Correlation between Albumin, Colon Leakage Score (CLS), and Anastomotic Leakage after Colorectal Cancer Resection

Reno Rudiman,[1] Putie Hapsari,[2] Novi Christina[3]
[1]Division of Digestive Surgery, Department of Surgery, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital Bandung, Indonesia
[2]Division of Vascular and Endovascular Surgery, Department of Surgery, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital Bandung, Indonesia
[3]Department of Surgery Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital Bandung, Indonesia

Abstract

Anastomotic leakage is still the most undesirable complication of colorectal surgery. The reported incidence of anastomotic leakage after colorectal surgery varies from 1.8% to 15.9%. The impact of anastomotic leakage is increased morbidity, mortality (12–30%), length of stay, and cost of hospitalization; hence, this complication should be prevented as much as possible. Several studies have shown a correlation between low albumin levels and increased anastomotic leakage. The colon leakage score (CLS) is a standard score for predicting anastomotic leakage, but this score does not include the albumin level as a parameter of anastomotic leakage despite the importance of the albumin level's contribution on the anastomotic leakage. Therefore, this study sought to analyze the correlation between the albumin level, CLS, and the incidence of anastomotic leakage after anastomotic resection surgery in colorectal cancer (CRC) patients at Dr. Hasan Sadikin General Hospital Bandung, Indonesia. This study was a cross-sectional retrospective analytical study on medical records of CRC patients over the age of 18 who underwent intestinal anastomotic resection surgery between 2016–2020. There were thirty-two patients with colorectal cancer underwent anastomotic resection during the study period, with two patients experienced anastomotic leakage. Correlation analysis showed that the correlation coefficient for the albumin level and anastomotic leakage was 0.209, while the correlation coefficient between CLS and anastomotic leakage was 0.110. There is no correlation between albumin level, CLS, and the incidence of anastomotic leakage after anastomotic resection surgery in CRC patients treated at Dr. Hasan Sadikin General Hospital Bandung, Indonesia.

Keywords: Anastomotic leakage, anastomotic resection, albumin, colon leakage score, colorectal cancer

Introduction

Colorectal cancer (CRC) is a malignancy originating from the large intestine, consisting of the colon (the longest part of the large intestine) and/or the rectum (the longest part of the large intestine) and/or the rectum (last small part of the large intestine before the anus). According to the American Cancer Society, CRC is the third most common cancer and the second leading cause of mortality in men and women in the United States. In 2014, there were 96,830 new cases of colon cancer and 40,000 new cases of rectal cancer. Overall, the risk of getting CRC is 1 in 20 people (5%).[1] From GLOBOCAN 2020 data, the incidence of CRC in Indonesia is 8.6% per 100,000 adult population, with a mortality rate of 6.7% of all cancer cases.[2] In the Digestive Surgery division of the Dr. Hasan Sadikin General Hospital, from 2016 to 2020 there were 920 cases of CRC, with an 8.46% of mortality rate in 2020.[3] CRC more cases in men than women. One of the treatments for CRC cases is anastomotic resection, but the complication is anastomotic leakage. Anastomotic leakage is still an undesirable complication of colorectal surgery.[4,5] The incidence of anastomotic leakage after colorectal surgery varies widely from 1.8% to 15.9% because of heterogeneity in the anastomotic leakage definition, different patient inclusion criteria, and the retrospective nature

