ORIGINAL ARTICLE

Bali Medical Journal (*Bali Med J*) 2020, Volume 9, Number 2: 511-515
P-ISSN.2089-1180, E-ISSN.2302-2914

Published by DiscoverSys

C-reactive protein levels as a predictor for anastomotic success in post-operative intestinal resection surgery

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ABSTRACT

Background: C-reactive protein (CRP) is widely used as an early predictor of anastomotic complications such as anastomotic leakage (AL) after abdominal surgery. There are no data available regarding the AL in A.W.Sjahranie Regional General Hospital (RSUD AWS). This study analyzed the CRP values and their relationship with AL after bowel resection and anastomosis surgery at RSUD AWS Samarinda.

Methods: This is an observational analytic cross-sectional study. Sample data were collected from the medical records of 40 patients who underwent bowel resection between May and December 2019. Patients were between 18-75 years old and showed clinical signs of AL. CRP laboratory data were examined on the fifth-day post-operation. After tabulation, the data were analyzed using Chi-square (Fisher's exact) test, t-test, and receiver operating characteristic curve analysis.

Results: The average sample age was 46.3 ± 1.31 years, with a 1:1 male and female ratio. The analysis showed that an increase in CRP values and white blood cell counts was not related to AL ($p > 0.05$). The mean CRP value of patients with AL (48.0±0.00 mg/L) was not significantly different if compared to non-AL patients (25.89 ± 18.93 mg/L) ($p = 0.139$). The CRP cut-off value of 36 mg/L had 100% sensitivity, 60.5% specificity, 71.7% positive predictive value and 100% negative predictive value with an area under the curve of 0.80 (p=0.153). These results showed that the CRP cut-off value of 36 mg/L couldn't be used as a predictor of AL.

Conclusion: CRP level of 36 mg/L can be used as a predictor of non-AL; therefore, it can be used as a criterion for patient discharge.

Keywords: Anastomotic leakage, bowel resection, CRP.

Cite This Article: Basuki, I., Kusuma, M.I., Suprapto, B., Hendarto, J. 2020. C-reactive protein levels as a predictor for anastomotic success in post-operative intestinal resection surgery. *Bali Medical Journal* 9(2): 511-515. DOI:10.15562/bmj.v9i2.1848

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Received: 2020-06-21
Accepted: 2020-07-25
Published: 2020-08-01

INTRODUCTION

Bowel resection and anastomosis is an operation performed to remove intestinal segments that have been damaged or cannot be kept and are done by connecting two viable segments of the intestine.[1] The success and integrity of intestinal anastomosis depend on three factors such as the operator's skill in connecting two viable intestinal segments, the patient condition, for instance, the adequacy of the patients' blood supply and the patients' mental state before and during the surgery, and the underlying process of the disease.[2,3] Anastomosis can be considered successful when anastomotic leakage (AL) does not occur. A successful anastomosis can reduce morbidity and shortens hospital stays. Early discharge benefits patients and reduces the cost of medical care but carries the risk of AL occurring after the patient discharged from the hospital. Therefore, a marker is needed to predict AL after bowel resection surgery.[4]

Complications after intestinal resection and anastomosis include bleeding, stricture, and AL.[3] AL is the most dreaded complication, with an incidence rate of 3-26%.[5] Post-operative AL has serious sequelae, such as infection, abscess, peritonitis, or sepsis, and can be difficult to detect. Delay in detection and intervention of an anastomotic failure contributes to an increased risk of death in patients.[6] Early diagnosis of AL is the key to reduce the morbidity and mortality associated with anastomotic failure.

