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Role of C-Reactive Protein (CRP) as a Predictive Marker of Anastomotic Leak in Colorectal Surgery: Is it Still Reliable?

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Keywords:

Colorectal surgery; Anastomotic leak; C-reactive protein

1. Abstract

1.1. Introduction: Anastomotic leaks after colorectal surgery is associated with serious morbidity and early diagnosis is critical. C-reactive protein (CRP) on postoperative day (POD) 3 to 5 has been described as a good predictor of anastomotic leak. Therefore, this study aims to review if CRP level of greater than 150mg/l is a reliable predictor of anastomotic leak.

1.2. Methodology: The study was conducted using a prospectively held database from Department of Colorectal Surgery, Singapore General Hospital. From 1 January 2011 to 31 October 2017, all patients who had anastomotic leaks after colorectal resection surgery were analysed retrospectively. Patients without postoperative CRP levels were excluded.

1.3. Results: Out of 42 patients who had anastomotic leaks, only 22 (52.4%) patients had CRP levels performed from POD3 to 5. 13 (59.1%) underwent an anterior resection, three (13.6%) had right hemicolectomy, three (13.6%) had a left hemicolectomy and three (13.6%) had subtotal or total colectomy. Nine (40.9%) were laparoscopic resections and none of the patients were on long term steroids or immunosuppressed nor had preoperative chemo-radiotherapy. Four (18.2%) patients did not have a raised CRP above 150mg/L from POD 3 to 5 but still developed an anastomotic leak. These patients were more likely associated with small defects in the anastomosis and a delay in diagnosis of an anastomotic leak and a longer duration of hospitalization.

1.4. Conclusion: Although CRP has a high negative predictive value, this study demonstrate that the current cut-off values may have to be reviewed to better predict anastomotic leaks and reduce morbidity rates.

2. Introduction

Anastomotic leakage is one of the most serious complications of colorectal resection and is associated with increased morbidity and mortality. The incidence varies from 3 to 19% depending on the type of operation and the site of anastomosis [1]. Although some leaks present early after surgery with patients developing severe sepsis, others can present with a more insidious course and may only manifest clinically as late as Postoperative Day (POD) 8–12 [2]. Anastomotic leaks are associated with prolonged duration of hospital stay, possible poor functional and oncologic outcomes and increased mortality of 6 to 22% [3-6]. Enhanced Recovery After Surgery (ERAS) protocols in management of colorectal cancer patients can reduce morbidity and shortens the hospital stay [7, 8]. However, early discharge associated with ERAS pathways carries potential risk of delayed presentation, diagnosis and management of anastomotic leak that could occur when the patient is out of hospital. Therefore, the need for a reliable marker to guide early discharge is necessary [9]. CRP is an acute phase protein with half-life of 19 hours. A previous study demonstrated that CRP of over 200 mg/L was most sensitive for detection of anastomotic leak on POD 3 after surgery [10]. A meta-analysis showed that CRP of over 172, 124 and 144 mg/L on post-operative day 3, 4 and 5 respectively had a negative predictive value of 97% for an anastomotic leak after colorectal surgery [2]. A systematic review concluded that CRP is useful marker to screen for a major anastomotic leak when greater than 150 mg/L [1]. Consid-

ering the increasing adoption of ERAS along with potential earlier discharges than the traditional five-day period and beyond, we decided to evaluate usefulness of a single cut-off CRP value for predicting anastomotic leaks. Therefore, this study aims to review if CRP levels of greater than 150 mg/L is truly a reliable predictor of anastomotic leak following colorectal resection surgery.

