Preoperative Albumin-to-Fibrinogen Ratio Predicts Postoperative Pneumonia in Patients with Esophageal Squamous Cell Carcinoma: A Retrospective Study

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Research

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Abstract

Background: Postoperative pneumonia is the most common postoperative complication in patients with esophageal cancer. Prediction of postoperative pneumonia by establishing a preoperative physiological function parameter model can help patients make adequate preoperative preparation, reduce treatment costs, and improve prognosis and quality of life. The purpose of this study was to investigate the relationship between albumin, fibrinogen, albumin-to-fibrinogen ratio (AFR), and other preoperative laboratory tests and postoperative pneumonia in patients with esophageal cancer after esophagectomy.

Methods: Retrospective analysis was performed on 177 consecutive patients who underwent esophagectomy in the Department of Thoracic Surgery, The First Affiliated Hospital of Zhengzhou University from December 2018 to December 2019. Postoperative pneumonia was defined according to the revised Uniform Pneumonia Score (rUPS). Patients were divided into pneumonia and non-pneumonia groups for comparison of baseline data, perioperative indicators, and laboratory examination data. (Receiver operating characteristic) ROC curve analysis was used to evaluate the efficacy, sensitivity and specificity of AFR, and Youden's index was used to calculate the cut-off values of AFR and other laboratory tests data. Univariate and multivariate logistic regression analyses were used to assess the risk factors for postoperative pneumonia.

Results: Of the 177 patients, 32 (18%) developed postoperative pneumonia. The AUC value predicted by AFR using ROC curve analysis was 0.767, 65.6% sensitivity and 83.4% specificity. Multivariate logistic regression analysis showed that albumin ($P=0.013$), creatinine ($P=0.01$), and AFR ($P=0.016$) were independent risk factors for postoperative pneumonia.

Conclusion: Preoperative AFR can effectively predict the occurrence of postoperative pneumonia in patients with esophageal cancer.

Background

Esophageal cancer is a common malignant tumor worldwide, with a wide range of distribution and a high mortality rate, which brings a great burden of life to people around the world (1). In a study on the causes of death of 508,585 cancer patients worldwide in 2018, the incidence of esophageal cancer ranks the seventh in the world, and the mortality ranks the sixth (2). At present, grade R0 surgical resection for early esophageal cancer or neoadjuvant chemoradiotherapy for locally advanced esophageal cancer (3) is still the main treatment method. In recent years, minimally invasive esophagectomy (MIE) has gradually become the mainstream instead of traditional open surgery. A Randomized Controlled Trial (RCT) showed MIE reduced hospital stay, lung infection, and short-term quality of life compared with traditional open surgery (4), meanwhile several studies have shown that the incidence of pulmonary complications after esophagectomy is still between 20% and 40%, which is the most common postoperative complication (5). Postoperative pneumonia, as the most common pulmonary complications, seriously affects the prognosis and the quality of life of patients with esophageal cancer (6). Therefore, the establishment of a

model to predict the possibility of postoperative pneumonia based on preoperative physiological function parameters of patients would be able to help patients make adequate preoperative preparation, reduce treatment costs, improve prognosis and quality of life.

In 2002, T. Nozoe proposed that preoperative nutritional status might predict postoperative complications in patients with esophageal cancer (7). Since then, a variety of nutritional factors, including neutrophils, lymphocytes, C-reactive protein, albumin, fibrinogen and related ratios, even grip strength, have been reported to be independent predictors of postoperative complications and prognosis (8-10, 15). Albumin, as an important biochemical index to evaluate nutritional status, has been shown to be associated with postoperative complications and prognosis in patients with a variety of tumors, including esophageal cancer (11-15). Meanwhile, fibrinogen, as an indicator of blood coagulation, has a relatively short half-life and can be used as an acute response protein to reflect systemic inflammation. Guan proposed that low preoperative fibrinogen level may be a potential risk factor for neurological complications after cardiac surgery (16). Recently, a new indicator, albumin-to-fibrinogen ratio (AFR), was proposed in a study to predict postoperative severe complications in elderly patients with gastric cancer (17). Although AFR has been proven to be associated with the prognosis of esophageal cancer (18), it is still unknown whether AFR can predict the occurrence of postoperative pneumonia in patients with esophageal cancer. Therefore, this study was devoted to exploring the relationship between albumin, fibrinogen, AFR and other preoperative laboratory tests and postoperative pneumonia in patients with esophageal cancer.

