Title: Preoperative albumin-to-fibrinogen ratio predicts postoperative pulmonary complications in patients after minimally invasive esophagectomy

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Research Article

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Abstract

Background

Postoperative pulmonary complications (PPCs) are the most common postoperative complications in patients with esophageal cancer. Prediction of PPCs 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-to-fibrinogen ratio (AFR), prognostic nutritional index (PNI), albumin-to-globulin ratio (AGR), neutrophils-to-lymphocyte ratio (NLR), platelet-to-lymphocyte (PLR), and monocyte-to -lymphocyte ratio (MLR) and other preoperative laboratory tests and PPCs in patients after esophagectomy.

Methods

Retrospective analysis was performed on total 712 consecutive patients who underwent esophagectomy in the Department of Thoracic Surgery, The First Affiliated Hospital of Zhengzhou University from July 2018 to December 2020. Patients were divided into training (535 patients) and validation (177) 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. Univariate and multivariate logistic regression analyses were used to assess the risk factors for PPCs in training group.

Results

112 (20.9%) in training group and 36 (20.3%) in validation group developed PPCs. The AUC value predicted by AFR using ROC curve analysis was 0.817, sensitivity 76.2% and specificity 78.7% in training group while AUC 0.803, sensitivity 69.4% and specificity 85.8%. Multivariate logistic regression analysis showed that smoking index, American Society of Anesthesiologists (ASA), AFR, and recurrent laryngeal nerve palsy were independent risk factors for PPCs.

Conclusion

Preoperative AFR can effectively predict the occurrence of PPCs 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, surgical resection for early esophageal cancer or neoadjuvant chemoradiotherapy followed by esophagectomy for locally advanced esophageal cancer[3] is still the main treatment method. Recently, 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 postoperative pulmonary complications (PPC) after esophagectomy is still between 20% and 40%, which is the most common postoperative complication[5], and postoperative pneumonia, as the most common pulmonary complication, 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 PPC is always required. Preoperative laboratory tests, such as white blood cell, albumin, globulin, are usually readily available for us. If we can find the association between laboratory tests and postoperative PPC would be able to help patients make adequate preoperative preparation, reduce treatment costs, improve prognosis and quality of life.

In 2002, T. Nozoel 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[8–11]. 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.el proposed that low preoperative fibrinogen level may be a potential risk factor for neurological complications after cardiac surgery[16]. Then, 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 PPC in patients with esophageal cancer. Therefore, this study was devoted to exploring the relationship between AFR and other well-known nutritional index and PPC after esophagectomy.

Material And Methods

Patients

A total of 712 consecutive patients who underwent radical MIE in the Department of Thoracic Surgery, the First Affiliated Hospital of Zhengzhou University from July 2018 to December 2020 were divided into two groups. The first group as the training group included 535 patients who underwent MIE between July 2018 and December 2019, and another as the validation group included 177 patients between January 2020 and December 2020 was collected prospectively. A total of 37 cases were excluded, among them 7 cases were excluded due to tumor invasion, 21 cases were excluded due to lack of data, 7 cases were excluded due to open surgery, 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 test, 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, and gastroscopy. If the patient's general condition allowed, neoadjuvant chemoradiotherapy or chemotherapy was performed after discussion in the thoracic department. 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 three types of surgery including Mckeown, Ivor Lewis and Sweet, but not traditional 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, and the location of the anastomotic site was built in neck or chest depending on the patient's condition and tumor location. Finally, the anastomotic site was wrapped around with greater omentum or a kind of high molecular tissue material which has been proved to prevent anastomotic leakage in our center[19]. Postoperative pathology showed that all the 712 patients had negative resection margin, which means R0 resection. The first day after the operation, bedside chest radiograph was usually performed. 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 on the third day after surgery. 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. Anyone who may have developed respiratory failure or other new organ dysfuntion is transferred to the intensive care unit (ICU) for treatment as soon as possible. The retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. In addition to this, we confirm that all methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all eligible patients.

Definition of postoperative pulmonary complications

The occurrence of PPCs was determined if any of the following occurred in hospital within 7 days:[20] atelectasis, pleural effusion, pneumothorax, bronchospasm, respiratory infection, respiratory failure, or aspiration pneumonitis. Atelectasis, pleural effusion and pneumothorax were diagnosed by X-rays or CT. Bronchospasm was defined as newly detected expiratory wheezing that required treatment with bronchodilators. The revised Uniform Pneumonia Score (rUPS) was used to define postoperative pneumonia. The score was based on the following three factors: body temperature(°C)(≥ 36.1 and $\leq 38.4 = 0$, ≤ 36.0 or $\geq 38.5 = 1$) and white blood cell count($\times 10^9$/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[21]. Respiratory failure is defined as partial arterial oxygen pressure of 60 mmHg in indoor air, partial arterial oxygen pressure/graded inhalation oxygen concentration of 300, or oxygen therapy is required and arterial oxygen saturation is 90%[22].

Data collection

Preoperative laboratory tests of all patients were 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 × years). In addition, based on previous studies, we calculated the following indicators: prognostic nutritional index (PNI): 10 × serum albumin (g/dL) 0.005×total lymphocyte count (per mm^3)[23], AFR as mentioned, albumin-to-globulin ratio (AGR), neutrophils-to-lymphocyte ratio (NLR), platelet-to-lymphocyte (PLR), and monocyte-to -lymphocyte ratio (MLR).

Statistical analysis

Receiver operating characteristic (ROC) curve analysis was established for determining the predictive value and cut-off value of AFR for PPCs. Training group was divided into two groups with and without PPCs, and the validation group was divided into high and low AFR according to cut-off value of AFR obtained by the training group. Meanwihle, based on the cut-off value in the training group, high and low AFR were used for ROC curve analysis both in training goup and validation group. All variables are expressed as means ± 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 training data with statistically significant differences was 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 22 (IBM Corporation, Armonk, NY, USA).

