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Prediction of esophagogastric anastomotic leakage by nomogram combined with preoperative nutritional status and clinical factors: a retrospective study of 775 patients

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Abstract

Aim The purpose was to explore the independent risk factors for esophagogastric anastomotic leakage (EGAL) and establish a nomogram.

Methods Patients who underwent esophagectomy were enrolled and randomly divided into a training cohort and a validation cohort at a ratio of 7:3. The differences between the two groups of factors were analyzed by difference analysis, and multivariate regression analysis was subsequently performed. A nomogram was established, and the feasibility of the nomogram was verified by analyzing the discrimination, calibration, and decision curves.

Results A total of 775 patients were enrolled, including 532 in the training cohort and 223 in the validation cohort. Multivariate regression analysis revealed that age, smoking history, drinking history, nutritional indicators, and anastomotic location were independent risk factors. In terms of discrimination, in the training group, the area under the curve was 0.757 ($P=0.025$). In the calibration curve, the curves and fitting lines before and after correction in the training group and the validation group were basically the same. The results of the Hosmer–Lemeshow test showed that the chi-square value of the training cohort was 5.48 ($P=0.791$). In the decision curve analysis of the training set, when the threshold probability was in the range of 5–63%, the net benefit of patients was greater than that of the two extreme curves.

Conclusion Preoperative malnutrition is an independent risk factor for EGAL. A diagnostic model, developed on age, anastomotic location, smoking status, and drinking history, was a reliable noninvasive tool to timely predict the occurrence of AL.

Keywords Anastomotic leakage, Nomogram, Nutritional status

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Background

According to the latest global tumor data released by the International Agency for Research on Cancer (IARC) in 2020, the incidence and mortality of esophageal cancer rank seventh and sixth respectively among all malignant tumors in the world (Sung et al. 2021). In recent years, perioperative treatment has been continuously improved and optimized, and the risk of postoperative complications has been significantly reduced. Esophagogastric anastomosis is currently the most commonly used upper gastrointestinal tract reconstruction method for esophagectomy. Esophagogastric anastomotic leakage (EGAL) is one of the most dangerous complications after surgery. It is reported that the incidence rate of EGAL is 4.9–19.6%, which can significantly increase perioperative mortality and tumor recurrence rate, and is also an important negative factor that reduces the long-term survival rate of patients (Verstegen et al. 2019). Therefore, avoiding the occurrence of anastomotic leakage as much as possible has always been a research goal in the field of thoracic surgery. Esophageal cancer is known to be a debilitating disease with a poor prognosis, with most patients losing weight due to malnutrition (Anandavadivelan and Lagergren 2016). In addition, studies have shown that among patients with esophageal cancer undergoing surgical treatment, patients with poor preoperative nutritional status have a poor overall prognosis (Gooszen et al. 2018; Goense et al. 2016). The Geriatric Nutritional Risk Index (GNRI), a nutritional assessment tool based on objective indicators such as serum albumin and body weight, has been widely recognized for its ability to identify malnutrition and predict clinical outcomes in various patient populations. Studies have demonstrated its effectiveness in evaluating nutritional status and its association with postoperative complications in patients undergoing esophagectomy (Bouillanne et al. 2005). However, there are few studies on the ability of preoperative nutritional status to predict EGAL. Therefore, the purpose of this study was to explore the independent risk factors for EGAL and establish a nomogram for EGAL based on preoperative nutritional status to assess the possibility of the occurrence of AL and to aid in clinical decisions regarding treatment selection.

Methods

Patient

This study retrospectively collected data from patients who underwent radical resection of esophageal cancer in our hospital between January 2018 and October 2023. Inclusion criteria are as follows: (1) The surgical procedure was minimally invasive esophagectomy, (2) patients who returned safely to the ward or ICU after surgery, and (3) preoperative gastroscopic biopsy or postoperative pathological examination confirming esophageal cancer. Exclusion criteria are as follows: (1) underwent palliative surgery due to distant metastasis; (2) had acute infectious disease before operation; (3) had severe failure of the heart, liver, kidney, or other important organs before the operation; (4) had benign lesions indicated by postoperative pathology; and (5) had missing important clinical data.

