (4.3-9.5)	0.122
II median (IQR)	11.4 (6.8-16.7)	9.5 (6.3-14.6)	15.2 (10.5-20.9)	<0.001
III median (IQR)	11 (6.5-17.7)	8.7 (5-15)	12.9 (8.5-20.7)	<0.001
IV median (IQR)	7 (4.1-13.1)	5.6 (3.3-10.6)	8.8 (4.6-15)	0.006
CRP LEVELS IN PATIENTS WITH MAJOR COMPLICATIONS (CD≥IIIa)				
I median (IQR)	7.5 (6.5-11.1)	7.9 (6.6-10.8)	7.5 (4.8-11.9)	0.968
II median (IQR)	16.6 (15.1-23.1)	15.9 (14.8-21)	22.5 (19-31.9)	0.142
III median (IQR)	19.2 (13.2-27.9)	18.3 (7.4-26.7)	24.4 (18.9-31.9)	0.153
IV median (IQR)	14 (9.6-24.7)	14 (8.5-24.7)	16.8 (11.9-31.1)	0.733
CRP LEVELS IN PATIENTS WITHOUT MAJOR COMPLICATIONS				
I median (IQR)	6 (4.2-8.2)	5.8 (4.2-7.7)	6.6 (4.1-9.3)	0.068
II median (IQR)	10.9 (6.5-16.4)	8.7 (6.1-13.3)	14.6(10.1-20.5)	<0.001
III median (IQR)	9.8 (6-16.6)	8.6 (4.6-13)	12.6 (8.1-20.4)	<0.001
IV median (IQR)	6.1 (4-12.3)	5.3 (3.2-9.3)	8.4 (4.6-14.3)	0.003

IQR: Interquartile range; IA: intracorporeal anastomosis; EA: extracorporeal anastomosis.

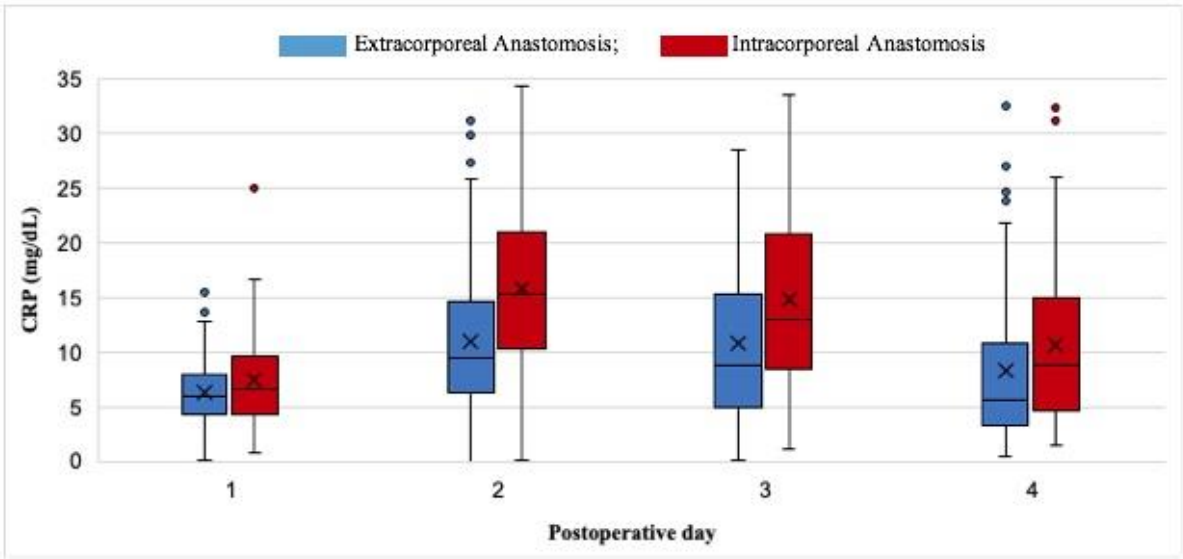


Figure 1. C-Reactive-Protein trend in all patients.