Corresponding Author:
Novi Christina
Department of General Surgery Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital Bandung, Indonesia
Email: novichristina88@gmail.com

of most studies.[1] Increased morbidity, mortality (12–30%), length of hospitalization, and costs are well-known consequences of anastomotic leakage in colorectal surgery, so it should be prevented as much as possible.[4,5] There are many risk factors associated with anastomotic leakage.[6] Risk factors can be categorized as patient-specific, intraoperative, and specific for low rectal anastomosis. Risk factors preoperatively include obesity. When anastomotic leaks occur <5 cm from the anal verge, there is a 33% leak rate in obese patients. Other patient-specific risk factors include malnutrition, tobacco use, and alcohol use. The nutritional state is an important factor in contributing to anastomotic leaks.[8] Low albumin levels have long been observed as an indicator of malnutrition. Traditionally, albumin has been considered a nutritional marker and a guide to enteral or parenteral nutrition therapy in preoperative hypoalbuminemia. Hypoalbuminemia is a strong predictor of morbidity in patients with postoperative gastrointestinal malignancy. Some studies consider albumin as a nutritional parameter, but other studies have questioned this relationship, especially in healthy patients and patients who do not undergo surgery.[8] Although albumin is a prognostic marker in postoperative patients, the importance of albumin as a nutritional parameter is still under debate. There is a lack of evidence on how changes in albumin levels are related to the inflammatory process and postoperative complications.[8] Several studies have shown a correlation between low albumin levels and increased anastomotic leakage.[6,7] Based on the studies that have been conducted, it is stated that malnutrition, weight loss, and low albumin levels are the strongest risk factors for anastomotic leakage.[6] Intraoperative risk factors are low level of anastomotic, suboptimal anastomotic blood flow, operating time of more than 2 hours, intestinal obstruction, perioperative blood transfusion, and intraoperative septic conditions.[6]

Dekker et al. created a Colon Leakage Score (CLS) scoring system that can evaluate the risk of anastomotic leaks and facilitate preoperative and post-operative planning. There are 11 parameters that are included in CLS, namely age, gender, ASA status, body mass index, history of intoxication (smoking, alcohol, steroid use), history of neoadjuvant therapy, history of emergency surgery, anastomotic distance from anal verge, additional procedure, amount of blood loss, and duration of surgery.[9,11] Colon Leakage Score is a clinically relevant scoring

system (sensitivity 84.6% and specificity 87.2%) in predicting preoperative anastomotic leaks. This system is based on patient condition and preoperative variables. In addition, there is also the Dutch Leakage Score (DLS) which can be used as a guide in predicting the early signs of postoperative leakage. However, DLS has limited practical value were 13 parameters were assessed and observed postoperatively.[10] Based on considerations of effectiveness, length of stay, risk of reoperation, and cost, it is necessary to predict an anastomotic leak before surgery. The CLS scoring system can be easily applied to predict anastomotic leaks where 11 parameters were assessed based on preoperative and intraoperative data and had a sensitivity and specificity higher than the DLS scoring system.

The standard CLS scoring system does not contain albumin levels as a parameter for anastomotic leakage, while albumin levels are an important factor that contributes to anastomotic leakage. This makes the central theme of the study assess whether there is a correlation between albumin levels in anastomotic leakage and whether it needs to be considered in the preoperative of CRC patients for anastomotic resection, accompanied by an assessment using the CLS scoring system. Therefore, researchers are interested in examining the correlation between albumin levels and CLS with the incidence of leakage anastomosis post-resection surgery in CRC patients at Dr. Hasan Sadikin General Hospital Bandung, Indonesia.

Methods

This study was conducted at Dr. Hasan Sadikin Bandung General Hospital with research subjects taken from medical records of CRC patients aged over 18 years who underwent intestinal anastomotic resection for the period January 1st, 2016–December 31st, 2020, which was carried out directly by consultant/ trainee in the colorectal division/ resident of digestive surgery under the supervision of consultant which is the inclusion criteria of this study. While the exclusion criteria were medical record data of patients who underwent post-colostomy anastomotic resection surgery who had previously undergone anastomotic resection surgery (resident cases), emergency rectal anastomotic resection surgery, and incomplete data. The study was approved by the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital number LB.02.01/X.6.5/309/2021.