3. Materials and Methods

From 1 January 2011 to 31 Oct 2017, all consecutive patients who had a colonic or rectal resection at the Department of Colorectal Surgery, Singapore General Hospital were evaluated retrospectively using a prospectively held database. Anastomotic leaks were identified from medical records, electronic records and Colorectal Department's Morbidity and Mortality records. Anastomotic leaks from ileostomy, colostomy closures and delayed enterotomy leaks were excluded from the study. As there is a lack of consensus amongst surgeons with regards to the definition of an anastomotic leak, they were defined as an anastomotic leak identified at reoperation, bowel content within drain or from the wound, presence of air or fluid in the anastomotic region visualized by CT scan that is indicative of anastomotic leak [11]. Patients without CRP performed from POD 3 to 5 were excluded. For the purpose of this study evaluation, CRP level of 150 mg/L on POD 3 to 5 was used as a cut-off to suggest an anastomotic leak. Demographics such as age, gender, comorbidities, tumour site and staging were prospectively collected. All statistical analyses were performed with SPSS version 26.0 (SPSS Inc., Chicago, IL). Comparisons of categorical variables were performed with chi-square test. Continuous variables that were not normally distributed were defined by median and range. Comparison of continuous variables was with the Mann-Whitney U test. The study was reviewed and approved by the Institutional Review Board (IRB) of Singapore General Hospital (2018/2317). The requirement for informed consent was waived by the IRB.

4. Results

There were a total of 3352 colon and rectal resections with anastomosis performed from 1 Jan 2011 to 31 Oct 2017. 42 (1.3%) patients had an anastomotic leak. 20 patients were excluded as CRP was not performed from POD 3 to 5. The final analysis included 22 (52.4%) patients. The clinical characteristics of patients with anastomotic leaks included in this study are as listed in Table 1. The median age was 66.5 years old (range: 47 to 92 years) and 13 (59.1%) had an anterior resection, three (13.6%) had a subtotal or total colectomy, three (13.6%) had a right hemicolectomy and three (13.6%) had a left hemicolectomy. Nine (40.9%) had the colorectal surgery performed laparoscopically and three (13.6%) had the initial surgery performed in an emergency setting. 17 (77.3%) were performed for colorectal malignancy. 15 (68.2%) patients had pre-operative oral mechanical bowel preparation, and none of the patients received additional oral antibiotics along with their bowel preparation. Five (22.7%) had prior abdominal surgery. Three (13.6%) had a proximal diverting colostomy performed at the initial operation and seven (31.8%) had pre-operative hypoalbuminemia (<35 g/L). None were on long term steroids or immunosuppression, and also none had pre-operative chemotherapy or radiotherapy. Three (13.6%) required ventilatory and inotropic support at the Intensive Care Unit (ICU) after the initial operation.

The median post-operative day in which an anastomotic leak was diagnosed in this case series was on day 7 after the initial operation (interquartile range [IQR]: 5 to 10). 13 (59%) patients had anastomotic leak diagnosed within 7th postoperative day (POD 3 to 7). 10 (45.5%) were diagnosed clinically and 12 (54.5%) were diagnosed with a CT scan. 20 (90.9%) patients required surgical intervention for the anastomotic leak, one patient was treated with percutaneous drainage of the intra-abdominal collection under radiological guidance and one patient was treated conservatively with antibiotics. Among the 22 patients with anastomotic leaks, 3 (13.6%) eventually died.

Four (18.2%) patients had a CRP level less than 150 mg/L. Out of these four patients, three patients had CRP performed on POD 3 and 4 and one had CRP performed only on POD 3. Two patients had CRP levels less than 75 mg/L. Two patients had an elevated CRP > 100 mg/L on POD 3 but the subsequent CRP level on POD 4 was lower. All were administered antibiotics postop and none had a proximal diverting stoma created at the initial surgery. Among these four patients, one had an anastomotic leak diagnosed on POD 7, two were diagnosed on POD 10 and one was diagnosed on POD 19. All four patients required surgical intervention for the anastomotic leak and two patients were found to have a small or pinpoint defect in the anastomosis. One patient was found to have ischemia of the anastomosis and another had a large anastomotic dehiscence.

With regards to the 18 (81.8%) patients with CRP level greater than 150 mg/L, eight were elevated on POD 3 only, two were elevated on POD 4 only, two were elevated on POD 5 only, three were elevated on POD 3 and 4 only, one was elevated on POD 3 and 5 only and two were on POD 3, 4 and 5. Among the eight patients with elevated CRP levels greater than 150 mg/L on POD3, four patients were diagnosed with anastomotic leaks from POD 3 to 6 while the other four patients had anastomotic leaks diagnosed from POD 8 to 11. Two patients with an elevated CRP on POD 3, 4 and 5 were diagnosed with an anastomotic leak on POD 6 and POD 8. The remaining eight patients were diagnosed with anastomotic leaks from POD 4 to 28. Among these 18 patients, 15 patients were administered antibiotics postop and 16 patients underwent surgical intervention for the anastomotic leak and only one patient was found to have a pinpoint defect in the anastomosis and four patients had ischemia of the anastomosis.