Patients And Methods

Patients

A total of 177 consecutive patients who underwent radical esophagectomy in the Department of Thoracic Surgery, The First Affiliated Hospital of Zhengzhou University from December 2018 to December 2019 were included in this study. 2 cases were excluded due to tumor invasion, 11 cases were excluded due to lack of data, and 2 cases were excluded due to simultaneous total gastrectomy. All patients underwent preoperative routine examination and evaluation, including complete blood count, biochemical examination of liver and kidney function, blood coagulation examination, pulmonary function examination, b-ultrasound of liver and gallbladder urinary system, b-ultrasound of the heart, chest and upper abdomen enhanced Computed Tomography (CT), skull CT, bone scan, electrocardiogram, gastroscopy and barium meal examination. If the patient's general condition allowed, neoadjuvant chemotherapy was performed after discussion in the thoracic department. The chemotherapy drug was cisplatin followed by the next drug: paclitaxel, docetaxel and gemcitabine. One day before the operation, department experts and anesthesiologists discussed and assessed the risks of the operation and preliminarily formulated the operation method. All the patients included in this study underwent mixed minimally invasive esophagectomy including laparoscopy, thoracoscopy and open surgery. The recurrent laryngeal nerve and thoracic duct should be protected during mediastinal stage. The reconstruction of digestive tract was performed by replacing esophagus with tubular stomach. The location of the anastomotic site was determined by neck or chest anastomosis depending on the patient's condition and

tumor location. Finally, the anastomotic site was wrapped around with greater omentum or high molecular tissue material to prevent anastomotic leakage (19). Postoperative pathology showed that all the 177 patients in this group had squamous cell carcinoma and negative resection margin (R0 resection). The first day after the operation, the patient was examined by bedside chest radiograph. Complete blood count, electrolyte examination, liver and kidney function tests were performed on the 1st and 3rd day after the operation. Chest CT was scheduled for the third day after surgery.

All patients who underwent surgery for more than 3 hours received antibiotics, and broad-spectrum antibiotics were routinely applied postoperatively. Tracheal sputum was collected from all patients with suspected pulmonary infection for culture, and the treatment regimen was adjusted on day 2 or 3 according to the patient's clinical manifestations and sputum culture results. All patients received oxygen inhalation, sputum - reducing drug inhalation, injection or analgesics, and intravenous infusion within a few days after surgery. When phlegm is sticky and difficult to cough out, affecting respiration, the patient will be made bedside or tracheobronchial mirror room sputum suction treatment. The retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent was obtained from all eligible patients

Definition of postoperative pneumonia

In this study, the revised Uniform Pneumonia Score (rUPS) was used to define postoperative pneumonia. The score was based on the following three factors: body temperature ($^{\circ}\text{C}$) (≥ 36.1 and $\leq 38.4 = 0$, ≤ 36.0 or $\geq 38.5 = 1$) and white blood cell count ($\times 10^9/\text{L}$) (≥ 4.0 and $\leq 11.0 = 0$, < 4.0 or $> 11.0 = 1$) and pulmonary radiological results (chest X-ray and/or CT scan, CT preferred) (no infiltrate = 0, diffused (or patchy) infiltrate = 1, well-circumscribed infiltrate = 2). A sum score of 2 points or higher, of which at least 1 point is assigned due to infiltrative findings on pulmonary radiography, indicates treatment of pneumonia (20).