Result

Baseline data of patients

Baseline information and perioperative data of training group was listed in Table 1. The average age was 65, with 144 females (26.9%) and 391 males (73.1%). According to whether the patients had PPCs, they were divided into the PPC group and the non-PPC group, of which 112 (20.9%) were in the PPC group. The results showed that age, history of smoking, smoking index, FEV1/pre, PNI, AFR, AGR, the American Society of Anesthesiologists (ASA) physical status, recurrent laryngeal nerve palsy, days in ICU and days in hospital after surgery were all significantly different between the two groups ($p < 0.05$). Others were not statistically significant ($p > 0.05$). Then, as Table 2 showed, all possible risk factors ($p < 0.05$) were included in univariate logistic regression analysis. Variables with $p < 0.1$ in univariate analysis were included in multivariate analysis. Multivariate logistic regression analysis revealed that smoking index (odds ratio [OR] 1.001, 95% confidence interval [CI] 1.000-1.002,$p = 0.024$), AFR (OR 0.599, 95% CI 0.511–

0.702, $p < 0.001$), ASA physical status □ (OR 7.865, 95% CI 1.684–36.737, $p = 0.009$) and recurrent laryngeal nerve palsy (OR 3.721, 95% CI 1.044–13.263, $p = 0.043$) were independent risk factors of PPC.

Table 1
Demographic and clinical characteristics in training group

Variables	**All patients [n = 535]**	**PPC group [n = 122]**	**Non-PPC group [n = 413]**	***p* - Value**
Gender, n (%)				0.756
Male	391 (73.1)	91 (74.6)	300 (72.6)	-
Female	144 (26.9)	31 (25.4)	113 (27.4)	-
Age, years (mean ± SD)	64.5 ± 7.7	65.9 ± 6.3	64.1 ± 8.0	**0.011***
BMI, kg/m^2 (mean ± SD)	23.7 ± 3.2	23.3 ± 3.5	23.8 ± 3.1	0.134
Comorbidities, n (%)				
Hypertension	185 (34.6)	41 (33.6)	144 (34.9)	0.797
Cerebral infarction	59 (11.0)	17 (13.9)	42 (10.2)	0.243
Coronary heart disease	70 (13.1)	13 (10.7)	57 (13.8)	0.365
COPD	39 (7.3)	13 (10.7)	26 (6.3)	0.104
Hepatitis	17 (3.2)	5 (4.1)	12 (2.9)	0.509
Diabetes	67 (12.5)	15 (12.3)	52 (12.6)	1.000
History of smoking, n (%)				**< 0.001***
Non-smoker	322 (60.2)	56 (45.9)	266 (64.4)	-
Ex-smoker	76 (14.2)	17 (13.9)	59 (14.3)	-
Current-smoker	137 (15.6)	49 (40.2)	88 (21.3)	-
Smoking index (mean ± SD)	279.3 ± 499.0	481.2 ± 698.9	219.7 ± 404.5	**< 0.001***
History of drinking, n (%)				0.226
Yes	148 (17.7)	39 (32.0)	109 (26.4)	-
No	387 (72.3)	83 (68.0)	304 (73.6)	-

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (%). *p* - Value were calculated by Chi-square test, Fisher exact test, Mann-Whitney U or T test.

Abbreviations: *PPC* postoperative pulmonary complication, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *FVC/pre* forced votal capacity/predicion, *FEV1/pre* forced expiratory volumn in one second/prediction, *PNI* prognostic nutritional index, *AFR* albumin-to-fibrinogen ratio, *AGR* albumin-to-globin ratio, *NLR* neutrophils-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *MLR* monocytes-lymphocyte ratio, *ASA* American Society of Anesthesiologists, *ICU* intensive care unit

Variables	All patients [n = 535]	PPC group [n = 122]	Non-PPC group [n = 413]	*p* - Value
History of chest surgery, n (%)	9 (1.7)	3 (2.5)	6 (1.5)	0.433
Location,n (%)				0.382
Upper	42 (7.9)	11 (9.0)	31 (7.5)	-
Middle	308 (57.6)	71 (58.2)	237 (57.4)	-
Lower	168 (31.4)	39 (32.0)	129 (31.2)	-
Esophagogastric junction	17 (3.2)	1(0.8)	16(3.9)	-
Tumor length, cm (mean ± SD)	3.1 ± 1.6	3.0 ± 1.6	3.2 ± 1.6	0.414
FVC/pre, % (mean ± SD)	104.9 ± 16.1	105.5 ± 17.0	104.7 ± 15.9	0.624
FEV1/pre, % (mean ± SD)	76.6 ± 8.7	74.9 ± 6.2	77.2 ± 9.2	**0.002***
Preoperative laboratory tests (mean ± SD)				
White blood cells, mm	6.0±2.0	6.1 ± 1.7	5.9 ± 2.0	0.625
Hemoglobin, g/dL	129.1 ± 15.3	128.7 ± 15.4	129.2 ± 15.3	0.781
Creatinine, mg/dL	67.4 ± 17.8	71.2 ± 21.0	66.2 ± 16.6	0.265
PNI	40.2 ± 5.0	37.1 ± 4.7	41.1 ± 4.7	**< 0.001***
AFR	12.4 ± 2.7	10.2 ± 2.4	13.0 ± 2.5	**< 0.001***
AGR	1.6 ± 0.4	1.4 ± 0.3	1.7 ± 0.4	**< 0.001***
NLR	2.8 ± 4.3	3.3 ± 4.8	2.6 ± 4.1	0.136
PLR	90.3 ± 50.0	88.5 ± 43.5	90.8 ± 51.7	0.645
MLR	0.3 ± 0.2	0.3 ± 0.2	0.3 ± 0.1	0.486
Neoadjuvant therapy, n (%)				0.271
Yes				
No				

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (%). *p* - Value were calculated by Chi-square test, Fisher exact test, Mann-Whitney U or T test.

