

**FULL PAPER**

# Hemoglobin level and albumin as a predictive factors for anastomotic leakage following after hemicolectomy: A prospective study for colon cancer

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Anastomotic leaks after colon surgery are associated with increased morbidity and mortality, the incidence and mortality rate reaches 6%-22% of total cases. Multiple risk factors for anastomotic leak have been identified for better prevention and an earlier diagnosis anastomosis leakage complication. Haemoglobin is related to perfusion and oxygenation of the anastomotic margins, and albumin is the protein with an essential factor for anastomotic healing. This study examined the relationship between albumin and haemoglobin levels with anastomotic leakage after hemicolectomy in colon cancer patients. A cohort study of all the colon cancer patients after hemicolectomy at Soetomo General Hospitals, Surabaya Indonesia between January 2018 and December 2022. A total of 31 out of 85 patients who developed anastomotic leak were analyzed. Albumin serum and haemoglobin level were analysed by univariate analysis and stepwise multiple logistic regression analysis. A comparison was made between the patients' intergroups according to the kind of operation. In this study, 31 patient (36.5%) anastomotic leaks were confirmed. The result showed that the preoperative variables significantly associated with anastomotic leakage included hypoalbumin *p-value* 0.01 OR: 2.3 (ROC curve analysis albumin level  $\leq$  2.7 g/dl with cut off value sensitivity of 66.7% a sensitivity 74.2%) and anemia *p-value* 0.007 and OR 3.4 (ROC curve serum haemoglobin level  $\leq$  10.3 g/dl with cut-off value sensitivity of 63.0% a sensitivity 61.3%) remained significant in the logistic regression model. The preoperative serum albumin level and haemoglobin levels are independent risk factors for anastomotic leakage in colon cancer patients after hemicolectomy.

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**KEYWORDS**

Albumin; haemoglobin; anastomotic leak; colon cancer.

**Introduction**

Anastomosis leakage is a very feared complication after hemicolectomy surgery, this is associated with increased post-

operative mortality and morbidity, based on existing data, the incidence of anastomosis leakage after colorectal surgery reaches 2-19% (1,2). In colon cancer patients, anastomotic leakage has a negative effect on

overall survival, disease-free survival, and local recurrence. Accordingly, early diagnosis and prevention of anastomotic leakage should be carried out. Many factors influence anastomosis leakage, factors that can be divided into local and general factors; pre-, intra- or postoperative factors; and modifiable or non-modifiable factors. Albumin and haemoglobin are factors that greatly influence the anastomosis healing process, especially in the colon (3,4). There is a lot of literature debating the effect of albumin on the healing of colon anastomosis. Some authors report preoperative albumin levels of less than 3.5 g/dL as a significant factor in leakage, but in the latest study, there was no significant difference in preoperative serum albumin levels between the anastomotic leak group and the non-anastomotic leak group, but the levels postoperative serum albumin was significantly lower in the anastomotic leak group. Albumin influences anastomosis healing through collagen synthesis because albumin is an essential amino acid in the process of collagen formation. Albumin plays an important role in intestinal healing by facilitating the immune response (6,7). Albumin, which is also classified as an acute phase protein, has been suggested as a potential marker of surgical stress and may serve as a predictor of postoperative complications (5,6).

In contrast to the role of haemoglobin in healing intestinal anastomoses, it is related to perfusion and oxygenation at the anastomotic edge, which is an important factor in anastomotic healing. Some studies have shown that anastomotic leaks are more likely to occur in patients who have preoperative anemia. Anemia was found to be a modifiable risk factor for anastomotic leaks. In a recent systematic review (47 cohort studies and two RCTs), higher intraoperative blood loss and preoperative anemia were associated with an increased risk of anastomotic leak. Large blood loss and anemia cause a decrease in oxygen transport capacity, resulting in tissue