C-reactive protein (CRP) is an acute-phase protein synthesized by the liver. It has been used as a predictor to detect complications arising after abdominal surgery, such as bowel or colon surgery.[7] Several new studies suggest that CRP has been identified as an early predictor of sepsis complications after resection of the esophagus, pancreas, colon, and rectum.[8] Multivariable analysis found that CRP on post-operative day 5 (POD5) was a patient factor statistically associated with an increased risk of AL.[9,10]

Many intestinal anastomosis resection surgeries have been performed in Abdul Wahab Sjahranie Regional General Hospital (RSUD A.W. Sjahranie), Samarinda, but there were no data regarding anastomotic failure rate after anastomosis resection surgery. It might be possible that the inflammation triggered by an anastomotic failure, in particular,

AL, after resection surgery was not detected quickly, which led to an increase in the patient's hospitalization time. Therefore, we conducted this study to predict the correlation between CRP values and AL, post-intestinal anastomosis, and resection performed in RSUD A.W. Sjahranie, Samarinda.

METHODS

Study design and data collection

This study used an analytical cross-sectional study design to determine the correlation of increased CRP levels, including the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CRP levels, with AL after intestinal resection and anastomosis surgery. Data on research subjects (age, sex, surgery characteristics, laboratory results) were obtained from patients' medical records with the inclusion criteria. Ethical clearance was obtained from the Research Ethics Committee of RSUD A.W. Sjahranie, Samarinda (No. 122/KEPK-AWS/VII/2019). The study was conducted from May to December 2019. There were 40 patients with inclusion criteria, namely, 18-75 years-old hospitalized adult patients after elective intestinal resection and anastomosis in RSUD A.W. Sjahranie, Samarinda, with clinical signs of anastomotic failures, such as localized peritonitis or ileus; CRP data values were available for the fifth-day post-operation. The exclusion criteria were as follows: severe comorbidities besides the primary disease that was resulting to intestinal resection and anastomosis, such as autoimmune diseases or HIV/AIDS; patients undergo emergency bowel resection and anastomosis surgeries at A.W. Sjahranie Hospital, Samarinda; and patients who experienced post-operative inflammation, such as infection after surgical injury without signs of anastomosis failure.

Data analysis

Categorical variables were reported in numbers and percentages, while CRP level values were expressed in mean ± standard deviation. The collected data were tabulated and then statistically analyzed using a Chi-square test to determine the correlation of patient's surgery characteristics and laboratory data with AL. T-test was used to compare the mean CRP value between patients with AL and non-AL. Receiver operating characteristic (ROC) curve analysis was used to predict the CRP cut-off value for AL and non-AL. Data was analyzed use SPSS version 23 for Windows.

Table 1 Baseline characteristics of patients

Characteristics		N=40	Percentage (%)
Age	Under 40 years	13	32.5
	41 – 60 years	22	55.0
	Over 61 years	5	12.5
Gender	Male	21	52.5
	Female	19	47.5
AL	Yes	2	5.0
	No	38	95.0

AL: anastomotic leakage

RESULTS

Sample distribution based on demography

From the medical records data of 40 patients who underwent elective resection and intestinal anastomosis, the following results were obtained: AL occurred in two (5%) patients. AL was assessed based on the presence or absence of localized peritonitis and ileus complaints. The average patient age (46.3 ±1.31 years) was normally distributed (p = 0.2), the largest age group was 41-60 years old, and the smallest was over 61 years old. Patient gender was equal between men and women (Table 1).

Correlation of patients' clinical characteristics and laboratory data with anastomotic leakage (AL)

Table 2 shows that the most common performed anastomosis surgery was the stapler method, with the end-to-end type. The sigmoid colon was the most common lesion location. There were no correlation between operation method (p = 1.000), anastomosis types (p = 0.799), and lesion location (p = 0.819) with AL. Laboratory data such as the increase in CRP values (p = 1.000) and white blood cell counts (p = 0.488) also did not correlate with AL.

