Medicine

Predictive value of postoperative serum prealbumin levels for early detection of anastomotic leak after esophagectomy
A retrospective study

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Abstract

The impact of serum prealbumin in patients with esophageal carcinoma after undergoing esophagectomy remains unclear, we speculated that serum prealbumin is associated with anastomotic leak (AL) after surgery, low serum prealbumin level may lead to AL. The aim of the study was to evaluate the relationship between serum prealbumin levels and AL after esophagectomy, to explore the value of serum prealbumin as an early predictor of AL after esophagectomy.

Between January 2014 and December 2018, 255 patients were enrolled in this study, their basic characteristics and perioperative serum prealbumin levels were retrospectively analyzed. Statistical analysis by t test, nonparametric test and logistic regression were used to analyze data for patients with and without AL. Based on a receiver operator characteristic curve, a cut-off value for serum prealbumin levels as a predictor of AL was determined.

Among the 255 patients, 18 patients were diagnosed with AL. The overall AL rate was 7.0% (18/255) including 12 cases of intrathoracic AL and 6 cases of cervical AL. By univariate analysis, we identified postoperative serum prealbumin level as a risk factor for AL ($P < .001$). Multivariate analysis also demonstrated postoperative serum prealbumin level ($P = .028$) to be an independent risk factor for AL. The best cut-off value of postoperative serum prealbumin level was 131 mg/L for predicting AL, with 83.3% sensitivity and 72.2% specificity.

Postoperative serum prealbumin level was significantly associated with AL. it may help the early prediction of postoperative AL.

Abbreviations: AL = anastomotic leak, AUC = area under the curve, BMI = body mass index, ROC = receiver operator characteristic.

Keywords: anastomotic leak, esophageal cancer, esophagectomy, serum prealbumin

1. Introduction

Esophageal cancer is the seventh most common cancer and the sixth cancer related death worldwide.[1,2] It is also the fourth most common cause of death in China.[3] Surgery remains the main treatment of esophageal cancer. Anastomotic leak (AL) is a common and serious complication after esophagectomy with the incidence varied between 5% and 20%, The mortality rate for patients suffering this threatening clinical situation can reach 60%.[1,4–6] Early prediction and timely management are crucial to prevent anastomotic leak.

In previous studies, many perioperative risk factors were associated with anastomotic leak including obesity, hypertension, diabetes, operation time, intraoperative blood loss, and amylase concentration.[7–13] But the predictive sensitivity and specificity is not ideal. Serum prealbumin is a nutritional indicator which can reflect the recent nutritional status of a patient. However, the relationship between serum prealbumin and postoperative anastomotic leak in esophageal cancer remains unclear, and few studies have reported the details of that. Considering the significance of the serum prealbumin, we hypothesized that serum prealbumin level is related to the AL

after esophagectomy for esophageal cancer, low serum prealbumin level may predict the poor growth of anastomotic site and anastomotic leak postopratively.

In the present study, we aimed to investigate the relationship between serum prealbumin levels and postoperative AL after esophagectomy, as well as to determine whether serum prealbumin levels could be used as an early predictive factor for AL after esophageal cancer surgery.

2. Methods

2.1. Patients

We retrospectively reviewed the medical records of patients who underwent esophagectomy for esophageal cancer at the Department of Thoracic Surgery in the First Affiliated Hospital of Chongqing Medical University between January 2014 and December 2018. The clinical data for eligible patients were retrospectively collected and analyzed. The inclusion criteria included clear pathological diagnosis and radical surgery, as well as serum prealbumin levels were assessed during the perioperative period. Exclusion criteria were:

1. neoadjuvant chemoradiotherapy patients;
2. radioactive seed implantation patients;
3. multiple primary tumor patients;
4. multiple metastases and locally advanced patients;
5. hypertension, diabetes, liver patients with cirrhosis, nephritis or severe cardiopulmonary dysfunction;
6. patients with anemia and hypoproteinemia; and
7. patients with severe infection, massive pleural effusion, empyema, and death after surgery.

This was a nonrandomized and retrospective study. The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

2.2. Diagnosis of anastomotic leak

The diagnosis criteria include clinical manifestation and examination. Clinical manifestation:

1. cervical AL: accompanied or not by fever, increased infection index, redness and swelling of neck incision skin, fluid accumulation below the incision accompanied by rancid smell, purulent secretion overflow or saliva, gastric juice overflow when the incision suture was removed;
2. intrathoracic AL: high fever, chest and back pain, shortness of breath, dyspnea, increased heart rate, chest tightness and palpitation, and even systemic toxic symptoms, turbid fluid, gastric juice, and bile fluid found in the thoracic duct.