hypoxia that affects the healing of the colorectal anastomosis. Low haemoglobin levels prevent the supply of sufficient oxygen and glucose to meet the metabolic needs of tissues, cells are forced to carry out anaerobic metabolism. Reduced efficiency of ATP production and carbon dioxide release is a consequence of the conversion of pyruvate to lactate. As a result, the ischemic tissue microenvironment is often characterized by increased lactate concentrations and decreased glucose and pyruvate levels. In addition, tissue pH will decrease due to CO<sub>2</sub> buildup. The microenvironment of ischemic tissue has higher levels of lactate and lower levels of glucose and pyruvate. CO<sub>2</sub> accumulation lowers tissue pH. Chronic ischemia causes cell injury and release of phospholipids, which damage cell membranes and produce glycerol and free fatty acids. This process may result in an increased likelihood of anastomotic leakage (5,8-9). This study examined the relationship between albumin and haemoglobin levels with anastomotic leakage after hemicolectomy and anastomosis in colon cancer patients.

## Method

a Cohort study of all the colon cancer patients after hemicolectomy at Soetomo General Hospitals, Surabaya Indonesia in the period between January 2018 and December 2022. Out of 85 cases, the patients developed anastomotic leakage after hemicolectomy (leakage group) and the other patients had no leakage (no-leakage group). Inclusion criteria for all patients who underwent a colon anastomosis for colon cancer between January 2018 and December 2022. The patients with lost follow-up or missing data, pregnancy, and age < 18 years were excluded. Preoperative workup detailed history taking and thorough clinical examination.

*Laboratory:* Albumin and haemoglobin were done for all cases.

*Radiological:* Plain X-ray of chest, C.T. abdomen and pelvis.

*Colonoscopy:* Complete colonoscopy up to beyond the caecum was done in almost all elective patients ± biopsy and Tumor Marker: CEA.

*Preoperative mechanical bowel preparation:* All elective patients received standard mechanical. The day before the operation, the cases got the prophylactic antibiotics. *The main operative techniques:* All patients were performed by qualified surgical teams with standard surgical procedures and techniques.

*Post-operative care:* All cases of albumin and haemoglobin were ordered for all patients daily for the 1st PODs. Anastomotic leakage was suspected in the presence of abnormal findings of vital signs, clinical examination, and laboratory tests, and also the radiologic tools were secured selectively for these patients.

## Data collection and statistical analysis

The interpretation and analysis of the data were performed using SPSS v-26 (IBM, Armonk, NY). When applicable, continuous data were represented as the mean and standard deviation; for categorical data, the median and range were utilized. To compare categorical variables, both Fisher's exact test and Pearson's chi-square test were employed. Univariate analyses (using odds ratios [OR]) with two-tailed 95% confidence intervals (CI) were employed to evaluate the potential relative risks associated with postoperative variables and predictors of anastomotic leakage.

## Result

In this study, the results showed that among 85 patients, 31 patients (36.5%) experienced anastomotic leakage (Table 1).

**TABLE 1** Incidence of leaks in colon cancer patients after hemicolectomy

	Frequency	Percentage (%)
Leakage Anastomosis (-)	54	63.5
Leakage Anastomosis (+)	31	36.5
Total	85	100.0

Leakage of anastomosis rate is high in this study and was influenced by preoperative factors, namely gender. In this study, it was found that men had a higher anastomosis leakage rate than women in 19 patients (61.3%), but no significant relationship was found (p-value 0.097 OR 0.4). Judging from the age factor, patients aged > 50 years had a higher anastomosis leakage rate of 47 patients (55.3%) compared to other age groups, but there was no statistically significant relationship (p-value 0.05). Based on location, there was no significant difference between

right and left colon cancer in the rate of anastomotic leakage. However, it is different in the surgical setting, where in surgery in an emergency setting the anastomotic leak rate was found to be higher and significantly related compared to the elective surgery setting, 17 patients (45.9%) (p-value 0.11). This is because in emergency surgery bowel preparation was not carried out properly. So in patients who did not undergo bowel preparation, the rate of anastomotic leakage was found to be higher in 17 patients (45.9%) (p-value 0.11), as presented in Table 2.