CRP values analysis for AL

Figure 1 shows that the mean CRP value in patients with AL (48 ± 0.00 mg/L) was not significantly different compared to non-AL patients (25.89 ± 18.93 mg/L) with p = 0.139. ROC curve analysis for AL showed that the CRP cut-off value of 36 mg/L had a higher sensitivity (100%) than specificity (60.5%), and a higher negative predictive value (NPV) (100%) than the positive predictive value (PPV) (71.7%) (Table 3), with the area under the curve (AUC) of 0.80 (p = 0.153) (Figure 2). These results showed that the mean CRP value of 48 mg/L and the CRP cut-off value of 36 mg/L could not be used as predictors of AL, because of the p values > 0.05. A lower specificity than sensitivity indicates that the CRP value is not specific as a predictor of AL. A higher NPV than PPV illustrates that the CRP value is a useful negative test but is not

Table 2 The correlation of patients' clinical characteristics and laboratory data with anastomotic leakage (AL)

Variable	AL group (N=2)	Non-AL group (N=38)	p
Operation method, n (%)			1.000
Hand sewn	1 (50.0)	15 (39.5)	
Stopler	1 (50.0)	23 (60.5)	
Anastomosis type, n (%)			0.799
End to end	2 (100.0)	27 (71.1)	
End to side	0	5 (13.1)	
Side to side	0	3 (7.9)	
Side to end	0	3 (7.9)	
Lesion location, n (%)			0.819
Caecum	0	2 (5.3)	
Ascending colon	1 (50.0)	11 (28.9)	
Descending colon	0	5 (13.2)	
Sigmoid colon	1 (50.0)	17 (44.7)	
Others	0	3 (7.9)	
CRP level, n (%)			1.000
Over 6 mg/L	2 (100.0)	26 (68.4)	
Less than or equal to 6 mg/L	0	12 (31.6)	
WBC counts, n (%)			0.488
Over 10000/mm^3	2 (100.0)	19 (50.0)	
Less than 10000/mm^3	0	19 (50.0)	

AL, anastomotic leakage; non-AL, non-anastomotic leakage; CRP, C-reactive protein; WBC, White blood cell; and data analysis with a chi-square test (Fisher's exact), *p<0.05 indicated a significant correlation with AL in Fisher's Exact Test

Table 3 CRP diagnostic level on POD5 used to identify AL

Cut off point	Sensitivity%	95% CI	Specificity%	95% CI	PPV %	NPV %
>9	100	15.81- 100	31.58	17.50-48.65	59.37	100
>18	100	15.81-100	47.37	30.98-64.18	65.51	100
>36	100	15.81-100.0%	60.53	43.39-75.96	71.7	100

CRP, C-reactive protein; POD, post-operative day; AL, anastomotic leakage; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value

a good positive predictor of AL.[4,9] Therefore, the CRP cut-off value of 36 mg/L can be used to predict non-AL.

DISCUSSION

Anastomotic failure, particularly AL, is a serious complication of gastrointestinal surgery that can increase mortality, morbidity, and length of hospital stay. Therefore, AL must be diagnosed as early as possible to reduce the consequences of mortality and morbidity. Delayed diagnosis of AL after POD5 has been associated with an 18% mortality rate, but morbidity can be minimized if diagnosis and therapy are carried out before POD5.[11] The incidence rate of AL ranges from 6-30% depending on patients' risk factors.[5] Factors that increase the risk of leakage include low anastomosis location are male and elderly patient, patient with a malignant tumor, has a high American Society of Anesthesiologists (ASA) score, duration of surgery, preoperative radiotherapy, and the amount of blood lost during surgery.[12,13]

In this study, there was no significant relationship between the surgical method, type of anastomosis, and lesion location with AL. Only two cases of AL (5%) were found. This leakage was assessed within seven days after repeated resection. A 71-year-old woman was diagnosed with sigmoid colon cancer, and a 41-year-old man was diagnosed