Examinations: confirmed by oral methylene blue injection, upper gastrointestinal angiography, gastroscopy, and computed tomography.[14]

2.3. Detection of serum prealbumin

We looked up the illness record of hospitalized esophageal cancer. All patients who met the criteria were included and serum prealbumin levels during the perioperative period were recorded. (Fasting venous blood was taken between 6–7 AM within a week before surgery and within 2 weeks after surgery.

All laboratory values were determined using routine automated analyzers at the Departments of Clinical Chemistry in laboratory department.)

2.4. Data collection

The following clinical characteristics of included patients were summarized; demographic information, drinking history, smoking history, operation type, operation time, and intraoperative blood loss. In addition to serum prealbumin, serum albumin and hemoglobin were measured for each patient.

2.5. Statistical analysis

Statistical analysis was performed using SPSS 23.0 software (SPSS, Inc, Chicago, IL). Data were assessed for normality and presented as mean and standard deviation or median and interquartile range. T-test, nonparametric test, and logistic regression were used to compare characteristics of patients with AL and those without. A receiver operator characteristic (ROC) curve was used to identify the best cut-off value for serum prealbumin as a predictive factor for AL. $P < .05$ was considered statistically significant. The main steps of methods section are summarized in Figure 1.

3. Results

3.1. Comparison of patient characteristics and surgical approach

Of the 255 patients included in the study, there were 212 males and 43 females. Of these patients 141 underwent sweet surgery, 9 underwent Ivor-Lewis surgery, 14 underwent McKeown surgery, and 91 underwent Minimally invasive esophagectomy surgery. There were 18 cases of anastomotic leak after operation, the incidence rate was 7.0% (18/255), including 6 cases of neck AL and 12 cases of intrathoracic AL. In order to analyze risk factors for AL, patients were divided into 2 groups based on whether they suffered anastomotic leak. As shown in Table 1, there was no difference in gender, age, smoking history, or drinking history between the groups. No statistical difference was observed in operation time, operation type, or intraoperative blood loss. There was no significant difference in serum albumin, hemoglobin, or preoperative serum prealbumin between the AL and non-AL group.

3.2. The relationship between serum prealbumin and risk of AL

To determine the risk factors for AL and further evaluate the relationship between perioperative serum prealbumin levels and AL, we performed univariate analysis and Multivariate analysis. As described in Table 2, univariate analysis found no statistically significant difference in gender, age, body mass index (BMI), smoking history, drinking history, preoperative hemoglobin, preoperative serum albumin, preoperative serum prealbumin, operation time, intraoperative blood loss, or operation type ($P > .05$). In contrast, postoperative serum prealbumin correlated with postoperative AL ($P < .001$). The results of multivariate analysis are shown in Table 3. Postoperative serum prealbumin was an independent risk factor for AL (95% CI: 0.948–0.999; $P = .028$).
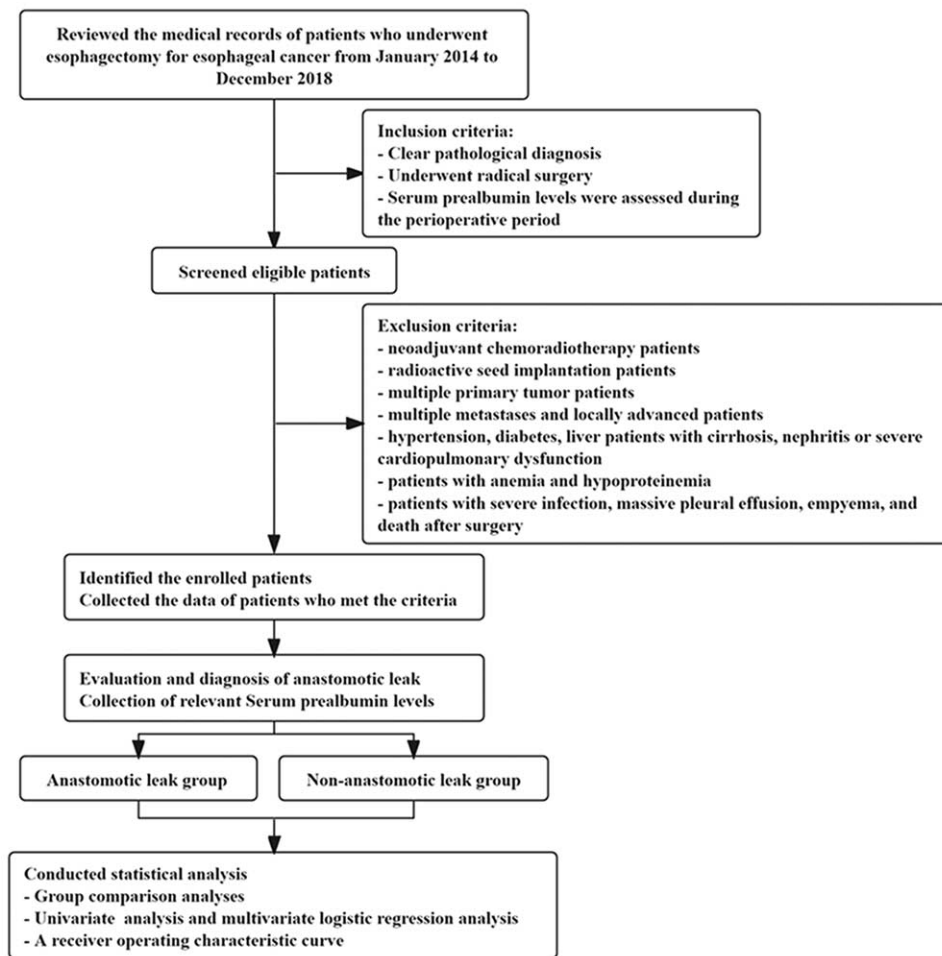
Figure 1. The flow chart of depicting main steps.