**TABLE 2** Preoperative anastomotic leakage factors

Variables	Anastomotic Leakage		Total	Sign. (p)	OR
	No	Yes			
Gender	Male	23 42.6%	19 61.3%	42 49.4%	0.097 (0.1-1.1)
	Female	31 57.4%	12 38.7%	43 50.6%	
Age	< 35 years old	4 7.4%	8 25.8%	12 14.1%	0.05
	35 - 50 years old	19 35.2%	7 22.6%	26 30.6%	
	> 50 years old	31 57.4%	16 51.6%	47 55.3%	
Location	Right colon	29 53.7%	15 48.4%	44 51.8%	0.63 (0.3-1.9)
	Left Colon	25 46.3%	15 48.4%	40 47.1%	0.85 (0.4-2.6)
Setting Operation	Emergency	20 54.1%	17 45.9%	37 100.0%	0.11 (0.1-1.1)
	Elective	34 70.8%	14 29.2%	48 100.0%	
Bowel Preparation	Bowel Preparation (+)	34 70.8%	14 29.2%	48 100.0%	0.11 (0.1-1.1)
	Bowel Preparation (-)	20 54.1%	17 45.9%	37 100.0%	

A statistically significant correlation was identified between anastomotic leakage and blood transfusions in 19 patients (61.3%); the odds ratio (OR) for this occurrence was 3.4 (1.3-8.6), and the corresponding p-value was 0.007 ( $p = 0.007$ ).

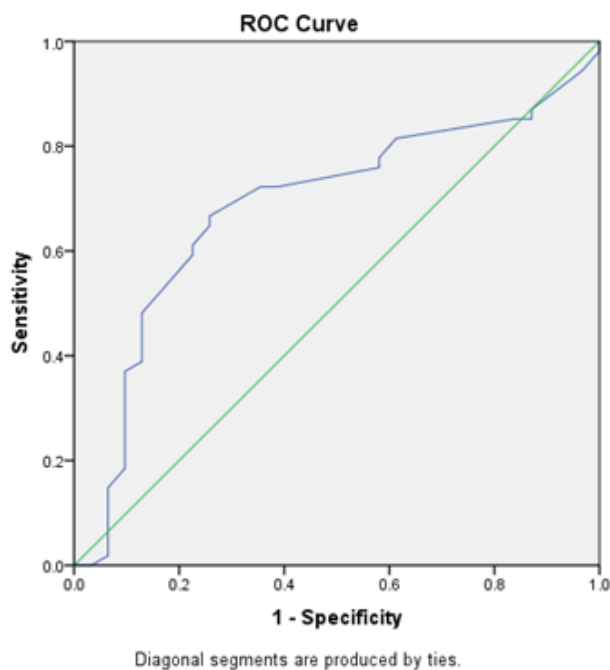
**TABLE 2** Intraoperative anastomotic leakage factors

Variables	Anastomotic Leakage		Total	Sign. (p)	OR
	No	Yes			
Blood Tranfusion	Tranfusion (-)	37 68.5%	12 38.7%	49 57.6%	0.007 (1.3-8.6)
	Tranfusion (+)	17 31.5%	19 61.3%	36 42.4%	

The relationship of haemoglobin and albumin levels to anastomotic leakage in colon cancer patients

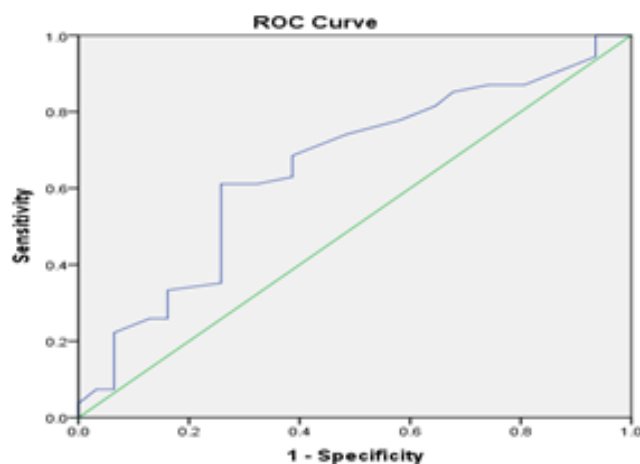
In this study, it was found that the cut-off point was assessed using ROC curve analysis post-operative albumin level  $\leq 2.7$  g/dl with a

cut-off value sensitivity of 66.7% and a sensitivity of 74.2% (Figure 1).