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Variables	All patients [n = 535]	PPC group [n = 122]	Non-PPC group [n = 413]	*p* - Value
	150 (28.0)	39 (32.0)	111 (26.9)	-
	385 (72.0)	83 (68.0)	302 (73.1)	-
ASA Physical Status, n (%)				**0.005***
[illegible]	44 (8.2)	2 (1.7)	42 (10.2)	-
[illegible]	416 (77.8)	105 (87.5)	311 (75.7)	-
[illegible]	71 (13.3)	13 (10.8)	58 (14.1)	-
Type of esophagectomy, n (%)				0.501
Mckeown	507 (94.8)	118 (96.7)	389 (94.2)	-
Ivor Lewis	6 (1.1)	1 (0.8)	5 (1.2)	-
Sweet	22 (4.1)	3 (2.5)	19 (4.6)	-
Length of operation, min (mean ± SD)	335.7 ± 73.5	335.7 ± 75.5	335.7 ± 72.9	1.000
Blood loss, ml (mean ± SD)	163.5 ± 78.1	159.6 ± 73.4	164.6 ± 79.5	0.537
Site of anastomotic, n (%)				0.702
Neck	504 (94.2)	116 (95.1)	388 (94.2)	-
Chest	30 (5.6)	6 (4.9)	24 (5.8)	-
Histology, n (%)				0.742
Squamous cell carcinoma	495 (92.5)	114 (93.4)	381 (92.3)	-
Adenocarcinoma	24 (4.5)	6 (4.9)	18 (4.4)	-
Small cell carcinoma	2 (0.4)	0	2 (0.5)	-
Others	14 (2.6)	2 (1.6)	12 (2.9)	-
Pathological depth of invasion, n (%)				0.851
pT0	71 (13.3)	19 (15.6)	52 (12.6)	-
pT1				
pT2				
pT3				
pT4				

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (%). *p* - Value were calculated by Chi-square test, Fisher exact test, Mann-Whitney U or T test.

Abbreviations: *PPC* postoperative pulmonary complication, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *FVC/pre* forced votal capacity/predicion, *FEV1/pre* forced expiratory volumn in one second/prediction, *PNI* prognostic nutritional index, *AFR* albumin-to-fibrinogen ratio, *AGR* albumin-to-globin ratio, *NLR* neutrophils-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *MLR* monocytes-lymphocyte ratio, *ASA* American Society of Anesthesiologists, *ICU* intensive care unit

Variables	All patients [n = 535]	PPC group [n = 122]	Non-PPC group [n = 413]	*p* - Value
	105 (19.6)	25 (20.5)	80 (19.4)	-
	125 (23.4)	25 (20.5)	100 (24.2)	-
	159 (29.7)	37 (30.3)	122 (29.5)	-
	75 (14.0)	16 (13.1)	59 (14.3)	-
Pathological depth of invasion, n (%)				0.560
pN0	347 (64.9)	78 (63.9)	269 (65.1)	-
pN1	110 (20.6)	23 (18.9)	87 (21.1)	-
pN2	61 (11.4)	18 (14.8)	43 (10.4)	-
pN3	17 (3.2)	14 (3.4)	3 (2.5)	-
Pathological distant metastasis, n (%)				0.132
pM0	532 (99.4)	120 (98.4)	412 (99.8)	-
pM1	3 (0.6)	2 (1.6)	1 (0.2)	-
Histologic grade, n (%)				0.104
G1	77 (14.4)	18 (14.8)	59 (14.3)	-
G1–2	39 (7.3)	9 (7.4)	30 (7.3)	-
G2	313 (58.5)	63 (51.6)	250 (60.5)	-
G2–3	57 (10.7)	21 (17.2)	36 (8.7)	-
G3	49 (9.2)	11 (9.0)	38 (9.2)	-
Postoperative complications, n (%)				
Anastomotic leak	42 (7.9)	5 (4.1)	37 (9.0)	0.079
Recurrent laryngeal nerve palsy	17 (3.2)	8 (6.6)	9 (2.2)	**0.033***
Thoracic duct injury				
Atrial fibrillation				
Wound infection				
Pulmonary embolism				
Reoperation				
Mortality				

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (%). *p* - Value were calculated by Chi-square test, Fisher exact test, Mann-Whitney U or T test.

Abbreviations: *PPC* postoperative pulmonary complication, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *FVC/pre* forced votal capacity/predicion, *FEV1/pre* forced expiratory volumn in one second/prediction, *PNI* prognostic nutritional index, *AFR* albumin-to-fibrinogen ratio, *AGR* albumin-to-globin ratio, *NLR* neutrophils-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *MLR* monocytes-lymphocyte ratio, *ASA* American Society of Anesthesiologists, *ICU* intensive care unit

Variables	All patients [n = 535]	PPC group [n = 122]	Non-PPC group [n = 413]	*p* - Value
	6 (1.1)	0 (0)	6 (1.5)	0.345
	16 (3.0)	1 (0.8)	15 (3.6)	0.137
	2 (0.4)	0	2 (0.5)	1.000
	3 (0.6)	0	3 (0.7)	1.000
	1 (0.2)	0	1 (0.2)	1.000
	3 (0.6)	0	3 (0.7)	1.000
Days in ICU after surgery (mean ± SD)	0.2 ± 1.6	0.6 ± 2.8	0.1 ± 0.9	**0.005***
Days in hospital after surgery (mean ± SD)	18.6 ± 8.0	20.6 ± 8.1	18.0 ± 8.0	**< 0.001***

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (%). *p* - Value were calculated by Chi-square test, Fisher exact test, Mann-Whitney U or T test.

Abbreviations: *PPC* postoperative pulmonary complication, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *FVC/pre* forced votal capacity/predicion, *FEV1/pre* forced expiratory volumn in one second/prediction, *PNI* prognostic nutritional index, *AFR* albumin-to-fibrinogen ratio, *AGR* albumin-to-globin ratio, *NLR* neutrophils-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *MLR* monocytes-lymphocyte ratio, *ASA* American Society of Anesthesiologists, *ICU* intensive care unit

Table 2
Risk factors of PPC by univariate and multivariate logistic regression analyses