As shown in Table 2, chi-square test showed that there were no significant differences in patients with anastomotic leak between those with elevated CRP and those without elevated CRP with regards to surgical approach, timing of operation, indication of initial operation, creation of proximal diverting stoma, preoperative hypoalbuminemia, postoperative antibiotics and postoperative need for ino-

tropic and ventilatory support. However, among those with anastomotic leaks but without elevated CRP above 150 mg/L, two (50%) patients had a pinpoint defect in the anastomosis while among those with elevated CRP above 150 mg/L only one (6.3%) patient had a pinpoint defect and this was statistically significant difference (p = 0.028).

The day of diagnosis of an anastomotic leak after the initial surgery was compared between the two groups and was observed to be not normally distributed. As shown in Table II, Mann-Whitney U test suggested that the day of diagnosis of an anastomotic leak was earlier in those with an elevated CRP (Median = 6) than those without an elevated CRP (Median = 10) and this approached statistical significance (p = 0.059). There was no significant difference between both groups with regards to the morbidity and mortality rates. However, the median duration of hospitalization stay was longer in those without an elevated CRP (Median = 76) compared to those with an elevated CRP (Median = 29) and this difference was statistically significant (p = 0.021).

Table 1: Characteristics of anastomotic leaks after colon or rectal resection (N=22).

Characteristic	N (%)
Age, median (yrs, range)	66.5 (47 – 92)
Surgery performed	
Anterior resection	13 (59.1)
Subtotal/ total colectomy	3 (13.6)
Right hemicolectomy	3 (13.6)
Left hemicolectomy	3 (13.6)
Laparoscopic	9 (40.9)
Emergency Surgery	3 (13.6)
Colorectal cancer	17 (77.3)
Preoperative oral bowel preparation	15 (68.2)
Prior abdominal surgery	5 (22.7)
Proximal diverting stoma	3 (13.6)
Hypoalbuminemia (<35 g/L) preop	7 (31.8)
Postoperative inotropic/ ventilatory support	3 (13.6)
Postoperative intravenous antibiotics	19 (86.4)

Table 2: Comparison of characteristics between patients with an anastomotic leak with a raised CRP (>150 mg/L) and those without a raised CRP (<150 mg/L) (N=22).

Characteristic	CRP<150 mg/L N=4	CRP>150 mg/L N=18	P-value
Surgical approach, N (%)			
Laparoscopic	2 (50)	7 (38.9)	0.683
Open	2 (50)	11 (61.1)	
Surgery Timing, N (%)			
Elective	4 (100)	15 (83.3)	0.38
Emergency	0 (0)	3 (16.7)	
Colorectal cancer, N (%)			
None	1 (25)	4 (22.2)	0.905
Present	3 (75)	14 (77.8)	
Preoperative oral bowel preparation, N (%)			
None	1 (25)	6 (33.3)	0.746
Present	3 (75)	12 (66.7)	
Prior abdominal surgery, N (%)			
None	2 (50)	15 (83.3)	0.15
Present	2 (50)	3 (16.7)	
Proximal diverting stoma, N (%)			

None	4 (100)	15 (83.3)	0.38
Present	0 (0)	3 (16.7)	
Hypoalbuminemia (<35 g/L) preop, N (%)			
None	5 (100)	10 (58.8)	0.116
Present	0 (0)	7 (41.2)	
Postoperative inotropic/ ventilatory support, N (%)			
None	4 (100)	15 (83.3)	0.38
Present	0 (0)	3 (16.7)	
Postoperative IV antibiotics, N (%)			
None	0 (0)	3 (16.7)	0.38
Present	4 (10)	15 (83.3)	
Postoperative day diagnosed with AL, median (days, IQR)	10 (8 – 17)	6 (4 – 9)	0.059
Anastomotic Leak (Pinpoint defect), N (%)			
None	2 (50)	15 (93.8)	0.028
Present	2 (50)	1 (6.3)	
Anastomotic Leak (Ischemic features), N (%)			
None	3 (75)	12 (75)	1
Present	1 (25)	4 (25)	
Surgical Intervention for AL, N (%)			
None	0 (0)	2 (11.1)	0.484
Present	4 (100)	16 (88.9)	
Morbidity, N (%)			
None	2 (50)	9 (50)	1
Present	2 (50)	9 (50)	
Mortality, N (%)			
None	4 (100)	15 (83.3)	0.38
Present	0 (0)	3 (16.7)	
Duration of hospitalization stay, median (days, IQR)	76 (41 – 90)	29 (17 – 34)	0.021