**FIGURE 1** ROC curve albumin level against anastomosis leakage

Meanwhile, haemoglobin levels were assessed using the ROC curve, serum haemoglobin level  $\leq 10.3$  g/dl with cut-off value, and a sensitivity of 63.0%, a sensitivity of 61.3% remained significant in the logistic regression model (Figure 2).



**FIGURE 2** ROC curve haemoglobin level towards anastomosis leakage

In this study, it was found that patients with anemia ( $Hb < 10.3$ ) had a higher post-hemicolectomy anastomosis leakage rate of 19 patients (61.3%) than patients in the group without anemia and a statistically significant relationship was found ( $p$ -value 0.007 OR 3.4). The same thing was also found in post-

operative albumin. Patients with hypo albumin (albumin  $< 2.7$ ) had a post-hemicolectomy anastomosis leakage rate that was 28 patients (90.3%) higher than patients in the normal albumin group and a statistically significant relationship was found ( $p$ -value 0.01 OR 2.3), as indicated in Table 3.

**TABLE 3** Relationship of hemoglobin and albumin to anastomosis leakage

Variables	Anastomotic Leakage		Total	Sign. (p)	OR
	Tidak	Yes			
HB	Normal	37 68.5%	12 38.7%	49 57.6%	0.007 (1.3-8.6)
	Anemia	17 31.5%	19 61.3%	36 42.4%	
Albumin	Normal	11 20.4%	3 9.7%	14 16.5%	0.01 (0.6-93)
	Hipoalbumin	43 79.6%	28 90.3%	71 83.5%	

## Discussion

Post-hemicolectomy leakage of anastomosis is the most avoided complication by surgeons, because of its high morbidity and mortality rates. In this study, it was found that the anastomosis leakage rate was 31%, this result tends to be higher than the results of a previous study conducted in Spain by Ortiz *et al.* (2016) on 7231 surgical patients undergoing anastomosis in Spain, and it was found that the anastomosis leakage rate was 10.0%. In a different study conducted by Gray *et al.* (2021), it was stated that the level of anastomotic leakage could occur in up to 24% of patients undergoing colon anastomosis surgery (5,10). In this study, it was found that men tend to have a higher rate of anastomotic leakage than women, although there was no statistically significant difference, this is explained because anastomotic leakage occurs more often in male patients because men's narrower pelvis makes dissection and anastomosis surgery more frequent. difficult (11). A retrospective analysis of 541 patients with colon and rectal anastomoses found an overall leak rate of 11% in men compared with only 3% in women. In terms of age distribution, it is known that patients with colon cancer who experienced anastomotic leaks were mostly aged > 50 years. These findings are consistent with research by Gray *et al.* (2021) who found that anastomotic leakage was more likely to occur in older adults (5). The results showed that the level of leakage after anastomotic resection surgery

was found to be the same between the right and left colon. These results are different from previous studies where patients who underwent left hemicolectomy with high ligation of the inferior mesenteric artery had a 2.35 increased risk of anastomotic leak. It was determined that 17 patients who underwent anastomotic resection surgery in an emergency (45.9%) had a greater risk of leakage than patients undergoing elective surgery. This difference may be explained by the fact that preoperative preparation- especially bowel preparation- is not performed in the emergency room. This did not occur in elective patients, who received bowel preparation in addition to other preparations such as condition improvement. This is the reason why in emergencies there is a higher rate of anastomotic leakage (12). In other studies, it was found that bowel preparation is very important to prevent anastomotic leakage; this is because, in patients who do not undergo bowel preparation, there is a fecal burden that affects the integrity of the anastomosis. For elective surgery, the goal of bowel preparation is to reduce the number of bacteria in the colon. A random sample of 267 patients participated in a human study in which leak rates varied between those who underwent bowel preparation (2%), namely 4%, and those who did not (4%); however, this difference did not reach statistical significance (p=0.28). The existing literature fails to provide a definitive response regarding the potential correlation between solid fecal colonization with bacteria and

anastomotic leakage. Although inconclusive findings are reported in the literature regarding the efficacy of gut preparations, they are still recommended to reduce the risk of contamination (6).