Observation target

Preoperative factors, including sex, age, weight, BMI, forced expiratory volume in the first second (FEV1), maximum ventilatory volume (MVV), previous history (hypertension, diabetes, and coronary heart disease), drinking history, smoking history, neoadjuvant therapy, tumor location, and pathological stage, were recorded through the digital electronic medical records data system of our center. Intraoperative factors included the following: the location of the anastomosis, operation method, operation time, and number of lymph dissections. Postoperative factors included drainage flow, drainage tube extubation time, hospitalization days, nerve infiltration, and vascular infiltration.

According to the smoking index, the smoking patients were divided into no smoking (smoking index = 0), moderate smoking (smoking index ≤ 400), and lots smoking (smoking index > 400). Smoking index = number of cigarettes/day × number of years smoked. Lots alcohol consumption was defined according to National Institute on Alcohol Abuse and Alcoholism as consuming more than 60 g of pure alcohol per day for men and 40 g per day for women, which corresponds to approximately five beers, two glasses of wine, or two glasses of hard liquor. Moderate alcohol consumption was defined as the presence of alcohol consumption that does not meet the definition of heavy drinking (Messager et al. 2017).

Definition of EGAL

All patients with esophageal cancer after surgery were routinely closely observed and monitored. Once anastomotic leakage is suspected, some diagnostic examinations (such as chest CT, gastroscopy, and even thoracotomy exploration) can be performed on the patient. Anastomotic leakage in the neck can easily appear due to their shallow location and are usually diagnosed and confirmed by direct observation of the incision in the neck or by oral methylene blue observation of the incision in the neck (National Institute on Alcohol Abuse and Alcoholism 2016). At our center, diagnostic tests are not routinely used but are performed immediately after suspicious symptoms appear. At the same time, because this study was a retrospective analysis, only EGAL that was clearly diagnosed in the electronic medical records was included.

Definition of the GNRI

The nutritional risk index of the elderly (GNRI) was calculated using two factors: albumin and body weight. The GNRI was calculated as follows (Bouillanne et al. 2005): $GNRI = 1.489 \times$ serum albumin value (g/L) $+ 41.7 \times$ (weight/WLo). WLo stands for the ideal weight and is calculated according to the Lorentz formula, for men WLo = (height [cm] − 100) − ((height − 150)/4) and for women WLo = (height [cm] − 100) − ((height − 150)/2), which specifies that the weight/WLo = 1 when the actual weight is greater than the ideal weight. WLo = (height [cm] − 100) − ((height − 150)/2), which specifies that when the actual weight exceeds the ideal weight, the weight/WLo = 1.

Statistical methods

Figure 1 shows the flow of data processing, model building, and model validation. Statistical analysis was performed with SPSS (v.26.0) and R (v.4.2.0) software. Measurement data are represented as the median (interquartile distance), and the Mann–Whitney U-test was used for analysis. Count data are expressed as frequencies (%), and the chi-square test was used for comparisons between groups. Analysis of the difference between the two groups revealed that the multiple logistic regression method is suitable for further screening of independent risk factors. Differences were considered statistically significant at $P < 0.05$. The nomogram used the adopts rms package; the fbROC package was used for differentiation analysis, and calibrate function and val.prob function in the rbs package were used for calibration and dca. The R package was used for decision curve. The receiver operating characteristic (ROC) curve was used to judge the discrimination between the predicted value and the true value, and the closer to 1, the better the discrimination. The calibration plot was a scatter plot of the actual and predicted probabilities, and the closer the two are, the better the fit is; decision curve analysis (DCA) was used to judge the clinical utility of the prediction model by calculating the risk probability.

Results

EGAL accounted for 13.8% (107/775) of all patients included. A total of 775 patients were included in this study and were randomly divided at a ratio of 7:3, including 542 patients in the training group and 233 patients in the validation group. All included patients underwent mechanical anastomosis using curved intraluminal stapler from Johnson & Johnson. There was no significant difference in the clinical data between the two groups. The demographic and clinical characteristics of the study participants are shown in Table 1.