Variables	Univariate analysis		Multivariate analysis	
	OR (95%CI)	***p*-Value**	**OR (95%CI)**	***p*-Value**
Gender				
female (referrence)	0.904 (0.570–1.435)	0.670		
Age	1.032 (1.004–1.060)	**0.024***	1.009 (0.973–1.046)	0.642
BMI	0.951 (0.891–1.016)	0.135		
COPD				
no (referrence)	1.775 (0.883–3.571)	0.107		
History of smoking				
Non-smoker (referrence)	1.000		1.000	
Current-smoker	2.645 (1.682–4.160)	**< 0.001***	1.095 (0.481–2.491)	0.830
Ex-smoker	1.369 (0.742–2.523)	0.315		
Smoking index	1.001 (1.001–1.001)	**< 0.001***	1.001 (1.000–1.002)	**0.024***
FEV1/pre	0.971 (0.949–0.993)	**0.011***	0.976 (0.947–1.006)	0.111
PNI	0.842 (0.804–0.881)	**< 0.001***	0.976 (0.912–1.045)	0.492
AFR	0.559 (0.492–0.635)	**< 0.001***	0.599 (0.511–0.702)	**< 0.001***
AGR	0.175 (0.091–0.335)	**< 0.001***	0.652 (0.296–1.436)	0.288
Neoadjuvant therapy				
no (referrence)	1.278 (0.825–1.982)	0.272		
ASA Physical Status				
[illegible] (referrence)	1.000			
[illegible]	7.090 (1.687–29.795)	**0.007***	7.865 (1.684–36.737)	**0.009***
[illegible]	4.707 (1.008–21.972)	**0.049***	2.804 (0.513–15.318)	0.234

Abbreviations: *PPC* postoperative pulmonary complication, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *FEV1/pre* forced expiratory volumn in one second/prediction, *PNI* prognostic nutritional index, *AFR* albumin-to-fibrinogen ratio, *AGR* albumin-to-globin ratio, *ASA* American Society of Anesthesiologists, *ICU* intensive care unit, *OR* Odds ratio, *CI* Confidence interval

Variables	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value
Type of esophagectomy				
Mckeown (referrence)	1.000			
Ivor Lewis	0.659 (0.076–5.699)	0.705		
Sweet	0.521 (0.151–1.790)	0.521		
Recurrent laryngeal nerve palsy				
no (referrence)	3.150 (1.188–8.350)	**0.021***	3.721 (1.044–13.263)	**0.043***
Days in ICU after surgery	1.178 (1.024–1.356)	**0.022***	1.238 (0.998–1.534)	0.052
Days in hospital after surgery	1.035 (1.012–1.060)	**0.003***	1.021 (0.990–1.052)	0.182
Abbreviations: *PPC* postoperative pulmonary complication, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *FEV1/pre* forced expiratory volumn in one second/prediction, *PNI* prognostic nutritional index, *AFR* albumin-to-fibrinogen ratio, *AGR* albumin-to-globin ratio, *ASA* American Society of Anesthesiologists, *ICU* intensive care unit, *OR* Odds ratio, *CI* Confidence interval				

Demographic and clinical characteristics in validation group were demonstrated in Table 3. The average age was 64, with 46 (26%) females and 131 (74%) males. Compared with the training group, only Mckeown and Ivor Lewis were operated, small cell carcinoma was not reported and no pulmonary embolism or mortality occurred. Between the high and low AFR group, gender, age, COPD, smoking index, FEV1/pre, ASA physical status, PPC and recurrent laryngeal nerve palsy were significantly different ($p < 0.05$).

Table 3
Demographic and clinical characteristics in validation group

Variables	All patients [n = 177]	AFR ≥ 11.1 [n = 129]	AFR < 11.1 [n = 48]	*p* - Value
Gender, n (%)				**0.013***
Male	131 (74.0)	89 (69.0)	42 (87.5)	-
Female	46 (26.0)	40 (31.0)	6 (12.5)	-
Age, years (mean ± SD)	64.0 ± 8.1	63.1 ± 8.1	66.4 ± 7.7	**0.017***
BMI, kg/m^2 (mean ± SD)	23.9 ± 3.0	23.9 ± 2.9	23.9 ± 3.5	0.996
Comorbidities, n (%)				
Hypertension	62 (35.0)	41 (31.8)	21 (43.8)	0.138
Cerebral infarction	18 (10.2)	11 (8.5)	7 (14.6)	0.266
Coronary heart disease	22 (12.4)	17 (13.2)	5 (10.4)	0.621
COPD	9 (5.1)	3 (2.3)	6 (12.5)	**0.013***
Hepatitis	6 (3.4)	4 (3.1)	2 (4.2)	0.663
Diabetes	22 (12.4)	13 (10.1)	9 (18.8)	0.120
History of smoking, n (%)				0.073
Non-smoker	91 (51.4)	73 (56.6)	18 (37.5)	-
Ex-smoker	19 (10.7)	13 (10.1)	6 (12.5)	-
Current-smoker	67 (37.9)	43 (33.3)	24 (50.0)	-
Smoking index (mean ± SD)	389.7 ± 635.0	673.3 ± 918.5	219.7 ± 404.5	**0.007***
History of drinking, n (%)				0.767
Yes	56 (31.6)	40 (31.0)	16 (33.3)	-
No	121 (68.4)	89 (69.0)	32 (66.7)	-
History of chest surgery, n (%)	6 (3.4)	3 (2.3)	3 (6.3)	0.346

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (%). *p* - Value were calculated by Chi-square test, Fisher exact test, Mann-Whitney U or T test.

Abbreviations: *AFR* albumin-to-fibrinogen ratio, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *FVC/pre* forced votal capacity/predicion, *FEV1/pre* forced expiratory volumn in one second/prediction, *ASA* American Society of Anesthesiologists, *PPC* postoperative pulmonary complication, *ICU* intensive care unit