5. Discussion

Anastomotic leakage after colorectal surgery is a dreaded complication with significant mortality of 6 to 22% [12, 13]. There is increased morbidity with need of increased reoperation, radiological interventions and longer hospital stay. Incidence of anastomotic leakage after colorectal surgery varies from 3 to 19 depending on patient characteristics and the type of surgery performed [1, 3, 12]. Anastomotic leaks are associated with delay in adjuvant chemotherapy or no chemotherapy at all [21]. Recent meta-analysis and systematic reviews suggest that anastomotic leaks may lead to increased local recurrence and reduced survival [22, 23]. Quality of life is also affected due to poor functional outcomes with high rates of permanent stoma formation [24]. Early diagnosis of anastomotic leak is essential but the clinical signs can be insidious. Anastomotic leakage usually occurs around the 5th to 8th postoperative day but it can also develop from any time from the day of the index surgery to the third postoperative week [12, 15]. Early detection is crucial for timely treatment as a delayed diagnosis is associated with higher mortality and morbidity. Therefore, several studies have attempted to establish a cut-off level for CRP in identifying patients at risk of an anastomotic leak prior to the development of clinical symptoms and signs [2, 17-20].

CRP is a serum acute-phase reactant synthesized by the liver and released in response to stimulation by pro-inflammatory cytokines. The production of CRP is part of a nonspecific acute-phase response to most forms of tissue damage, infection, inflammation, and malignant neoplasia. In healthy young patients, the median concentration of CRP is approximately 0.8 mg/L but following an acute-phase stimulus, values may increase to more than 500 mg/L. The plasma half-life is 19 hours. Following colorectal surgery, CRP will show a rapid increase on POD 1 and peaks on POD 2 followed by steady decline to a normal level thereafter [7, 14]. Multiple studies and meta-analyses have evaluated the predictive value of CRP for infectious complications after colorectal surgery. Singh et. al., published a meta-analysis (n =2483) that showed that CRP as a predictor of anastomotic leak on POD 3, 4 and 5. The study concluded that CRP at the three above mentioned time points have very high negative predictive test of 97% but not a good positive predictor of anastomotic leak

[2]. An elevated CRP after surgery could be multifactorial such as pneumonia, surgical site infection, thrombophlebitis, intra-abdominal collections and is not specific to diagnosis of an anastomotic leak. Hence, the clinical application of CRP in post-surgical care will be as a useful adjunct in excluding an anastomotic leak given the high negative predictive value of the test.

Many studies have used the receiver operating character (ROC) curve and area under the curve (AUC) to establish a suitable cut-off level for CRP as a predictor for anastomotic leak [17-20]. However, this study attempts to review the CRP levels among the anastomotic leaks and evaluate the reliability of CRP with a cut-off value of 150 mg/L as a predictor for anastomotic leaks on POD 3, 4 and 5. The choice of this cut-off value was based on a systematic review which concluded that CRP is useful marker to screen for a major anastomotic leak when greater than 150 mg/L on POD 3, 4, and 51. Another rationale for a single cut-off value of 150 mg/L instead of the sequential values on POD 3, 4, 5 as per the meta-analysis was that it would be more pragmatic for clinicians to make decisions based on a single cut-off value instead of the different values on different post-operative days. Currently, CRP is not routinely performed after a colorectal resection in our institution and therefore will be challenging for the surgeon to apply varying cut-off values on POD 3, 4, 5 to determine if patients are safe for discharge. A single cut-off value will facilitate application of CRP into current ERAS protocols and clinical pathways. This is particularly useful in ERAS when earlier discharges before POD 5 is not uncommon. Despite different meta-analyses concluding that CRP had a high negative predictive value, in this case series four (18.2%) patients had CRP levels of less than 150mg/L from POD 3 to 5 but still developed an anastomotic leak eventually. A possible reason why the CRP level may not be elevated could be due to the nature of the anastomotic leak. In this case series, some of those without an elevated CRP of more than 150 mg/L were associated with a small or pinpoint defect in the anastomosis that was discovered during surgical intervention for the anastomotic leak. The suspicion of an anastomotic leak in these two patients were confirmed on CT scan prior to surgery. This suggests that patients with very small defects in anastomosis are more likely to be associated with CRP levels that are less than 150 mg/L. An elevated CRP might be due to another source of sepsis such as wound infection, pneumonia or urinary tract infection. The clinician will be more suspicious of an anastomotic leak and will monitor more closely for clinical features and signs that are suggestive of an anastomotic leak. This case series also suggests that patients with an elevated CRP of more than 150 mg/L are associated with an earlier diagnosis of an anastomotic leak and shorter hospitalization stay compared to patients with CRP levels of less than 150 mg/L. Therefore, patients who actually have an anastomotic leak but do not have an elevated CRP of more than 150 mg/L are likely to be diagnosed with the leak at a later day and have a longer hospitalization stay. Hence, patients with low CRP levels but with a possible anastomotic leak may be at an increased risk of a delayed diagnosis and potentially may be associated with increased morbidity or mortality and longer hospitalization stay.