We conducted a difference analysis on the basic data and found that there were no significant differences between the two groups (EGAL group and no-EGAL group) in preoperative indicators such as age, smoking history, alcohol consumption, FEV1, MVV and GNRI, intraoperative indicators such as the position of anastomosis, and postoperative indicators such as hospital stay and drainage tube retention time. For further analysis, considering that the purpose of this study was to predict the occurrence of EGAL, only preoperative and intraoperative indicators were included. Therefore, age, smoking history, alcohol consumption, FEV1, MVV and GNRI, and anastomotic location were included. The results of multivariate regression analysis indicated that age, smoking history, and anastomotic location, alcohol consumption, and GNRI score were independent risk factors for EGAL. Based on the results of multivariate regression analysis, a nomogram was constructed, as shown in Fig. 2.

RCO was constructed with the above model. The training group had the area under the curve (AUC) of 0.757 (95% CI: 0.715–0.853, $P = 0.025$), while the AUC of the validation group was 0.746 (95% CI: 0.6588–0.839, $P = 0.045$). The results show that the model has good differentiation (Figs. 3 and 4).

The calibration curves and fitting lines before and after correction in the training group and the validation group were basically the same, indicating that the model fit was fairly good (see Figs. 5 and 6) The Hosmer–Lemeshow test was performed on the prediction model. The chi-square value of the training set was 5.48 ($P = 0.791$), and the chi-square value of the validation set was 10.32 ($P = 0.325$). It was proved that the prediction model was well fitted.

The decision curve analysis (DCA) curve of the prediction model was drawn for the training set (Figs. 7 and 8 show the validation group). When the threshold probability was in the range of 5 to 63%, the net benefit of patients was greater than the two extreme curves in the figure, indicating that the range had clinical validity.

Discussion

Anastomotic leakage (AL) remains one of the most serious complications after esophagectomy and is the main cause of increased risk of postoperative death (Verstegen et al. 2019). In addition, EGAL also affects the long-term prognosis of patients, and the overall survival and disease-free survival of patients with severe anastomotic leakage are significantly reduced (Rutegård et al. 2012; Markar et al. 2015). If the possibility of postoperative anastomotic leakage can be evaluated before surgery