Data collection

Preoperative laboratory tests of all patients in this group was completed within one week before surgery. Baseline data included sex, age, comorbidities, and perioperative indicators. The severity of smoking was indicated by the smoking index (cigarettes/day $\times$ year), and respiratory diseases included chronic bronchitis, emphysema, and chronic obstructive pulmonary disease. In addition, based on previous studies, we calculated the following indicators: AFR, neutrophils-to-lymphocyte ratio (NLR), platelet-to-lymphocyte (PLR), and monocyte to lymphocyte ratio (MLR).

Statistical analysis

Receiver operating characteristic (ROC) curve analysis using Youden's Index was established for determining the predictive value and cut-off threshold of AFR for postoperative pneumonia. Baseline data were divided into two groups with and without pneumonia, in which variables are expressed as means $\pm$ standard deviation (SD) or numbers with percentage (n, %). Continuous variables were compared using

Mann–Whitney U test or Student t test, whereas categorical variables using Chi-square test or Fisher exact test as appropriate, and data with statistically significant differences were included in univariate and multivariate logistic analysis. All the probabilities are double-tailed probabilities. When P value is less than 0.05, there is a statistical difference. All statistical analyses were performed by SPSS version 26 (IBM, Armonk, NY, USA).

Result

Baseline data of patients

Baseline information and perioperative data of all 177 patients were listed in Table 1. The average age was 64, with 46 females (26%) and 131 males (74%). According to whether the patients had postoperative pneumonia, they were divided into the pneumonia group and the non-pneumonia group, of which 32 (18%) were in the pneumonia group. The results showed that patients with previous respiratory diseases were more likely to develop postoperative pneumonia ($P < 0.05$). Other data such as gender, age, BMI, comorbidities except respiratory diseases, neoadjuvant chemotherapy, length of hospital stay, ASA classification, surgical method, anesthesia intubation method, anastomotic site, intraoperative blood loss, fluid infusion, operative time, tumor location, length, and degree of differentiation were not statistically significant ($P > 0.05$).

Table 1 Demographic and clinical characteristics

Parameters	Postoperative pneumonia		P value
	YESn=32	NO n=145	
Gender,n (%)			P=0.140
Male	2784.4	10471.7	-
Female	515.6	4128.3	-
Age(year)	65.5±8.4	63.7±8.0	P=0.259
BMI(kg/m ²)	23.3±3.2	24.0±3.0	P=0.235
Comorbidities, n (%)			
Hypertension	1443.8	4732.4	P=0.220
Cerebral infarction	412.5	1414.7	P=0.746
Coronary heart disease	39.4	1913.1	P=0.769
Respiratory diseases	515.6	42.8	P=0.011
Hepatitis	26.3	42.8	P=0.297
Diabetes	412.5	1913.1	P=1.000
The history of drinking,n (%)			P=0.637
No	2371.9	9867.6	-
Yes	928.1	4732.4	-
Smoking index	317±453.1	250.1±429.0	P=0.425
History of chest surgery,n (%)	13.1	53.4	P=1.000
The length of hospital stay(day)	18.3±8.1	17.3±5.4	P=0.895
Neoadjuvant chemotherapy,n (%)			P=0.071
Yes	1340.6	3624.8	
No	1959.4	10975.2	
ASA Grade,n (%)			P=0.316
I	26.2	21.4	-
II	2268.8	12586.2	-
III	825.0	1812.4	-
Surgical method,n (%)			P=0.553
MIE	2784.4	14297.9	