As part of ERAS, some centres have used a low CRP level as a marker for a safe and early discharge [12, 14]. However, this case series suggests that CRP despite its relatively high negative predictive value may not exhibit an elevation in patients with small or early defects in anastomosis. These patients are also likely to have a delayed diagnosis of an anastomotic leak and may be associated with an increased morbidity and mortality after subsequent surgical intervention.

The main limitation of the study is the small sample size and a single centre study. However, it is difficult to accrue sufficient numbers of anastomotic leaks after colorectal resections given its low incidence in most institutions and our study sample size is reasonable and comparable to other studies [18, 20]. The small numbers were also attributed from the inclusion of only colorectal resections with primary anastomosis and exclusion of anastomotic leaks from ileostomy, colostomy closure or even delayed enterotomy leaks. This strict exclusion criteria was to assess the pragmatic application of CRP cut-off values into clinical pathways and ERAS protocols for patients who undergo colectomies. CRP is also not routinely performed after colorectal surgery in this institution and also not performed on a standardized set of days. Therefore, this case series may not be an accurate reflection of the predictive value of CRP in anastomotic leaks given the variations in practice amongst surgeons in this institution with regards to preoperative preparations and postoperative care. However, it does suggest the need for future studies with higher number of patients and standardized preoperative and postoperative care to better analyse the predictive value of CRP in anastomotic leaks.

Anastomotic leak is a dreaded complication that carries a major burden on patients with higher morbidity and mortality, increased reoperation rate, higher stoma rate, higher cancer recurrence, poor functional outcomes, poor quality of life and increased financial costs [3-6]. This case series demonstrates the importance of relying on thorough daily clinical evaluation to ensure that an anastomotic leak is diagnosed early and appropriate intervention taken to minimize the mortality and morbidity associated with it. A low CRP threshold value can be a useful adjunct but should not lead to false reassurance for absence of an anastomotic leak. This case series shows that a low CRP value may not have as high a negative predictive value as described in previous literatures [1,2]. This is particularly crucial in current ERAS protocols where earlier discharges are getting more common and as this study shows delayed anastomotic leaks may hence occur.

6. Conclusion

Early detection of anastomotic leaks can minimize postoperative complications and morbidity rates. Despite the relatively high negative predictive value of CRP for anastomotic leaks, this retrospective case series demonstrate that up to 18.2% of cases had low CRP

values below the previously considered threshold. This study raises the need for caution against primarily relying on CRP as a diagnostic marker of anastomotic leak in colorectal resections with primary anastomosis. This study puts into question the previously considered threshold of 150 mg/L postoperative day 3 as a negative predictive marker of anastomotic leak. This may suggest that overdependence of CRP alone as negative predictive marker for AL has its limitations and may not be as highly accurate as previously considered, especially in this era of ERAS with its potential shorter postoperative length of stay. Therefore, it is important to have a combination of assessments including clinical, biochemical and radiological when considering the possibility of an anastomotic leak during postoperative care after colorectal surgery.

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