3.3. Confirmation of serum prealbumin cut-off value as the predictor for AL

The serum prealbumin level after operation are analyzed by ROC curve. As shown in Figure 2, The area under the curve (AUC) and the optimal cutoff was calculated. Results showed the best cut-off value to be 131 mg/L, with a sensitivity and a specificity of 83.3% and 72.2%, respectively. The AUC area was 0.805 ($P < .001$). When serum prealbumin levels were below 131 mg/L, AL would be predicted.

4. Discussion

Our study indicated that patients with low postoperative serum prealbumin levels tend to suffer from AL after esophagectomy. Postoperative serum prealbumin is an independent predictor of AL. AL is the most serious postoperative complications of esophageal cancer,[4,5] this fatal complication still affects the prognosis of esophageal cancer.[15,16] In clinical practice, AL needs to be predicted in advance for surgeon so special precaution will be took for the high risk patients. Factors influencing AL postoperatively have always been a research focus, especially those related to infection and malnutrition. Some studies have shown that poor nutrition status is a potentially serious condition which is often simultaneous with cancer.[17] Patients with esophageal cancer often suffer from

malnutrition due to decreased nutrient intake and increased tumor metabolism, with 80% of esophageal cancer patients exhibits protein-malnutrition.[18] Malnutrition directly impacts the incidence of AL in postoperative patients with esophageal cancer. To some extent, patients with esophageal cancer have lowered immunity, with trauma caused by surgery and postoperative stress contributing to insufficient nutrition. So, the body is in a state of negative nitrogen balance with poor tissue growth and healing capacity. Furthermore, the operation area and the anastomotic site are inflamed and edematous. Edema of the intestinal mucosa results in a nutrient absorption disorder, which further aggravates malnutrition. Therefore, early identification of malnutrition and early nutritional support promote anastomotic healing, and avoiding AL.

There are a variety of clinical methods by which to evaluate malnutrition in cancer patients, ranging from clinical symptoms and signs to anthropometric and biochemical tests. However, evaluation technologies are highly variable and lack reliable and short-term screening methods. Studies have shown serum prealbumin levels effectively reflect the short-term nutritional status of cancer patients.[19,20] Prealbumin is a protein status indicator. Its half-life is shorter than albumin, about 2 days, with storage within the body much smaller than albumin. Changes in prealbumin are more sensitive than albumin with measured values and storage value synchronous. Serum prealbumin

Table 1

Comparison between patients who leaked and patients who did not: patient characteristics.