Variables	All patients [n = 177]	AFR ≥ 11.1 [n = 129]	AFR < 11.1 [n = 48]	*p* - Value
Location,n (%)				0.352
Upper	13 (7.3)	12 (9.3)	1 (2.1)	-
Middle	84 (47.5)	62 (48.1)	22 (45.8)	-
Lower	66 (37.3)	45 (34.9)	21 (43.8)	-
Esophagogastric junction	14 (7.9)	1(0.8)	16(3.9)	-
Tumor length, n (%)				0.326
≥ 3	100 (56.5)	70 (54.3)	30 (62.5)	
< 3	77 (43.5)	59 (45.7)	18 (37.5)	
FVC/pre, % (mean ± SD)	106.1 ± 17.0	107.3 ± 17.4	102.7 ± 15.5	0.110
FEV1/pre, % (mean ± SD)	76.3 ± 8.3	75.2 ± 7.6	79.0 ± 9.5	**0.007***
Neoadjuvant therapy, n (%)				0.271
Yes	49 (27.7)	30 (23.3)	19 (39.6)	-
No	128 (72.3)	99 (76.7)	29 (60.4)	-
ASA Physical Status, n (%)				**0.030***
[illegible]	4 (2.3)	2 (1.6)	2 (4.2)	-
[illegible]	147 (83.1)	113 (87.6)	34 (70.8)	-
[illegible]	26 (14.7)	14 (10.9)	12 (25.0)	-
Type of esophagectomy, n (%)				0.501
Mckeown	164 (927)	120 (93.0)	44 (91.7)	-
Ivor Lewis	13 (7.3)	9 (7.0)	4 (8.3)	-
Length of operation, min (mean ± SD)	363.9 ± 71.0	358.3 ± 72.0	379.0 ± 66.7	0.085
Blood loss, ml (mean ± SD)	184.1 ± 65.0	181.3 ± 72.2	191.7 ± 39.0	0.225

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (%). *p* - Value were calculated by Chi-square test, Fisher exact test, Mann-Whitney U or T test.

Abbreviations: *AFR* albumin-to-fibrinogen ratio, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *FVC/pre* forced votal capacity/predicion, *FEV1/pre* forced expiratory volumn in one second/prediction, *ASA* American Society of Anesthesiologists, *PPC* postoperative pulmonary complication, *ICU* intensive care unit

Variables	All patients [n = 177]	AFR ≥ 11.1 [n = 129]	AFR < 11.1 [n = 48]	*p* - Value
Site of anastomotic, n (%)				0.578
Neck	159 (89.8)	117 (90.7)	42 (87.5)	-
Chest	30 (5.6)	12 (9.3)	6 (12.5)	-
Histology, n (%)				0.742
Squamous cell carcinoma	154 (87.0)	111 (86.0)	43 (89.6)	-
Adenocarcinoma	19 (10.7)	14 (10.9)	5 (10.4)	-
Others	4 (2.3)	4 (3.1)	0	-
Pathological depth of invasion, n (%)				0.680
pT0	19 (10.7)	16 (12.4)	3 (6.3)	-
pT1	11 (6.2)	8 (6.2)	3 (6.3)	-
pT2	32 (18.1)	24 (18.6)	8 (16.7)	-
pT3	40 (22.6)	30 (23.3)	10 (20.8)	-
pT4	75 (42.4)	51 (39.5)	24 (50.0)	-
Pathological depth of invasion, n (%)				0.560
pN0	118 (66.7)	90 (69.8)	28 (58.3)	-
pN1	32 (18.1)	21 (16.3)	11 (22.9)	-
pN2	20 (11.3)	14 (10.9)	6 (12.5)	-
pN3	7 (4.0)	4 (3.0)	3 (6.3)	-
Histologic grade, n (%)				0.437
G1	18 (10.2)	12 (9.3)	6 (12.5)	-
G1−2	22 (12.4)	14 (10.9)	8 (16.7)	-
G2	125 (70.6)	92 (71.3)	33 (68.8)	-
G2−3				
G3				

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (%). *p* - Value were calculated by Chi-square test, Fisher exact test, Mann-Whitney U or T test.

Abbreviations: *AFR* albumin-to-fibrinogen ratio, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *FVC/pre* forced votal capacity/predicion, *FEV1/pre* forced expiratory volumn in one second/prediction, *ASA* American Society of Anesthesiologists, *PPC* postoperative pulmonary complication, *ICU* intensive care unit

Variables	All patients [n = 177]	AFR ≥ 11.1 [n = 129]	AFR < 11.1 [n = 48]	*p* - Value
	5 (2.8)	5 (3.9)	0	-
	7 (4.0)	6 (4.7)	1 (2.1)	-
Postoperative complications, n (%)				
PPC	36 (20.3)	11 (8.5)	25 (52.1)	**< 0.001***
Anastomotic leak	21 (11.9)	14 (10.9)	7 (14.6)	0.459
Recurrent laryngeal nerve palsy	7 (4.0)	2 (1.6)	5 (10.4)	**0.016***
Thoracic duct injury	3 (1.7)	0 (0)	6 (1.5)	0.345
Atrial fibrillation	13 (7.3)	10 (7.8)	3 (6.3)	1.000
Wound infection	2 (1.1)	2 (1.6)	0	1.000
Reoperation	2 (1.1)	2 (1.6)	0	1.000
Days in ICU after surgery (mean ± SD)	0.2 ± 1.6	0.3 ± 1.3	0.4 ± 1.6	0.861
Days in hospital after surgery (mean ± SD)	18.6 ± 8.0	14.2 ± 5.7	15.1 ± 6.8	0.418

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (%). *p* - Value were calculated by Chi-square test, Fisher exact test, Mann-Whitney U or T test.

Abbreviations: *AFR* albumin-to-fibrinogen ratio, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *FVC/pre* forced votal capacity/predicion, *FEV1/pre* forced expiratory volumn in one second/prediction, *ASA* American Society of Anesthesiologists, *PPC* postoperative pulmonary complication, *ICU* intensive care unit

The predictive value of AFR for PPC

ROC curve analysis was used to assess the predictive value of AFR for PPC. As shown in Fig. 1, preoperative AFR in training group predicted PPC with the area under the curve (AUC) of 0.817, 95% CI of 0.771–0.864, the optimal cut-off value was 11.1, with a sensitivity of 76.2%, and specificity of 78.7% ($p < 0.001$). The AUC of binary classification of AFR was 0.771, 95% CI of 0.721–0.820, sensitivity 75.4% and specificity 78.7% ($p < 0.001$) (Fig. 2).

In validation group, the AFR predicted PPC with the AUC of 0.803, 95% CI of 0.711–0.895, cut-off value 10.8, sensitivity of 69.4% and specificity of 85.8%, respectively ($p < 0.001$) (Fig. 3). The AUC of binary classification of AFR was 0.766, 95% CI of 0.670–0.861, sensitivity 69.4% and specificity 83.9% ($p < 0.001$) (Fig. 4).