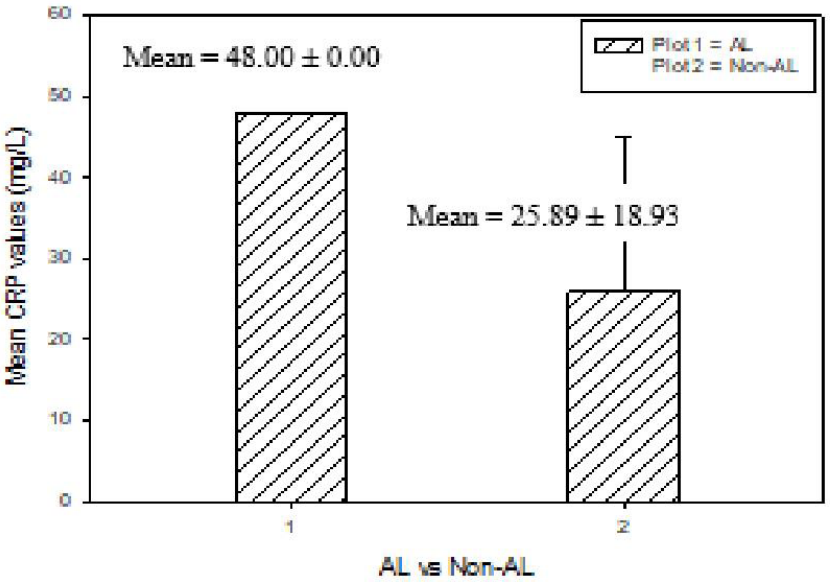

Figure 1 Mean CRP values of patients with AL and non-AL
AL, anastomotic leakage; Non-AL, non anastomotic leakage; CRP, C-reactive protein; Data analysis with t-test (p = 0.139); *p<0.05 indicated a significant difference

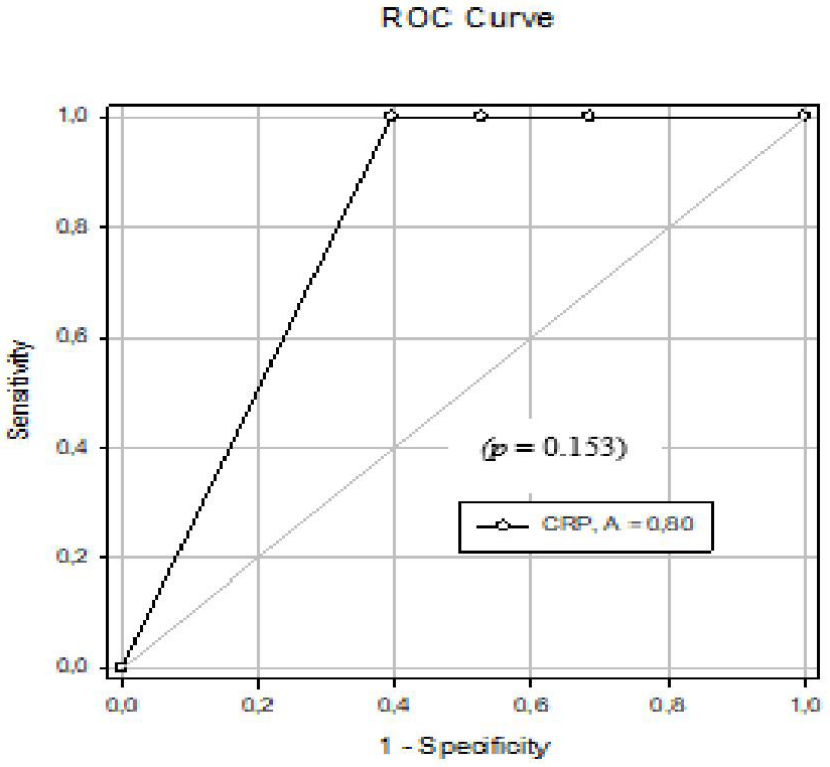

Figure 2 ROC curves of CRP cut-off values in patients with AL
(ROC, receiver operating characteristic; CRP, C-reactive protein; AL, anastomotic leakage; A, area under the ROC curved)

with an ascending colon tumor. It was unknown whether these patients had other comorbidities, such as preoperative radiotherapy or immunocompromised condition such as diabetes mellitus. This finding was consistent with the literature, which stated that the incidence rate of AL ranges from 6-30%,[5] and following the results of other studies that describe the incidence rate of AL can be 2-7% when the resections are performed by experienced operators.[14]