	Anastomotic leakage	None anastomotic leakage	P value
Sex			.324
Female	1	42	
Male	17	195	
Age			.599
<60	7	73	
≥60	11	164	
BMI			
<20	2	55	.378
≥20	16	182	
Smoking history			.288
Yes	15	164	
No	3	73	
Drinking history			.07
Yes	15	139	
No	3	98	
Preoperative Hemoglobin (g/L)	142.78 ± 14.73	138.7 ± 13.72	.227[*]
Preoperative serum albumin (g/L)	43.5 (42–47.75)	43.5 (40–46)	.247[**]
Preoperative serum Prealbumin (mg/L)	233.33 ± 46.33	239.23 ± 46.99	.595[*]
Postoperative serum Prealbumin (mg/L)	113.56 ± 32.27	160.44 ± 44.73	<.001[**]
Minimum serum Prealbumin (mg/L)	95 (81.5–115.75)	133 (107–170)	<.001[***]
Operation type			
Sweet	10	131	.483
Ivor-Lewis	2	7	
McKeown	1	13	
MIE	5	86	
Operation time (min)	311 (246.25–392.5)	310 (240–370)	.216[**]
Blood loss (ml)	200 (200–375)	200 (100–250)	.063[**]

BMI = body mass index, MIE = minimally invasive esophagectomy.
[*] Statistically significant (P < .05).
[*] Normal distribution, T-test, Data are presented as mean ± standard deviation.
[**] Nonnormal distribution, rank sum test, Data are presented as median and interquartile range.

Table 2

Univariate analysis of risk factors for anastomotic leakage.

Variables	HR (95% CI)	P value
Sex		.213
Female	1	
Male	0.273 (0.035–2.109)	
Age		.478
<60	1	
≥60	0.699 (0.261–1.877)	
BMI		.249
<20	1	
≥20	0.414 (0.092–1.855)	
Smoking history		.217
No	1	
Yes	0.449 (0.126–1.600)	
Drinking history		.284
No	1	
Yes	0.284 (0.08–1.006)	
Preoperative hemoglobin (g/L)	1.022 (0.987–1.058)	.227
Preoperative serum albumin (g/L)	1.098 (0.971–1.242)	.134
Preoperative serum Prealbumin (mg/L)	1.003 (0.993–1.013)	.594
Postoperative serum Prealbumin (mg/L)	0.970 (0.955–0.985)	<.001[*]
Minimum serum Prealbumin (mg/L)	0.971 (0.956–0.987)	<.001[*]
Operation type		
Sweet	1	.388
Ivor-Lewis	0.756 (0.082–6.993)	.805
McKeown	3.714 (0.284–48.545)	.317
MIE	0.992 (0.118–8.377)	.994
Operation time (min)	1.004 (0.999–1.009)	.108
Blood loss (ml)	1.002 (1.001–1.005)	.108

BMI = body mass index, MIE = minimally invasive esophagectomy.
[*] Statistically significant (P < .05).

reflects the recent nutritional status of a patient better than albumin and can identify malnutrition at an early stage.[21–23] Thus a determination of serum prealbumin level is an effective and objective method by which to assess the nutritional status of patients and as well monitor the effect of nutritional support.[19,20]

In recent years, some studies have shown that serum prealbumin is associated with prognosis of disease and postoperative complications, including the therapeutic of tuberculosis patients, adverse cardiac events in hospital, surgical site infection and postoperative wound complications.[24–28] But the relationship between serum prealbumin and AL is not clear. Moreover, there are no definitive predictors for AL. In this study, the relationship between serum prealbumin levels and AL after esophagectomy was explored as a means by which to predict AL. Results showed no significant difference in age (P = .324), gender (P = .599), body mass index (BMI; P = .378), smoking history

(P = .288), and drinking history (P = .07) between AL and non-AL patients. Univariate analysis showed that postoperative serum prealbumin levels were significantly associated with postoperative AL (P < .001). Preoperative serum prealbumin levels were not a risk factor for AL (P = .594). Multivariate regression analysis showed that postoperative serum prealbumin levels were independent risk factors for AL (95% CI: 0.948–0.999; P = .028). We found there was no statistically significant risk factor for age (P = .478), gender (P = .213), BMI (P = .249), smoking history (P = .217), drinking history (P = .284), hemoglobin (P = .227), serum albumin (P = .134), operation time (P = .108), intraoperative blood loss (P = .108), or operation type (P = .388, P = .994, P = .805, P = .317). From clinical data, operation time, anemia, hypoxia, and the anastomotic site have been shown to impact postoperative AL. For patients with a long operation time and large amounts of bleeding, there is a general effect of surgical trauma. Further, in response to stress, inflammatory mediators are released, which can lead to anastomotic stoma ischemia, necrosis, and leakage. Further, cervical anastomosis is more likely to cause AL than intrathoracic anastomosis. During cervical anastomosis, the tubular stomach needs to be pulled from the abdominal cavity through the thoracic cavity. Compared with the intrathoracic tubular stomach, tension is increased and blood supply is decreased, increasing the possibility for AL.[3,29] It is worth noting that this is a single-center retrospective study, we speculate that it may be caused by the small sample size.