The study consisted of the dependent variable in the form of intestinal anastomotic leakage which was assessed based on albumin and CLS levels which were independent variables in this study. This study is a retrospective analytic study with a cross-sectional study design with medical record data collected to be analyzed the correlation of albumin and CLS levels with the incidence of bowel leakage after anastomotic resection surgery in CRC patients. The sample size taken from the calculation of the correlation formula is 31 patients with a 95% confidence level and 90% power test. The sampling method used consecutive sampling by taking each subject that includes in the inclusion criteria. The data analyzed were intestinal anastomotic leakage, weight and height, age, gender, ASA degree, body mass index, history of intoxication, history of neoadjuvant therapy, history of emergency surgery, anastomotic distance to the anal verge, additional procedures, amount of blood loss, duration of surgery, calculation of CLS and albumin levels. Data were analyzed using statistical calculation of correlation with the contingency coefficient. The statistical test results are said to be meaningful if the p-value is 0.05. The data obtained were recorded using Microsoft Excel 365 software and then processed through the SPSS version 25.0 program for Windows. Data were analyzed to descript of the proportion of each variable that will be presented descriptively. The data in the form of categorical such as age, gender, degree of ASA, intoxication, neoadjuvant therapy, emergency surgery, anastomotic distance from the anal verge, additional procedures, blood loss, blood transfusion, duration of patient surgery, CLS score and albumin then the coding and presented as a frequency distribution and a percentage. The analysis carried out must be following the type of research problem and the data used, namely to determine the correlation between albumin levels, CLS score, and anastomotic leakage after anastomotic resection surgery in CRC patients. The data will be analyzed using statistical calculations of correlation with contingency coefficient. The r value obtained shows a correlation between variables, the r value 0.81–0.99 indicates a strong relationship, 0.41–0.60 indicates a moderate relationship, and 0.01–0.20 indicates a very weak relationship. With a p-value <0.05, it shows a significant result. The value of albumin is divided into two categories which are ≥3.5 g/dL and <3.5 g/dL. The value of the CLS score is also divided into two categories that are ≤11 low risks and >11 high risks of leakage. The data were analyzed with correlation contingency.

Results

In this study, 37 patients with CRC underwent anastomotic resection and 5 patients were excluded because the medical record data was incomplete and had been retained. There were 32 patients with CRC who underwent anastomotic resection that include in the inclusion criteria, that are 30 patients without leakage, and 2 patients with postoperative leakage.

Table 1 describes the characteristics of the study subjects of colorectal cancer patients who underwent anastomotic resection based on gender, age, ASA, BMI, intoxication, neoadjuvant therapy, emergency surgery, anastomotic distance–anal verge, additional procedures, blood loss, duration of surgery, albumin levels and CLS.

In this study, the highest albumin level <3.5 g/dL that were 19 of 32 patients and albumin levels ≥3.5 g/dL were 13 of 32 patient . There were 2 of 32 patients with anastomotic leakage with albumin <3.5 and 17 of 32 patients with no leakage. P value 0.227 was obtained, which means that there is no statistically significant difference between albumin levels and anastomotic leakage. For the most CLS scores in this study with CLS ≤11, namely 27 of 32 patients and CLS scores >11, namely 5 of 32 patients. There were 2 of 32 patients with anastomotic leakage and low risk CLS. Patients with low risk CLS and no anastomotic leakage that were 25 of 32 patients. P value obtained of 0.530 that means there is no statistically significant difference between CLS and anastomotic leakage. Analysis about correlation between albumin levels and CLS score listed in Table 2.

The correlation between albumin levels and anastomotic leakage has a correlation coefficient of 0.209 with a positive direction. This correlation is weak and not statistically significant, which means that there is no correlation between albumin levels and anastomotic leakage.

The correlation between CLS and anastomotic leakage has a coefficient value of 0.110 with a positive direction. This correlation is also very weak and not statistically significant, which means that there is no correlation between CLS and anastomotic leakage.

