Original Article

JCMCTA 2025 ; 36 (2) : 35-40
DOI: https://doi.org/10.3329/jcmcta.v36i2.86930

Association between Perioperative Hypoalbuminemia and Anastomotic Leakage in Esophageal Carcinoma Patients Undergoing Esophageal Resection

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Abstract

Background: Anastomotic Leakage (AL) is a serious complication after esophagectomy, increasing morbidity, hospital stay, and mortality. Hypoalbuminemia may predict AL, but its early postoperative role is unclear. To assess the association between early postoperative serum albumin and AL in esophageal cancer patients underwent esophagectomy.

Materials and methods: In this prospective study, 84 patients with confirmed esophageal carcinoma underwent curative esophagectomy. Serum albumin was measured on postoperative day one. Patients were monitored for AL and other complications. Chi-square, t-test, and multivariate logistic regression were used to identify predictors of AL.

Results: Mean age was 55.8 ± 9.1 years, 78.6% were male. AL occurred in 20.2% (17/84). Hypoalbuminemia (<3.5 g/dL) on day one was strongly associated with AL ($p < 0.001$). Among patients with albumin <2.5 g/dL, 69.2% developed leakage, no AL occurred in patients with albumin ≥ 3.5 g/dL. Hypoalbuminemia remained an independent predictor (Adjusted OR: 10.94, 95% CI: 3.12–38.36, $p < 0.001$). AL patients had longer hospital stays (33.2 ± 11.9 vs. 15.1 ± 7.9 days; $p < 0.001$).

Conclusion: Early postoperative hypoalbuminemia is strongly linked to AL after esophagectomy. Serum albumin on day one may serve as an early biomarker to guide risk stratification and postoperative care.

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Submitted on : 31.08.2025
Accepted on : 16.11.2025

Key words: Anastomotic leakage; Esophageal carcinoma; Esophagectomy; Hypoalbuminemia; Postoperative complication; Risk prediction; Serum albumin.

Introduction

Esophageal Cancer (EC) is a highly aggressive malignancy with a rising global burden, ranking as the seventh most common cancer and the sixth leading cause of cancer-related mortality worldwide.[1,2] According to GLOBOCAN 2020 data, there were over 604,000 new cases and more than 544,000 deaths attributed to EC, with the highest prevalence observed in Eastern Asia, Southern and Eastern Africa and parts of South Asia, which bears a significant share of the global incidence.[3] Esophagectomy, which is frequently performed alongside lymphadenectomy to ensure comprehensive removal of potentially affected lymph nodes, continues to be the primary and most effective curative treatment option for patients diagnosed with resectable esophageal carcinoma.[4] Despite advances in surgical techniques and perioperative care, Anastomotic Leakage (AL) continues to be one of the most feared postoperative complications, with an incidence ranging from 5% to 20%, depending on surgical approach, tumor location and comorbidities.[5] AL is associated with significantly increased morbidity, prolonged hospital stays, higher rates of reoperation, and has been shown to cause up to a fivefold increase in postoperative mortality, underscoring the critical importance of early risk identification and timely intervention.[6] Among various predictive factors, nutritional status-particularly serum albumin levels-has garnered increasing attention, as hypoalbuminemia, commonly defined as serum albumin below 3.5 g/dL, serves as an important marker reflecting both poor nutritional reserves and underlying systemic inflammation.[7] Hypoalbuminemia is believed to impair collagen synthesis, reduce tissue oxygenation and

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compromise immune function, all of which are essential physiological processes critical for effective anastomotic healing and overall surgical recovery.[8-10] A growing body of evidence suggests that perioperative hypoalbuminemia, both preoperative and early postoperative, may significantly increase the risk of AL in gastrointestinal surgery, including esophagectomy.[11] Low preoperative albumin levels are independently associated with a two- to threefold increased risk of AL.[12] However, while hypoalbuminemia has been widely studied in colorectal and gastric surgery, literature focusing specifically on its impact in esophageal resection for carcinoma remains sparse and often limited by retrospective designs or small cohorts.[13] Furthermore, fluctuations in serum albumin during the perioperative period-affected by surgical stress, fluid shifts, and systemic inflammation-may also play a critical role, yet this dynamic component is frequently overlooked.[14] As such, understanding the relationship between perioperative hypoalbuminemia and AL in esophageal cancer patients may not only provide a reliable prognostic marker but also offer a modifiable risk factor.[14] Optimizing nutritional status through prehabilitation, early enteral feeding, or albumin supplementation may serve as valuable strategies to reduce postoperative complications.[15] This prospective study aims to investigate the association between perioperative hypoalbuminemia and anastomotic leakage in esophageal cancer surgery to guide evidence-based nutritional interventions and improve postoperative outcomes.

Materials and materials

This cross-sectional analytical study was conducted in the Department of Thoracic Surgery at the National Institute of Diseases of the Chest and Hospital (NIDCH) Dhaka, Bangladesh, from January 2022 to June 2023. The Institutional Ethics Committee of NIDCH approved the protocol and all procedures adhered to the Declaration of Helsinki. Informed written consent was obtained from all participants.