In this study, the results showed that postoperative serum prealbumin levels were significantly lower than preoperative level. especially in the AL group, serum prealbumin was

Table 3

Multivariate logistic regression analysis of risk factors for anastomotic leakage.

Variables	HR (95% CI)	P value
Sex		.676
Female	1	
Male	0.536 (0.029–9.998)	
Age		.295
<60	1	
≥60	1.898 (0.573–6.293)	
BMI		.236
<20	1	
≥20	0.367 (0.070–1.928)	
Smoking history		.879
No	1	
Yes	1.152 (0.185–7.185)	
Drinking history		.212
No	1	
Yes	0.364 (0.074–1.783)	
Preoperative hemoglobin (g/L)	0.988 (0.940–1.040)	.650
Preoperative serum albumin (g/L)	1.102 (0.926–1.312)	.273
Preoperative serum Prealbumin (mg/L)	1.008 (0.994–1.023)	.272
Postoperative serum Prealbumin (mg/L)	0.973 (0.948–0.999)	.028*
Minimum serum prealbumin (mg/L)	0.990 (0.962–1.018)	.465
Operation type		
Sweet	1	.946
Ivor-Lewis	0.491 (0.038–6.392)	.587
McKeown	0.686 (0.027–17.430)	.819
MIE	0.720 (0.062–8.351)	.793
Operation time (min)	1.002 (0.995–1.010)	.598
Blood loss (ml)	1.001 (0.996–1.004)	.907

BMI = body mass index, MIE = minimally invasive esophagectomy.
* Statistically significant (P < .05).

extremely low compared to the level before operation. According to the ROC curve, the postoperative serum prealbumin concentration cut-off value was 131 mg/L, with 83.3% sensitivity, and 72.2% specificity. The AUC was 0.833 (P < .001). It showed that low postoperative serum prealbumin level was likely to lead to AL, which is consistent with the results
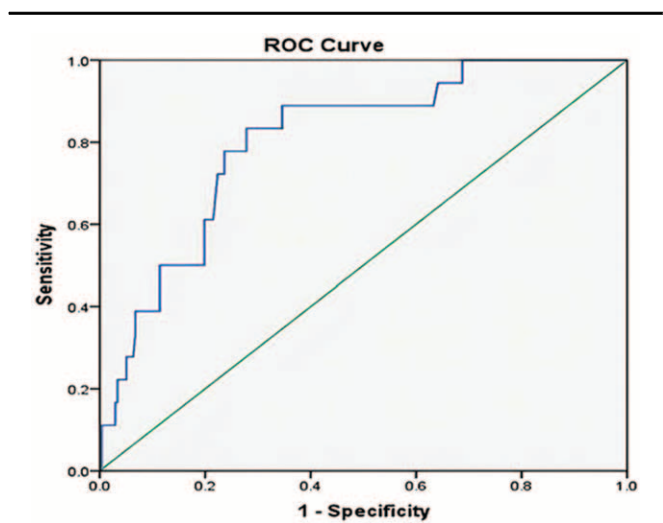

Figure 2. Receiver operating characteristic (ROC) curve for the association of postoperative serum prealbumin and anastomotic leak. Area under the curve was 0.805, and the cut-off value was determined as 131 mg/L according to the ROC curve.

of other studies.[30] Multivariate analysis showed serum prealbumin levels after surgery to be an independent risk factor for AL. Therefore, postoperative serum prealbumin levels could be used as an early predictive factor of AL after esophagectomy. Routine monitoring of serum prealbumin levels after surgery and dynamic follow-up will help determine the degree of malnutrition and give an early warning of AL. If the clinical test value is lower than 131 mg/L, AL may occur. Therefore, a reasonable, appropriate, and comprehensive nutritional treatment schemes should be implemented to improve protein-malnutrition status, and to facilitate the growth and healing of anastomotic stoma.

There are several possible limitations of this study. First, this was a single-center retrospective study, and the sample size might be small. Second, Serum prealbumin has been described as a negative acute phase reactant, that may be affected by inflammation or infection.[21,31,32] Patients have more or less an inflammatory response after esophagectomy, that potential factors may lead to a decrease in prealbumin levels. Thus, further multi-center prospective studies with large sample are warranted.

5. Conclusion

In summary, the results of this study demonstrated that postoperative serum prealbumin levels can early predict AL after esophagectomy. Low serum prealbumin levels suggest that the risk of AL is significantly increased especially in patients with serum prealbumin level below 131 mg/L. It is important to develop a suitable clinical treatment strategy to reduce the incidence of AL, and to improve the prognosis of patients.

Author contributions

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