4. Discussion

The study examined different trajectories of CRP values during the first four PODs in patients who underwent laparoscopic right-side hemicolectomy for CRC with EA or IA in a referral centre. CRP values in the second, third and fourth PODs were higher in patients with IA and without significant differences in the complication rate. Both groups had similar CRP-level trajectories.

Different studies have reported correlations between CRP values and postoperative complications, such as ALs [13–15,30]. In a recent study, Yeung et al. conducted a systematic review and meta-analysis of the CRP values of 6677 patients and found a higher inflammatory index value in patients with AL [13]. In particular, the study identified CRP cut-off values associated with ALs on the fourth through seventh PODs of 12.3 mg/dL, 11.5 mg/dL, 10.5 mg/dL and 9.6 mg/dL, respectively, with a sensitivity and specificity of 100%. In a large systematic review, Singh et al. reported that CRP values were a useful negative predictive test for the development of ALs following CRS [30]. In that report, the authors analysed seven studies, with a total of 2483 patients, and derived CRP cut-off values of 17.2 mg/dL on the third POD and 12.4 mg/dL on the fourth POD, corresponding to a negative predictive value of 97%.

Our results showed that absolute CRP levels on POD 2, 3 and 4 were higher in the IA group, but the trend of the curves was similar in both groups (Figure 1 and Table 4). Furthermore, the increased CRP values were not correlated with the development of major complications. This finding casts doubt on the value of considering a single postoperative CRP value as an effective indicator of complications, as opposed to the trend of CRP levels in the days following surgery.

To explain our results, we analysed the surgical procedures used in our study. We hypothesised that faecal contamination in the abdomen and the trocars site during the anastomosis procedure could modify the inflammatory response in the IA group. Alternatively, using a self-retaining ring retractor and covering the surgical site during EA could provide better asepsis and control of the operating field, resulting in lower contamination. For these reasons, a single CRP value should be considered a useful tool in predicting complications but would not be completely reliable, particularly in IA patients.

In a paper by Milone et al., the authors considered surgical stress and metabolic response after total laparoscopic right colectomies. They described a significant difference in CRP trajectories, which is in contrast to our data [31]. In their cohort, CRP on the third POD was significantly higher in the EA than in the IA group. In that study, the authors justified advocating for a total laparoscopic approach when performing a right colectomy for CRC. However, the small sample size (they analysed 50 patients) could have underestimated the role of IA in causing an increase in the

inflammatory index; although, changes in this response would not alter preferentially performing an IA after laparoscopic right hemicolectomy. This conclusion has also been confirmed by Van Oostendorp et al. in a systematic review and meta-analysis describing different outcomes after a laparoscopic right hemicolectomy with IA and EA [32]. That study analysed 1492 patients and found that IA procedures were associated with reduced short-term morbidity and a decreased hospital stay duration, suggesting faster recovery. In a recent meta-analysis of randomised controlled trials comparing IA versus EA in minimally invasive right hemicolectomies, Zhang et al. showed that IA reduced the risk of postoperative paralytic ileus and shortened the incision length but prolonged the operative time [33]. No significant differences in bleeding, ALs, overall peri-operative morbidity or length of hospital stay were found. Our results are partially aligned with these studies. In terms of hospital stay for both groups, we found that patients were discharged from hospital in a median of seven days. However, overall complications were greater in the IA group (35.2% vs 31.5%, respectively).

Our study was limited by its retrospective design and lacked a dedicated study protocol. However, we used a large, prospectively collected register from a single high-volume centre and included a well-trained surgeon.

5. Conclusion

In conclusion, this study shows that postoperative CRP values in patients who underwent laparoscopic right hemicolectomy significantly differed between patients with IA and EA, despite comparable complication rates and clinical outcomes. The usefulness of CRP values for detecting complications should be carefully evaluated. Future studies and randomised clinical trials are needed to further assess CRP trajectories in patients undergoing CRS with IA and EA for CRC to evaluate its reliability as a predictor of complications.

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Informed Consent Statement: Patient consent was waived due to retrospective and anonymous nature of the present study.

Data availability statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to hospital policy.

Conflicts of Interest: The authors declare no conflict of interest.

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