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, with the most common complications being PPCs, which increased the postoperative mortality rate by nearly 10% and decreased 5-year overall survival rate by 12%[24–26]. Although the incidence of PPCs can be reduced by MIE, persuading patients to quit smoking before surgery, exercising respiratory related muscles before surgery, and relieving postoperative wound pain[27], there is still lack of a readily available model that can effectively predict the incidence of PPCs. In this study, we finally found that smoking index, AFR, ASA physical status □, and recurrent laryngeal nerve palsy were independent risk factors for PPCs in patients with esophageal cancer using univariate and multivariate logistic analysis. Through two types and two groups of ROC curve analysis, it was found that preoperative AFR could well predict PPCs. The AUC value were 0.817 in the training group and 0.803 in the validation group, which was the highest among the collected laboratory tests data with good sensitivity (76.2%), specificity (78.7%) and sensitivity (69.4%), specificity (85.8%) ($p < 0.001$). Binary AFR also demonstrated preferable prediction with AUC 0.771, sensitivity (75.4%), specificity (78.7%) and AUC 0.766, sensitivity (69.4%), specificity (83.9%) ($p < 0.001$).

The nutritional status of cancer patients is an important factor in determining postoperative prognosis, morbidity and mortality[22]. Although PNI, prognostic nutritional index, has been proven to predict postoperative complications and outcomes in varies cancer patients[22,28–30], it is not the independent risk factor or the best predictive signature in our study with AUC 0.730. 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. The results of both groups in this study indicated that lower AFR, which seems means lower albumin or higher fibrinogen, was more prone to PPCs. Increasing albumin to prevent postoperative complications is correlated with previous reports that low serum albumin may lead to a higher risk of worsening disease and poor prognosis in cancer patients[13]. 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]. Fibrinogen, a fibrin-based soluble clotting substrate that plays a central role in hemostasis and thrombosis, is associated with cardiovascular event risk and pre-thrombosis status in experimental models[31], and is also widely reported as an acute phase protein involved in inflammatory response. Fibrinogen synthesis is regulated by a number of inflammatory cytokines, including interleukin-1 (IL-1) and IL-6[32]. Thus, elevated FIB within a range may indicate a higher likelihood of thrombosis and attack by inflammatory factors. Theoretically, it may hamper the patient's recovery after surgery. As for AFR, a new indicator, represents the combined effect of the two blood factors mentioned, enhancing sensitivity to assess inflammation and nutritional status. In various models of acute ST-segment elevation myocardial infarction (STEMI)[33], non small cell lung cancer (NSCLC)[34], soft tissue sarcoma[35], 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 PPCs has a stronger correlation with prognosis. To our knowledge, the present study is the first to demonstrate the association between AFR and PPCs after MIE.

Plenty of studies have demonstrated that current smoking status is associated with PPCs[36], and smoking cessation decrease the incidence of PPCs[27,37]. But none of these studies seemed to include smoking index that reflects the degree of smoking rather than the status of smoking in some aspect. When including both smoking status and smoking index in the logistic regression analysis, we found that only smoking index (OR 1.001, 95% CI 1.000-1.002, p = 0.024) was a significant risk factor and was also significantly different in validation group which might mean that the amount of smoking, rather than smoking status, is a better predictor of PPCs, although it is needed validation among large sample and multiple centers.

Similar to previous studies[38–41], our work confirmed that ASA was an independent risk factor for PPCs, while only grade □ was significant taking grade □ as reference. ASA system was to assess the general health and comorbidities of patients before surgery[39]. Our study provides evidence for the foregoing and future related research.

The recurrent laryngeal nerve plays an important role in spinal cord coordination. RLN originates from the vagus nerve and provides ipsilateral motor innervation to the internal laryngeal muscles except the cricothyroid. These muscles play an important role in speech, swallowing and breathing[27]. As reported before, the incidence was from 0–29.3%[42], and Ivor Lewis could decrease the incidence to 0.9%[43]. However, the occurrence of recurrent laryngeal nerve palsy showed a strong correlation with postoperative pneumonia[44]. In this study, the incidence was 3.2% in training group and 4% in validation group. Its association with PPCs was verified by both sets of data ($p < 0.05$).

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, which may explain why age, body mass index (BMI) and FEV1/pre[5,17,22] were not independent risk factors as reported before. In addition, it is not clear whether preoperative intervention to change AFR level can reduce the incidence of PPCs. 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.

Conclusions

First of all, this study found that preoperative AFR can effectively predict the occurrence of PPCs in patients with esophageal cancer as an independent influence factor. Secondly, our study confirmed that

ASA, smoking index and recurrent laryngeal nerve palsy are independent risk factors for PPC

Abbreviations

MIE: minimally invasive esophagectomy; RCT: randomized controlled trial; PPC: postoperative pulmonary complication; CT: computed tomography; AFR: Albumin-to-fibrinogen ratio; ICU: intense care unit; rUPS: the revised Uniform Pneumonia Score; PNI: prognostic nutritional index; AGR: albumin-to-globulin ratio; ASA: American Society of Anesthesiologists; NLR: neutrophils-to-lymphocyte ratio; PLR: platelet-to-lymphocyte; MLR: monocyte–to-lymphocyte ratio; ROC: Receiver operating characteristic; SD: standard deviation BMI: Body mass index; CI: Confidence interval; OR: Odds ratio; STEMI: ST-segment elevation myocardial infarction; NSCLC: nonsmall 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. Written informed consent was obtained from all eligible patients. All of the procedures were performed in accordance with the Declaration of Helsinki and relevant policies in China.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Data Writing – Original Draft Preparation, Zhang Peng

Writing – Review & Editing, Visualization, Supervision, Project Administration, Zhao Song