This study found that patients who receive blood transfusions have a significant risk of anastomotic leakage because blood transfusions can interfere with cellular immune responses, thereby increasing the risk of infection and inhibiting the healing process around the anastomosis. This is following the study of Bharathwaj and Arvind (2004) blood loss during surgery is a major risk factor. Blood loss due to surgery causes tissue ischemia and accelerates healing of the anastomosis, both of which increase the possibility of leakage. In a study that included all cases of colectomy with primary anastomosis, a significant correlation was observed between intraoperative surgical blood loss exceeding 100 mL (OR 1.62; 95% CI: 1.10 to 2.40;  $p = 0.02$ ) and 300 mL (OR 2.22; 95% CI: 1, 32 to 3.76;  $p = 0.003$ ) and the possibility of developing anastomotic leakage ( $p = 0.003$ ) (13).

### **Haemoglobin and post-operative serum albumin levels with anastomotic leakage**

Haemoglobin and Postoperative albumin levels have a significant relationship with the level of anastomotic leakage ( $p$ -value  $<0.05$ ). This occurs because haemoglobin levels below 10.3 g/dL increase the risk of leakage and ischemia by reducing the oxygen transport capacity to the tissue and are also related to perfusion and oxygenation of the anastomosis. This level is very important for anastomosis. Haemoglobin is related to perfusion and oxygenation at the edge of the anastomosis, which is important for anastomosis healing (8). Blood loss can cause ischemia of the anastomosis, which can hinder healing of the anastomosis. The area around the anastomosis becomes more susceptible to infectious pathogens. A less efficient form of

ATP production occurs when pyruvate is converted to lactate, resulting in  $\text{CO}_2$  emissions, the accumulation of  $\text{CO}_2$  will result in a decrease in tissue pH. Prolonged ischemic conditions result in cell damage and subsequent release of phospholipids, which facilitate the formation of glycerol and free fatty acids. This process potentially increases the possibility of anastomotic leakage (5,9). The findings of this investigation are in line with research by Zarnescu, Zarnescu, and Costea (2021) which identified anemia as a risk factor for leaks. In this study, it was found that post-operative serum albumin levels  $<2.3$  had a higher risk of anastomotic leak than the normal group. Albumin, which is also classified as an acute-phase protein, has been suggested as a potential predictor of postoperative complications and an indicator of surgical stress (5,6). Hypoalbuminemia has also been proposed as a risk factor for anastomotic leak during colon resection (5). Albumin impacts anastomotic healing through its ability to synthesize collagen. In addition, it reduces host immunocompetence and increases their susceptibility to anastomotic leakage (7,9). Morse *et al.* also showed a significant relationship between leakage and albumin. Patients with low serum albumin ( $\leq 20$  mg/dl) were found to have a 5.8 times higher risk of anastomotic leak compared with other groups ( $p=0.001$ ) (7,9).

### **Conclusion**

Albumin serum below 2.7g/dl and haemoglobin level below 10.3 g/dl, respectively, are regarded as host-related predictive markers for anastomotic leakage in colon cancer patients undergoing large bowel resections and anastomosis.

### **Acknowledgements**

This work was supported by the Department of Surgery, Dr Soetomo General Hospital, Indonesia.

## Funding

None.

## Authors' Contributions

The study's design and methodology were developed by Desak GA Suprabawati, who also carried out formal research, analysis and wrote the initial draught of the paper, edited the manuscript, curated the data, supplied resources, and oversaw project administration, in addition to validating and supervising the study.

## Conflict of Interest

The authors have no conflict of interest to declare

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**How to cite this article:** Edwin Danardono, Nazila Hana, Sahudi, Hemoglobin level and albumin as a predictive factors for anastomotic leakage following after hemicolectomy: A prospective study for colon cancer. *Journal of Medicinal and Pharmaceutical Chemistry Research*, 2024, 6(9), 1460-1468. **Link:** [https://jmpcr.samipubco.com/article\\_194931.html](https://jmpcr.samipubco.com/article_194931.html)