CRP is a marker that is widely used to detect acute inflammatory responses. CRP is produced exclusively by liver hepatocytes after being stimulated by interleukin (IL)-6, tumor necrosis factor-α, and IL-1β originating from the inflammation site. After stimulation, serum CRP levels rise above normal within six-hour and reach a peak at approximately 48 h. CRP has a mostly constant serum half-life of approximately 19 h. Therefore, serum CRP concentrations are determined by the rate of synthesis, reflecting the acute inflammatory response. Thus, CRP is ideal as a biomarker of disease progressivity, inflammatory responses, and post-operative recovery.[15,16,17] The low level of tissue perfusion can cause ischemia in the suturing area that triggers an intense inflammatory response in patients with AL. As inflammation develops, there is an increase in CRP production. Although the CRP level reached its peak on day four after colorectal resection surgery, it still has high accuracy, even with POD5 and POD7 levels.[11] Therefore, in this study, the POD5 CRP levels were recorded. There was no significant relationship between the increase in CRP levels (POD5) with AL after intestinal resection surgery. The mean CRP value supported this result in patients with AL that was not significantly different from patients with non-AL (p> 0.05) (Figure 1). This result showed that the mean CRP value of 48 mg/L was not a marker for AL. To find out whether the CRP value can act as a predictor of AL or non-AL, a ROC curve analysis showed the results as in table 3 and figure 2. CRP cut-off value of 36 mg/L (AUC of 0.80 with p>0.05) was sensitive, but not specific as a biomarker for AL. The higher NPV compared to PPV indicated that the CRP cut-off value of 36 mg/L was a good negative test for AL. Therefore, it can be used to predict non-AL, and the CRP cut-off value of 36 mg/ L (POD5) can be used as a biomarker for patient discharge.

Previous studies have found an association between increased CRP levels and post-operative infection complications, such as AL and intra-abdominal abscesses. These studies determined the minimum (cut-off) CRP value that can be used as a predictor.[8,18] However, these studies yielded different conclusions, including the PPV of CRP. A meta-analysis conducted in a previous study collected six studies that examined POD4 CRP levels in patients discharged after surgery. The cut-off value obtained on the 4th day was 135 mg/L with 68% sensitivity, 83% specificity, 89% NPV and an AUC of 0.810.[19] Another study yielded different

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values. This study used POD3 CRP levels with a cut-off value of 190 mg/L. The resulting sensitivity was 77%, with 80% specificity, and an AUC of 0.84.[20] Another study suggested that CRP alone cannot be used to diagnose major post-operation complications. This was because CRP levels can also increase in patients who experience heavy bleeding, lengthy surgery, and high intraoperative stress.[21] Based on these studies, CRP is better used to accelerate the discharge of patients with low CRP levels. This is because CRP has better specificity than sensitivity. In other words, patients with low CRP levels are less likely to have AL complications. However, a high CRP value does not necessarily indicate the presence of AL. The limitation of this study is the small sample size due to limitations in sample collection. Future research with a larger number of samples will give better results.

CONCLUSION

CRP cut-off value of 36 mg/L on the fifth day after intestinal resection and anastomosis surgery in RSUD A.W. Sjahranie Samarinda can be used as a predictor of anastomotic success (non-AL), and as a criterion for patient discharge.

CONFLICT OF INTEREST

The authors declare that no conflicts of interest in this work.

ETHICAL CONSIDERATIONS

Our research protocol has been approved by the Research Ethics Committee of RSUD AWS Samarinda with letter number "122/KEPK-AWS/VII/2019".

FUNDING

The study was self-funded by the authors.

AUTHOR CONTRIBUTION

The authors gave equal contributions from designing and conducting the study, to the writing of the manuscript.

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