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Figures

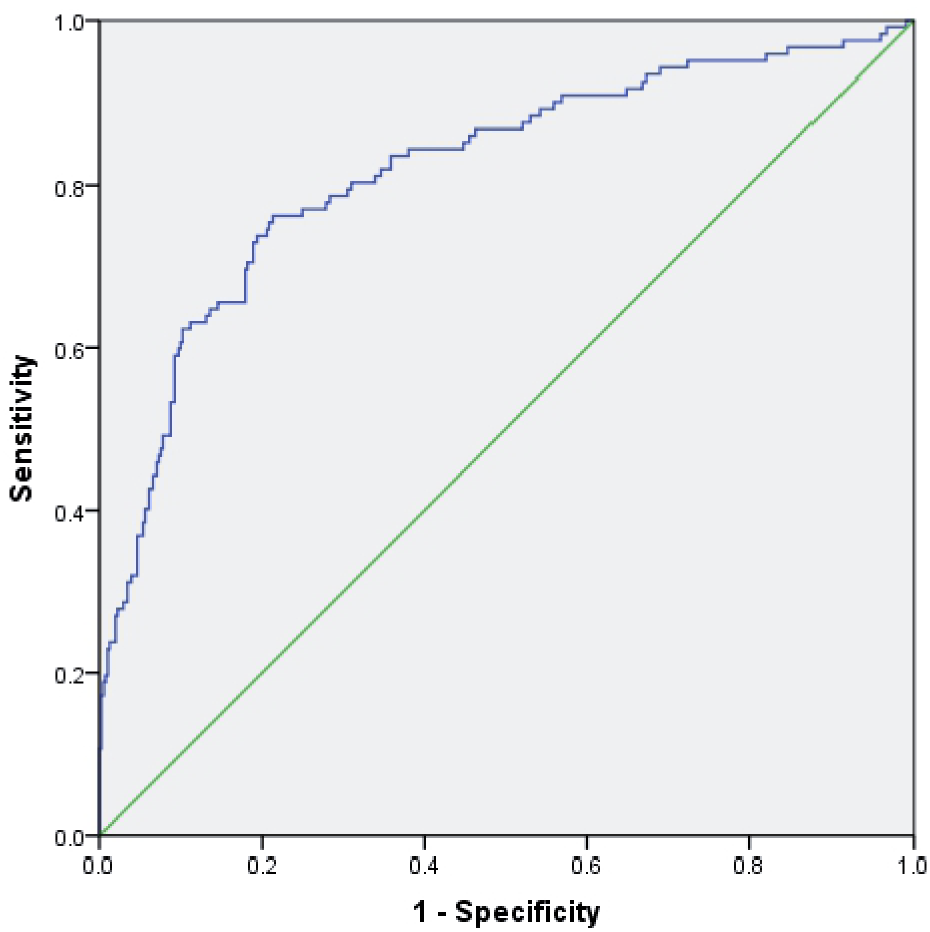

Figure 1

ROC curve analysis of AFR for PPC in training group Notes: Predictive value of AFR for PPC in training group by ROC curve analysis. The result indicated preoperative AFR as a potential predictive factor with an AUC of 0.817, 95%CI of 0.771–0.864, cut-off value of 11.1, sensitivity 76.2% and specificity 78.7%, respectively ($p < 0.001$). Abbreviations: ROC receiver operating characteristic, AFR, albumin-to-fibrinogen ratio, PPC postoperative pulmonary complication, AUC the area under the curve, CI confidence interval

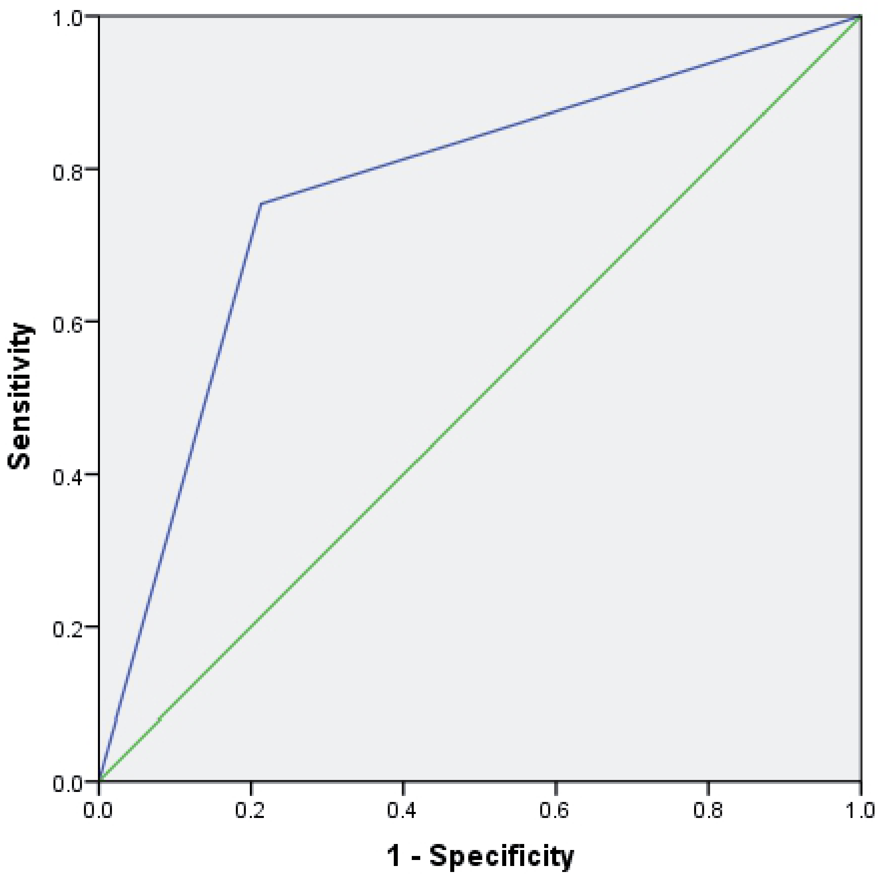

Figure 2

ROC curve analysis of AFR based on cut-off value for PPC in training group Notes: Predictive value of AFR based on cut-off value by ROC curve analysis. AUC 0.771, 95% CI 0.721–0.820, sensitivity 75.4% and specificity 78.7%, respectively ($p < 0.001$). Abbreviations: ROC receiver operating characteristic, AFR albumin-to-fibrinogen ratio,PPC postoperative pulmonary complication, AUC the area under the curve, CI confidence interval