Open	5015.6	302.1	
Intubation method,n (%)			P=1.000
Single	103.1	503.4	-
Double	31096.9	140096.6	-
Anastomotic site,n (%)			P=0.328
Neck	27084.4	132091.0	-
Chest	5015.6	1309.0	-
Blood loss(ml)	192.2±44.2	182.3±68.7	P=0.309
Intraoperative fluid utilization(ml)	2348.4±619.0	2303.5±664.5	P=0.715
Operative time(min)	317.4±77.6	362.3±70.0	P=0.546
Tumor location,n (%)			P=0.447
Upper	309.4	1107.6	-
Middle	12037.5	72049.7	-
Lower	17053.2	62042.8	-
Tumor length(cm)			P=0.975
<3	14043.8	63043.4	-
≥3	18056.3	82056.6	-
Differentiation,n (%)			P=0.159
Low	7021.9	32022.1	-
Middle	23071.9	84057.9	-
High	206.3	29020	-

Notes:P-values were calculated by Chi-square test, Fisher exact test, Mann-Whitney U or t test

Abbreviations:*BMI* Body mass index,*Smoking index* cigarettes/day×year,*ASA* American Society of Anesthesiologists

Laboratory tests data

Preoperative laboratory tests of patients with and without pneumonia were shown in Table 2. Creatinine, albumin, white blood cells, platelets, central granulophils, monocytes, fibrinogen, AFR, PLR were

statistically different between the two groups ($P < 0.05$), and the P values of fibrinogen and AFR were < 0.001 .

Table 2 Laboratory tests

Laboratory test	Postoperative pneumonia		P value
	YES	NO	
Creatinine($\mu\text{mol/L}$)	76.3 $\pm$ 16.2	71.28 $\pm$ 16.3	P=0.037
Albumin(g/L)	39.1 $\pm$ 5.1	41.8 $\pm$ 3.3	P=0.005
Globulin(g/L)	26.8 $\pm$ 4.8	25.5 $\pm$ 4.3	P=0.151
WBC($\times 10^9/\text{L}$)	7.2 $\pm$ 3.1	5.8 $\pm$ 1.8	P=0.018
Hemoglobin(g/L)	126.1 $\pm$ 18.7	129.3 $\pm$ 15.1	P=0.3
Platelet($\times 10^9$)	230.3 $\pm$ 58.4	200.4 $\pm$ 6.6	P=0.016
Neutrophils($\times 10^9/\text{L}$)	4.6 $\pm$ 2.9	4.2 $\pm$ 6.6	P=0.004
Lymphocyte($\times 10^9/\text{L}$)	1.8 $\pm$ 0.7	1.7 $\pm$ 0.5	P=0.690
Monocytes($\times 10^9/\text{L}$)	0.6 $\pm$ 0.2	0.5 $\pm$ 0.1	P=0.015
Fibrinogen(mg/dL)	3.9 $\pm$ 0.8	3.2 $\pm$ 0.7	P $\leq$ 0.001
AFR	10.6 $\pm$ 3.2	13.6 $\pm$ 3.0	P $\leq$ 0.001
NLR	3.1 $\pm$ 2.8	2.7 $\pm$ 3.7	P=0.1
PLR	144.6 $\pm$ 56.4	126.8 $\pm$ 58.8	P=0.048
MLR	0.72 $\pm$ 2.1	0.3 $\pm$ 0.2	P=0.103

Notes: P-values were calculated by Mann-Whitney U or t test

Abbreviations: *WBC* White blood cell, *AFR* Albumin-to-fibrinogen ratio, *NLR* Neutrophils-to-Lymphocyte ratio, *PLR* Platelet-to-Lymphocyte ratio, *MLR* Monocytes-Lymphocyte ratio

The predictive value of AFR for postoperative pneumonia

ROC curve analysis was used to assess the predictive value of AFR for postoperative pneumonia and the cut-off value of statistically significant laboratory test results. As shown in Figure 1, preoperative AFR level predicted postoperative pneumonia with an AUC area of 0.767, a sensitivity of 65.6%, and a specificity of 83.4%. The cut-off values of AFR, creatinine and albumin were obtained based on the Youden's Index. Then, according to the cut-off value, all patients were divided into two groups: high level group and low level group.