A total of 84 adult patients with histologically confirmed esophageal carcinoma underwent elective Ivor Lewis or Sweet's esophagectomy under general anesthesia were enrolled using convenience sampling. Patients with hepatic, renal, heart, or respiratory failure, and inoperable cases were excluded. Demographic, clinical, tumor-related and perioperative data were collected prospectively using a structured, prevalidated form, including age, sex, BMI, comorbidities, tumor location, histopathology, operative duration, ICU stay, estimated blood loss, and total postoperative hospital stay. Serum albumin was measured on the first postoperative day and categorized as <2.5, 2.5–2.9, 3.0–3.4 and ≥3.5 g/dL. The primary outcome was anastomotic leakage, diagnosed clinically or radiologically, secondary outcomes included other postoperative complications and length of hospital stay. Statistical analysis was performed using SPSS v 26. Categorical variables were expressed as frequencies and percentages, continuous variables as mean ± SD or median (IQR). Associations between serum albumin and leakage were evaluated with chi-square, and hospital stay compared using independent t-test. Multivariate logistic regression identified independent predictors of leakage, including variables with $p < 0.2$ in univariate analysis. Adjusted odds ratios and 95% confidence intervals were calculated, with $p < 0.05$ considered significant.

Results

Table I Demographic and clinical characteristics of the study population (n = 84)

Variable	Frequency (n)	Percentage (%)
Age (Years)		
31-50	21	25.00
51-70	61	72.62
71-90	2	2.38
Mean ± SD	55.83 ± 9.102	
Gender		
Male	66	78.57
Female	18	21.43
BMI (kg/m²)		
Mean ± SD	22.8 ± 3.2	
Comorbidity		
Hypertension	32	38.10
Diabetes Mellitus	22	26.19
COPD	10	11.90
Tumor Location		
Lower third	55	65.48
Middle third	22	26.19
Upper third	7	8.33
Histopathology		
Squamous Cell Carcinoma	62	73.81
Adenocarcinoma	22	26.19
Surgical Procedure		
Ivor Lewis Esophagectomy	68	80.95
Sweet's Procedure	16	19.05

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Table II Surgical outcome

Characteristic	Mean ± SD
Duration of Surgery (Hours)	5.1 ± 1.0
ICU Stay (Days)	3.2 ± 1.1
Estimated Blood Loss (mL)	310 ± 130
Postoperative Hospital Stay (Days)	17.4 ± 6.5

Table III Distribution of serum albumin levels on postoperative day 1 in the study population

Serum Albumin Level (g/dL)	Frequency (n)	Percentage (%)
<2.5	13	15.48
2.5–2.9	19	22.62
3.0–3.4	29	34.52
≥3.5	23	27.38

Table IV Postoperative complications observed in the study population

Complication	Frequency (n)	Percentage (%)
Anastomotic Leakage	17	20.24
Pneumonia	10	11.90
Wound Infection	8	9.52
Respiratory Failure	7	8.33
Pleural Effusion/Empyema	4	4.76
Sepsis	4	4.76
Reoperation	3	3.57
30-day Mortality	1	1.19

Table V Association between postoperative day 1 albumin levels and anastomotic leak in the study population

Albumin Level (g/dL)	Leak (n, %)	No Leak (n, %)	Total (n)	p-value
<2.5	9 (69.23)	4 (30.77)	13	
2.5–2.9	5 (26.32)	14 (73.68)	19	
3.0–3.4	3 (10.34)	26 (89.66)	29	<0.001
≥3.5	0 (0.00)	23 (100.00)	23	
Total	17 (20.24)	67 (79.76)	84	

Table VI Length of hospital stay according to anastomotic leak status in the study population

Leak Status	Mean (days) ± SD	Median (IQR)	p-value
Leak Present (n=17)	33.2 ± 11.9	32 (26–43)	<0.001
No Leak (n=67)	15.1 ± 7.9	13 (10–18)	

Table VII Multivariate logistic regression identifying predictors of anastomotic leakage in the study population

Predictor	Adjusted OR (95% CI)	p-value
Hypoalbuminemia (<3.5 g/dL)	10.94 (3.12–38.36)	<0.001
Operative Duration >5 hours	1.93 (0.68–5.51)	0.221
Age ≥ 65 years	1.38 (0.43–4.46)	0.593
Male Sex	0.84 (0.24–2.95)	0.783