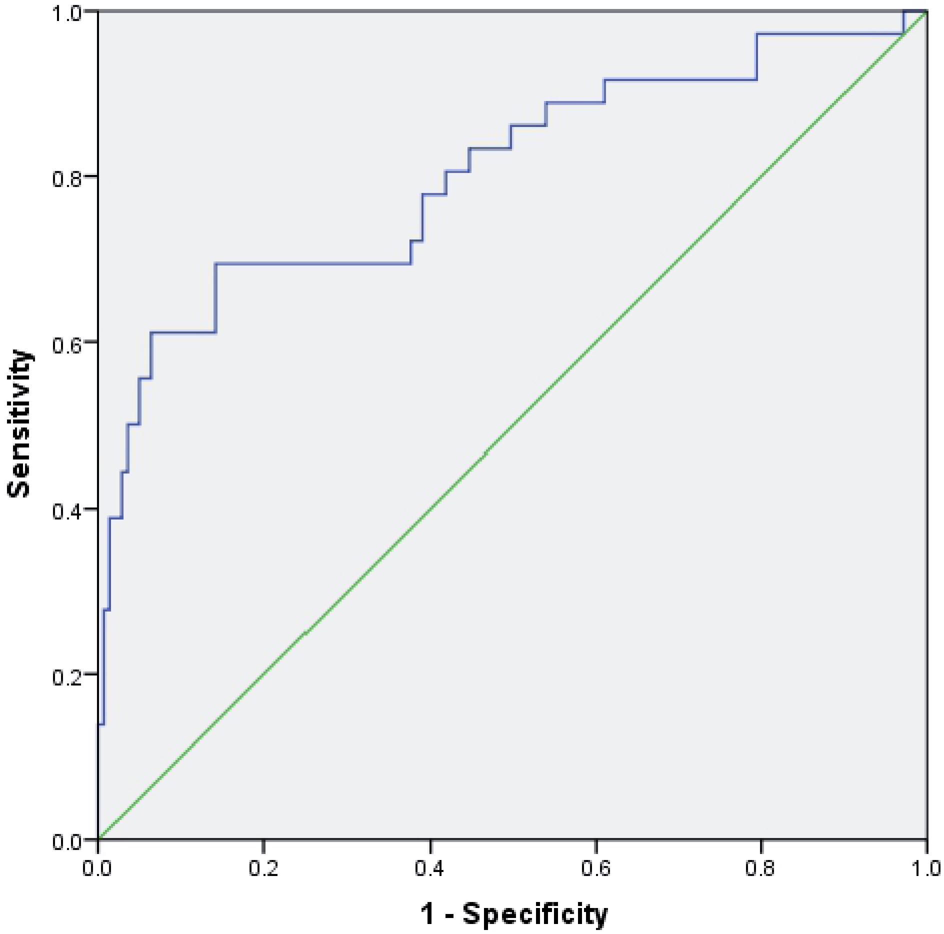

Figure 3

ROC curve analysis of AFR for PPC in validated group Notes: The results indicated preoperative AFR as a potential predictive factor with AUC 0.803, 95% CI 0.711–0.895, cut-off value 10.8, sensitivity of 69.4% and specificity of 85.8%, respectively ($p < 0.001$). Abbreviations: ROC receiver operating characteristic, AFR albumin-to-fibrinogen ratio, PPC postoperative pulmonary complication, AUC the area under the curve, CI confidence interval

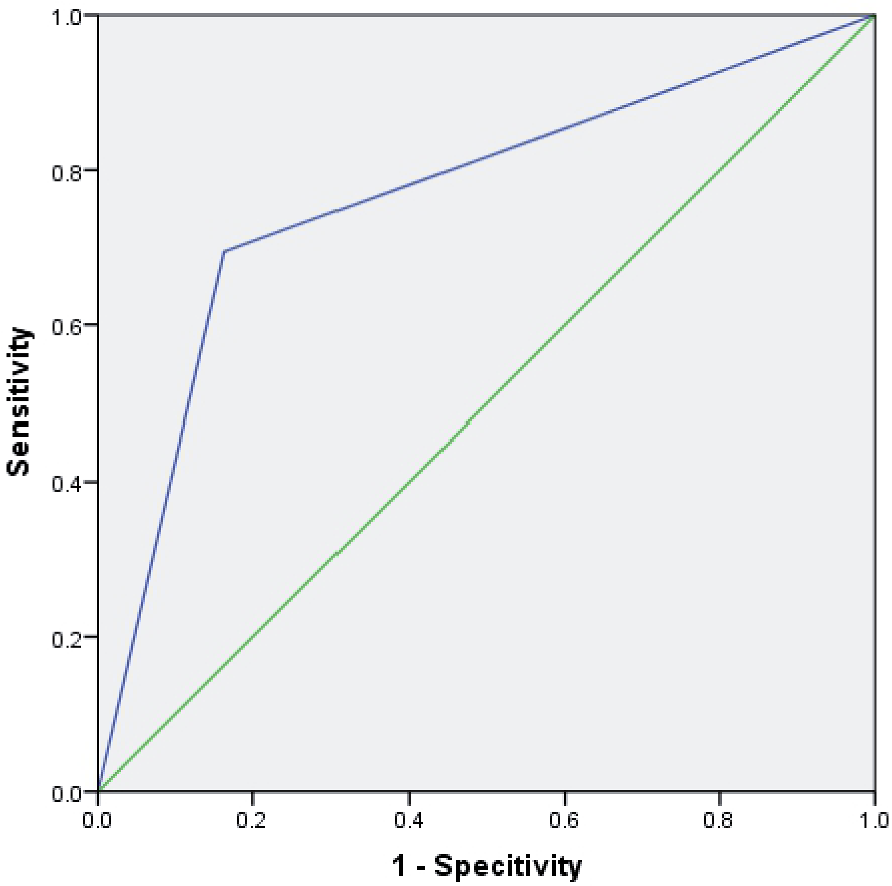

Figure 4

ROC curve analysis of AFR based on cut-off value for PPC in validated group Notes: The results indicated AUC 0.766, 95% CI 0.670–0.861, sensitivity 69.4% and specificity 83.9% respectively ($p < 0.001$). Abbreviations: ROC receiver operating characteristic, AFR albumin-to-fibrinogen ratio, PPC postoperative pulmonary complication, AUC the area under the curve, CI confidence interval