Risk factors for postoperative pneumonia

All possible risk factors ($P < 0.05$) were included in univariate and multivariate logistic regression analysis. Variables with $P < 0.1$ in univariate analysis were included in multivariate analysis. Multivariate logistic regression analysis showed that low creatinine, albumin and high AFR levels were independent risk factors for postoperative pneumonia in patients after radical esophagectomy.

Table 3 Risk factors by univariate and multivariate logistic regression analyses

Variables	Univariate		Multivariate	
	OR[95%CI]	P value	OR[95%CI]	P value
Respiratory diseases (yes vs no)	1.646-25.889	0.008		
Creatinine (high vs low)	1.219-6.499	0.015	0.081-0.712	0.01
Albumin (high vs low)	0.07-0.366	<0.001	1.268-11.656	0.017
WBC (high vs low)	1.678-8.190	0.001		
Platelet(high vs low)	1.426-6.928	0.005		
Neutrophils (high vs low)	1.906-12.633	0.001		
Monocytes (high vs low)	1.738-9.392	0.001		
Fibrinogen (high vs low)	2.201-11.140	0.001		
AFR (high vs low)	0.044-0.243	0.001	1.350-14.469	0.014
PLR (high vs low)	1.180-7.135	0.02		

Notes:The high vs low levels were categorized using the cut-off value based on the Youden's Index

Abbreviations: *WBC* White blood cell, *AFR* Albumin-to-fibrinogen ratio, *PLR* Platelet-to-Lymphocyte ratio, *OR* Odds ratio, *CI* Confidence interval

Discussion

With the development of surgical techniques, postoperative complications of esophageal cancer have been significantly reduced(4).Unfortunately, surgically related complications still occur in more than half of patients with esophageal cancer (21), with pneumonia and other pulmonary complications playing an important role in the morbidity and mortality of patients undergoing esophagectomy.Postoperative pneumonia increased the postoperative mortality rate by nearly 10% and the 5-year overall survival rate by 12% (22).Although the incidence of postoperative pneumonia can be reduced by using minimally invasive surgical techniques, persuading patients to quit smoking before surgery, exercising respiratory related muscles before surgery, and relieving postoperative wound pain (23), there is still a lack of a

biological model that can effectively predict the incidence of postoperative pneumonia in patients. In this study, we finally found that the value of preoperative creatinine, albumin and AFR were independent influencing factors for postoperative pneumonia in patients with esophageal cancer through univariate and multivariate logistic analysis. Through ROC curve analysis, it was found that preoperative AFR value could well predict whether patients with esophageal cancer would develop pneumonia after surgery. The AUC value was 0.767, which was the highest among the collected laboratory tests data with good sensitivity (65.6%) and specificity (83.4%).

In previous studies, the definition of pneumonia has been uncertain. Of the 56 studies included in a meta-analysis of postoperative complications, 18 defined pneumonia, but 16 of those definitions were different (24), so the reported incidence of pneumonia ranged from 2% to 39%. In this study, we used rUPS to define postoperative pneumonia and found that 32 out of 177 patients (18%) developed postoperative pneumonia, and patients with respiratory disease appeared to be more susceptible to postoperative pneumonia, which was consistent with the results of the two studies (25.5). To our surprise, although a growing body of evidence indicates that age is pancreatotomy, laparoscopic gastrectomy, robot assisted lung resection and other operation types of independent risk factor for postoperative complications (17), but this study (5) and another group of research did not find same age differences between two groups of patients, this could be due to different sample sizes, types of surgery and perioperative management. Since only 8 open surgeries were included, it is not reliable that there was no statistically significant difference between the two groups. In addition, a new independent factor, creatinine, was identified by univariate and multivariate logistic analysis. Creatinine as a blood indicator for evaluating renal function has been found to be an independent influence factor for postoperative acute kidney injury (AKI) in patients with esophageal cancer (26). A study included 24233 patients found high creatinine is a independent risk factor for esophageal cancer surgery related death (27), but its association with postoperative pulmonary complications has not been studied to our knowledge. Whether preoperative serum creatinine can be used as a new marker to predict postoperative pulmonary complications and the specific mechanism in patients with esophageal cancer needs to be explored in larger sample clinical trials and basic experiments.