From above, the analysis correlation of albumin levels and CLS with the incidence of postoperative anastomotic leaks, the researchers

Table 1 Characteristics of Research Subjects

Characteristics		Total (n=32)	Anastomosis		P value*
			No Leakage (n=30)	Leakage (n=2)	
Gender	Male	16	15	1	1.000
	Female	16	15	1	
Age (years)	>18–<60	23	23	0	0.041
	60–69	8	6	2	
	70–79	1	1	0	
	≥80 years old	0	0	0	
ASA[19]	ASA I	4	4	0	0.659
	ASA II	23	21	2	
	ASA III	5	5	0	
	ASA IV	0	0	0	
BMI (kg/m^2)	19–24	20	19	1	0.560
	25–30	7	6	1	
	>30/<19, or weight loss (>5kg /6 months)	5	5	0	
Intoxication	No	31	29	2	0.793
	Smoking	1	1	0	
Neoadjuvant therapy	No	29	27	2	0.639
	Chemoradiation	3	3	0	
Emergency surgery	No	32	30	2	* NA
	Yes	0	0	0	
Distance of Anastomosis to *anal verge*[16]	>10 cm	22	20	2	0.616
	5–10 cm	9	9	0	
	<5 cm	1	1	0	
Hecting	Hand Sewing	25	24	1	0.320
	Stapler	7	6	1	
Additional procedure	Yes	2	1	1	0.008
	No	30	29	1	
Blood loss and transfusion[17]	<500 ml	20	19	1	0.735
	500–1000 ml	9	8	1	
	1001–2000 ml	3	3	0	
	> 2000 ml	0	0	0	
Duration of Operation[18]	2:00–2:59	5	5	0	0.616
	3:00–3:59	5	5	0	
	≥ 4:00	22	20	2	
Albumin	< 3,5	19	17	2	0.227
	≥ 3,5	13	13	0	
CLS	≤ 11	27	25	2	0.530
	>11	5	5	0	

Notes: *=obtained P *value* with chi-square test, with a significance value based on p-value <0.05 means statistically significant

Table 2 Correlation of Albumin Levels and CLS with Anastomotic Leakage

Albumin and CLS	Anastomosis Leakage		R	P-value*
	Leakage	No Leakage		
Albumin				
<3.5	2	17	0.209	0.227
≥3.5	0	13		
CLS				
≤11	2	25	0.110	0.530
>11	0	5		

Note: *Coefficient Contingency Correlation test

analyze a correlation between albumin levels and CLS scores of high-risk and low-risk anastomotic leaks listed in Table 3.

The correlation between albumin levels and CLS scores of high risk and low risk of anastomotic leakage has a correlation coefficient of 0.005 with a positive direction. This correlation is very weak and statistically not significant, which means there is no correlation between albumin levels, high risk, and low risk of CLS scores with anastomotic leakage.

Discussion

Anastomotic leakage is an unwanted complication of colorectal surgery. The impact of anastomotic leakage influences increasing morbidity, mortality, length of stay, and cost of hospitalization.[3,4] Many risk factors are associated with anastomotic leakage.[6] Risk factors are categorized as preoperative, intraoperative patient factors and the distance of anastomosis from the anal verge.[8] Preoperative factors are smoking, alcohol, and nutritional status. Nutritional status is important in contributing to anastomotic leakage.[6] Albumin has long been observed as a nutritional marker.[8] Although albumin is a prognostic marker in postoperative patients, the importance of albumin as a

nutritional marker is still debated.[8] this study aimed to explore the correlation of albumin levels with the incidence of bowel leakage after anastomotic resection surgery in CRC patients. Dekker et al.,[11] created a CLS scoring system that can evaluate the risk of anastomotic leaks and facilitate preoperative and postoperative planning. In the CLS scoring system, the parameter was gender, age, ASA, body mass index, history of intoxication (smoking, alcohol, steroid usage), history of neoadjuvant therapy, history of emergency surgery, the distance of anastomotic from the anal verge, additional procedures, amount of blood loss and duration of surgery.