Discussion

Esophagectomy is central to curative treatment of esophageal carcinoma but carries high postoperative morbidity, with Anastomotic Leakage (AL) being a major complication.[16] AL rates range from 10% to 25%, influenced by tumor factors, surgical technique, and perioperative care,[17] Recently, serum albumin and other biochemical markers have gained attention for their prognostic value.[17] This study demonstrates a significant link between early postoperative hypoalbuminemia and AL after esophageal resection, supporting serum albumin as a predictive marker of complications. Participants had a mean age of 55.8 ± 9.1 years, with 78.6% male. Most tumors were in the lower third of the esophagus (65.5%) and squamous cell carcinoma was predominant (73.8%) reflecting global trends, especially in Asian populations.[18,19] In this study, AL occurred in 20.2% of cases, within the reported global range of 10–25% after esophagectomy. Rutegård et al. reported a similar rate of 21.2% in 1,174 Swedish patients, while Kassis et al. found a 13.3% incidence in the Society of Thoracic Surgeons database, identifying AL as the most common postoperative complication.[20,5] Our findings align with large cohorts, supporting their external validity. Postoperative day 1 hypoalbuminemia was strongly associated with AL: nearly 70% of patients with albumin <2.5 g/dL developed leakage, while no AL occurred in those with ≥3.5 g/dL. Multivariate analysis showed an adjusted OR of 10.94 for albumin <3.5 g/dL. International studies, including Zhuge et al., similarly reported higher AL incidence in patients with albumin <3.5 g/dL after esophagectomy, with a multivariate OR of 1.84.[7] Shimura et al. reported that lower albumin on postoperative days 1 and 3 in colorectal cancer patients was strongly associated with AL, with an adjusted OR of 7.53.[21] A prospective study in Tanzania found that a ≥10 g/L drop in albumin on day 1 increased overall postoperative complications, including AL, threefold.[22] Huang et al. showed that a postoperative prealbumin <131 mg/L independently predicted AL after esophagectomy, with 83% sensitivity and 72% specificity.[23] These findings support the present study's observation that postoperative day 1 hypoalbuminemia is a

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strong independent predictor of AL after esophageal resection. While preoperative albumin reflects nutritional reserve, postoperative hypoalbuminemia likely reflects surgical stress and acute inflammation. Labgaa et al. found early postoperative markers, including hypoalbuminemia, better predicted AL than preoperative nutritional indices, with a • Alb cut-off of 11 g/L on day 1 linked to higher risk and confirmed as an independent predictor of major complications.[24] In contrast, this study found no significant association between AL and age ≥65, male sex, or prolonged operative time, although van Workum et al. reported operative time >6 hours and age ≥70 as independent AL risk factors.[25] Moreover, our data also revealed that patients with AL had a significantly longer hospital stay (mean 33.2 days) compared to those without (Mean 15.1 days), mirroring the findings of a retrospective analysis by Booka et al., which demonstrated that AL increased hospital stay by an average of 18 days.[26] In contrast to our findings, a study by Wang et al. did not find a statistically significant relationship between postoperative albumin levels and AL, instead attributing risk predominantly to neoadjuvant therapy and cervical anastomotic sites.[11] Furthermore, the relationship between systemic inflammation and albumin levels offers a plausible mechanistic explanation. As documented by Soeters et al. surgical trauma triggers a cytokine-mediated acute phase response that reduces hepatic albumin synthesis and increases capillary permeability, leading to hypoalbuminemia.[27] Therefore, serum albumin on postoperative day 1 may serve as an indirect marker of the inflammatory load, with lower levels signaling impaired healing and increased risk of dehiscence.[28] Recent interest has also focused on dynamic albumin changes postoperatively. A study by Labgaa et al. observed that a steep decline in albumin levels within the first 48 hours post-esophagectomy was a more accurate predictor of AL than absolute preoperative values.[9] While our study did not measure albumin trends serially, our results nonetheless corroborate the prognostic relevance of early postoperative hypoalbuminemia as a static measure.[24]

Limitation

This study has limitations. It was single-center, limiting generalizability. Only postoperative day 1 serum albumin was measured, without preoperative or dynamic trends. Inflammatory markers like C-reactive protein were not analyzed. The small sample size may reduce statistical power, especially for rare complications.

Conclusion

This study shows that early postoperative hypoalbuminemia is an independent predictor of Anastomotic Leakage (AL) after esophagectomy for esophageal carcinoma. Patients with albumin <3.5 g/dL on day one had higher AL rates and longer hospital stays, while no leakage occurred in those with ≥3.5 g/dL. Measuring serum albumin on the first postoperative day can serve as a simple, reliable biomarker to identify high-risk patients, enabling early interventions and optimized postoperative care to reduce AL- related morbidity.

Recommendations

Serum albumin should be measured on postoperative day one in esophagectomy patients. Those with hypoalbuminemia (<3.5• g/dL) require close monitoring for anastomotic leakage and targeted nutritional support. Early intervention may reduce complications, shorten hospital stay, and improve outcomes. Multicenter studies are needed to confirm albumin as a reliable early predictive marker.

Acknowledgement

We are deeply grateful to our parents for their unwavering love, encouragement, and support during this study. We also extend our appreciation to all the patients who took part, as well as the staff of the Department of Thoracic Surgery at the National Institute of Diseases of the Chest and Hospital, Dhaka, for their help with patient care and data collection.

Contribution of authors

MKH-Acquisition of data, data analysis, interpretation of data, drafting, critical revision & final approval.

SB-Conception, design, data analysis, interpretation of data, critical revision & final approval.

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YK-Acquisition of data, data analysis, drafting & final approval.

MAR-Acquisition of data, interpretation of data, critical revision

MRC-Acquisition of data, interpretation of data, critical revision & final approval.

Disclosure

All the authors declared no conflicts of interest.

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