As mentioned above, many studies have been conducted on albumin and AFR as independent influencing factors to predict postoperative complications and prognosis in tumor patients. In this study, albumin levels were found to be statistically different between the two groups, consistent with previous findings (12) and associated with postoperative complications in a study on the ratio of C-reactive protein to albumin (15). From the results, increasing albumin levels to a certain extent can prevent postoperative complications, which is correlated with previous reports that low serum albumin may lead to a higher risk of worsening disease and poor prognosis in cancer patients. This might be due to malnutrition can weaken the immune system, increase the chance of infection, and albumin may help stabilize the DNA replication and cell growth, regulate the body's reaction, enhance immunity, prevention of malignant disease (18).

AFR, as a new indicator, represents the combined effect of two blood factors, enhancing sensitivity to assess inflammation and nutritional status. In various models of acute ST-segment elevation myocardial infarction (STEMI) (28), non-small cell lung cancer (NSCLC) (29), soft tissue sarcoma (30), and esophageal cancer (18), the combination of albumin and fibrinogen has been reported to be superior to albumin and fibrinogen alone, and has been widely recommended as a prognostic factor. It should be noted that in a report on the prediction of prognosis of esophageal cancer by AFR (18), postoperative complications of patients were not included in the study, so it was not possible to assess whether the prognosis of patients after esophageal cancer was caused by the occurrence of postoperative complications. However, it remains to be further explored whether AFR or postoperative pneumonia has a stronger correlation with prognosis. To date, this study is the first retrospective study of the relationship between AFR and postoperative pneumonia in patients with esophageal cancer.

However, there are still several deficiencies in our study. First of all, this study is a retrospective, single-center study, which is likely to cause selective bias, and it needs to be verified by prospective, multi-centers, large-sample trials in the future. In addition, it is not clear whether preoperative intervention to change AFR level can reduce the incidence of postoperative pneumonia in patients with esophageal cancer. Finally, the mechanism that how AFR can predict postoperative pneumonia in patients with esophageal cancer is still unclear, and the molecular mechanism may be found through relevant basic experiments.

Conclusion

First of all, this study found that preoperative AFR can effectively predict the occurrence of postoperative pneumonia in patients with esophageal cancer as an independent influence factor. Secondly, creatinine, as another independent influence factor, may provide a new direction for research in this field in the future.

Abbreviations

MIE: minimally invasive esophagectomy; RCT: randomized controlled trial; CT: computed tomography; AFR: Albumin-to-fibrinogen ratio; rUPS: the revised Uniform Pneumonia Score; ASA: American Society of Anesthesiologists; NLR: neutrophils-to-lymphocyte ratio; PLR: platelet-to-lymphocyte; MLR: monocyte-to-lymphocyte ratio; BMI: Body mass index; CI: Confidence interval; OR: Odds ratio; WBC: White blood cell; AKI: acute kidney injury; STEMI: ST-segment elevation myocardial infarction; NSCLC: non-small cell lung cancer.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the The Ethics Committee of Scientific Research and Clinical Trial of The First Affiliated Hospital of Zhengzhou University, and the requirement for informed patient

consent was waived due to the retrospective nature of this study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Writing, review, Zhang Peng; editing, Zhao Song

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Figures

Figure 1

ROC curve analysis of AFR for postoperative pneumonia Notes: Predictive value of AFR for postoperative pneumonia by ROC curve analysis. The results indicated preoperative AFR as a potential predictive factor with an AUC of 0.767, 95%CI of 0.678–0.857, a cut-off value of 10.805, a sensitivity of 65.6% and a specificity of 83.4%, respectively ($P < 0.001$). Abbreviations: AFR, albumin-to-fibrinogen ratio; ROC, receiver operating characteristic; AUC, the area under the curve; CI, confidence interval