In this study, gender, ASA, body mass index, history of intoxication (smoking, alcohol, steroid usage), history of neoadjuvant therapy, history of emergency surgery, distance anastomotic from anal verge, amount of blood loss and duration of surgery are not statistically significant with a p value >0.05 that mean there are no correlation with leakage anastomotic.

Age can affect anastomotic healing. The older one has a slower healing process, and all phases of healing are affected. The inflammatory response is decreased, as is the proliferative response. Renovation occurs but to a lesser extent, and the collagen formed is qualitatively different.[14] In this study, age was assessed as

Table 3 Correlation between Albumin levels and CLS Scores of High Risk and Low Risk of Anastomotic Leaks

Variable	CLS		R	P-value*
	Low Risk	High Risk		
Albumin				
<3.5	16	3	0.005	0.975
≥3.5	11	2		

Note: * Coefficient Contingency Correlation test

directly related to anastomotic leakage and the correlation between patient age and incidence of bowel leakage was statistically significant with a p-value of 0.041 in Table 1.

Several studies have shown a correlation between low albumin levels and increased anastomotic leakage.[5,6] One case-control study found that malnutrition (serum albumin < 3.5 g/dL) was a substantial risk factor for anastomotic leakage by multivariate analysis, with the odds ratio of 13.2 (95% CI, 2.83 61.85).[5,9] In this study, 19 patients with albumin levels <3.5 were found, consisting of 2 patients with an anastomotic leak, and the remaining 17 patients who had no anastomotic leak. Calculations of p-value 0.227 and correlation coefficient value 0.209 with a positive direction are listed in Table 2. This correlation is weak and statistically not significant, which means there is no correlation between albumin levels and anastomotic leakage. In this study, albumin levels were not significant, and the correlation was weak, this is because the data was taken from patients who did not undergo emergency surgery, so the condition of patients with low albumin levels still tolerated the stress of surgery compared to patients who underwent emergency surgery. Another factor is the possibility of a decreased postoperative condition which was not assessed in this study, thus becoming a biased in this study.

Logistic regression analysis was performed in Dekker's study and the odds ratio was 1.74 (AUC=0.95 CI 1.32–2.28, p<0.01), it was concluded that CLS can accurately predict the risk of anastomotic leak.[11] In this study, CLS was calculated for each patient who underwent anastomosis. CLS score ≤11 was obtained for 27 of 32 patients consisting of 2 of 32 patients who had anastomotic leaks and the remaining 25 of 32 patients who did not have anastomotic leaks. While the CLS score >11 was obtained in 5 of 32 patients and all of them did not experience anastomotic leakage. Then an analysis got a p-value of 0.530 and the correlation value was 0.110 with a positive direction listed in Table 2. This correlation is very weak and not statistically significant, which means that there is no correlation between CLS and anastomotic leakage. The results of this study were not significant and had a very weak correlation because patients with anastomotic leakage had a CLS score of ≤11. Meanwhile, patients who had CLS score >11 but did not experience anastomotic leakage, perhaps because, in this study, patients were not grouped based on the stadium of CRC and in this study the data on CRC patients were not grouped based on the location of the tumor in colon or rectum. This study, although it did not provide a significant correlation between albumin levels and CLS with the incidence of intestinal leakage after anastomotic resection surgery in CRC patients, did not rule out other positive values from the results of this study, namely age and additional procedures which had p values of 0.041 and 0.008 which were statistically significant.

The limitations of the study were that the research subjects only found 2 patients with anastomotic leaks, and there were no data related to emergency anastomotic resection surgery. In this study, the researchers also did not divide the research subject based on the stadium of CRC which might provide more meaningful results if an analysis was carried out based on the stage of CRC.

This study shows that there is no correlation between albumin levels and CLS with the incidence of anastomotic leakage after anastomotic resection surgery in CRC patients at Dr. Hasan Sadikin General Hospital Bandung, Indonesia.

References

1. National Cancer Combating Commission. National guidelines for colorectal cancer management medical services. colorectal cancer management guidelines. Jakarta: Ministerial Decree of Health of the Republic of Indonesia; 2018.
2. WHO. Global Cancer Observatory. Indonesia GLOBOCAN 2020. 360-indonesia-fact-sheets. International Agency for Research on Cancer World Health Organization March 2021. Available from: https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf.
3. Dr. Hasan Sadikin General Hospital. Inpatient data from January 2016–December 2020. Digestive Surgery. Bandung. 2021.
4. Frasson M, Flor-Lorente B, Rodríguez JL, Granero-Castro P, Hervás D, Alvarez Rico MA, et al. Risk factors for anastomotic leak after colon resection for cancer: multivariate analysis and nomogram from a multicentric, prospective, national study with 3193 Patients. Ann Surg. 2015;262(2):321–30.
5. An V, Chandra R, Lawrence M. Anastomotic failure in colorectal surgery: where are we at?. Indian J Surg. 2018;80(2):163–70.
6. Zarnescu EC, Zarnescu NO, Costea R. Updates

of risk factors for anastomotic leakage after colorectal surgery. Diagnostics (Basel). 2021;11(12):2382.

7. Calin MD, Bălălău C, Popa F, Voiculescu S, Scăunașu RV. Colic anastomotic leakage risk factors. J Med Life. 2013;6(4):420–3.

8. Galata C, Busse L, Birgin E, Weiß C, Hardt J, Reißfelder C, et al. Role of albumin as a nutritional and prognostic marker in elective intestinal surgery. Can J Gastroenterol Hepatol. 2020;2020:7028216.

9. Yu XQ, Zhao B, Zhou WP, Han LZ, Cai GH, Fang ZW, et al. Utility of colon leakage score in left-sided colorectal surgery. J Surg Res. 2016;202(2):398–402.

10. den Dulk M, Witvliet MJ, Kortram K, Neijenhuis PA, de Hingh IH, Engel AF, et al. The DULK (Dutch leakage) and modified DULK score compared: actively seek the leak. Colorectal Dis. 2013;15(9):e528–33.

11. Dekker JW, Liefers GJ, de Mol van Otterloo JC, Putter H, Tollenaar RA. Predicting the risk of anastomotic leakage in left-sided colorectal surgery using a colon leakage score. J Surg Res. 2011;166(1):e27–34.

12. Pierpont YN, Dinh TP, Salas RE, Johnson EL, Wright TG, Robson MC, et al. Obesity and surgical wound healing: a current review. ISRN Obes. 2014;2014:638936.

13. Mohamed AA, Atrayee B, Sehwan J, Seong HY, Jun WY, Frank JG, et al. CYP2E1 potentiates binge alcohol-induced gut leakiness, steatohepatitis and apoptosis. Free Radic Biol Med. 2013;65:1238–45.

14. Gould LJ, Fulton AT. Wound healing in older adults. R I Med J (2013). 2016;99(2):34–6.

15. Tomasz S, Monika R, Anna D, Ewa N, Tomasz A, Katarzyna, et al. A Review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis. Cancers (Basel). 2021;13(9):2025.

16. Jeannete M, Jennifer H. Anastomotic technique-how to optimize success and minimize leak rates. Clin Colon Rectal Surg. 2021;34:371–8.

17. Ahmed AYA. Effects of blood transfusion in outcome of elective bowel anastomosis. Global J Med Res. 2012;12(8):34–8.

18. Cortina CS, Alex GC, Vercillo KN, Fleetwood VA, Smolevitz JB, Poirier J, et.al. Longer operative time and intraoperative blood transfusion are associated with postoperative anastomotic leak after lower gastrointestinal surgery. Am Surg. 2019;85(2):136–41.

19. Erin EH, Michelle S, Sandhya RV, Charles FZ, Sarah MS, Abu M, et.al. Adding Examples to the asa-physical status classification improves correct assignment to patients. Anesthesiology. 2017;126(4):614–22.