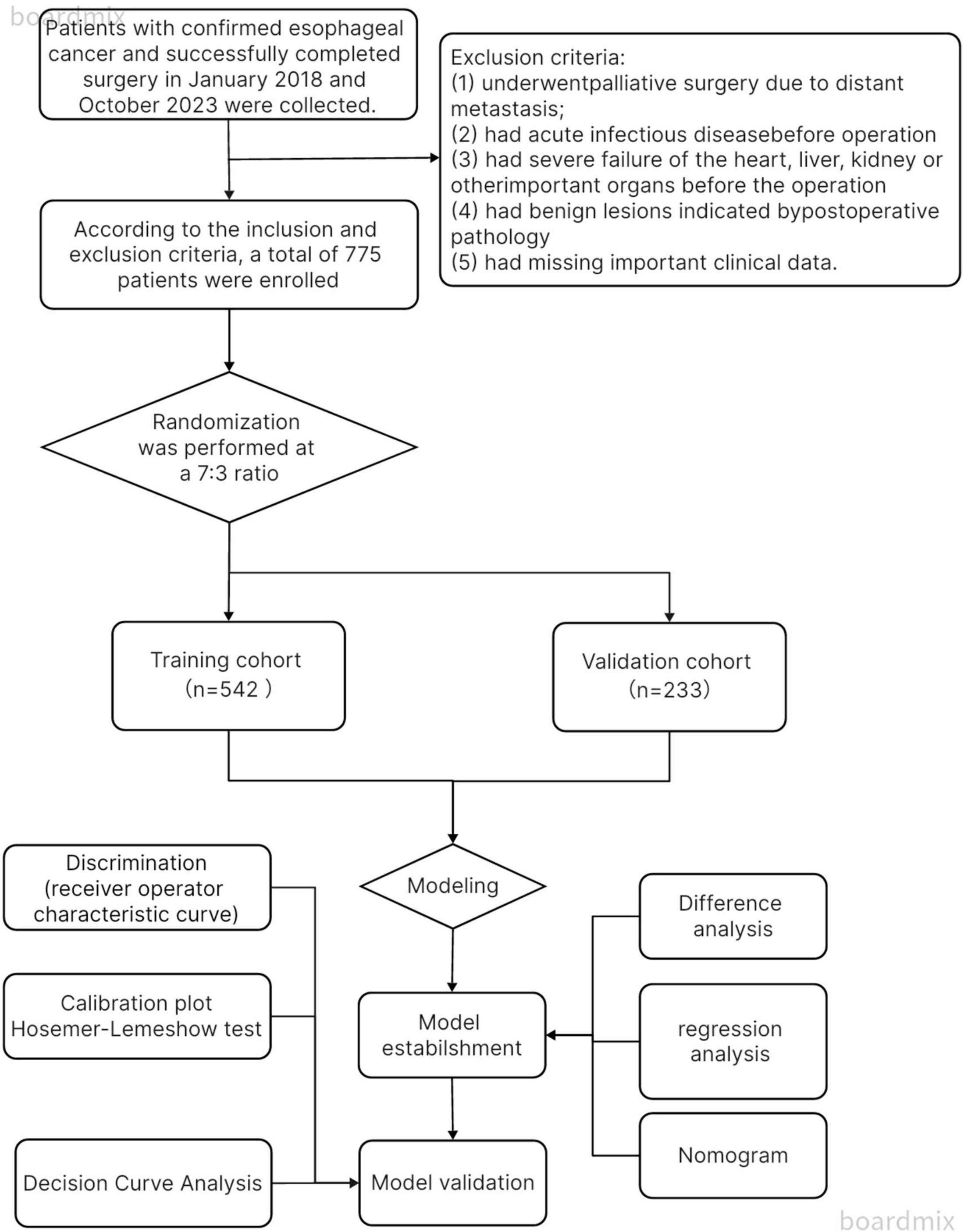

Fig. 1 Analysis workflow for data management and model development

and active measures are taken to prevent it, postoperative recovery of patients can be promoted. Therefore, this study combined preoperative factors to construct a nomogram to predict the possibility of AL, aid in clinical decision-making regarding treatment selection, and improve patient the prognosis.

The nutritional assessment of patients with esophageal cancer is particularly important, because it is helpful for carrying out reasonable and effective nutritional intervention and treatment, improving the nutritional status of patients with malnutrition, reducing the occurrence of complications, and improving the prognosis. For

Table 1 Clinical characteristics in the training and validation cohorts

	ALL ($n=775$)	Validation cohorts ($n=233$)	Training cohorts ($n=542$)	*P*
Group				0.449
No-EGAL	668 (86.2%)	197 (84.5%)	471 (86.9%)	
EGAL	107 (13.8%)	36 (15.5%)	71 (13.1%)	
Sex (male), *n* (%)	609 (78.6%)	179 (76.8%)	430 (79.3%)	0.493
Age (years)	62.0 [56.0; 67.0]	63.0 [57.0; 67.0]	62.0 [56.0; 67.0]	0.522
Smoking history				0.563
None	336 (43.4%)	106 (45.5%)	230 (42.4%)	
Moderate	151 (19.5%)	47 (20.2%)	104 (19.2%)	
Lots	288 (37.2%)	80 (34.3%)	208 (38.4%)	
BMI (kg/m^2)	21.9 [20.1; 23.8]	22.0 [20.2; 23.9]	21.7 [20.1; 23.7]	0.277
Weight (kg)	60.0 [53.5; 67.0]	61.0 [54.5; 66.0]	60.0 [53.0; 67.0]	0.375
GNRI	102 [97.9; 106]	102 [98.1; 106]	102 [97.9; 107]	0.843
FEV1 (L)	2.65 [2.16; 3.08]	2.59 [2.18; 3.12]	2.67 [2.14; 3.08]	0.938
MVV (L)	98.5 [82.7; 111]	98.7 [83.3; 111]	98.5 [82.7; 111]	0.497
Alcohol consumption				0.120
None	531 (68.5%)	162 (69.5%)	369 (68.1%)	
Moderate	63 (8.13%)	12 (5.15%)	51 (9.41%)	
Lots	181 (23.4%)	59 (25.3%)	122 (22.5%)	
Hypertension (+), *n* (%)	153 (19.7%)	44 (18.9%)	109 (20.1%)	0.768
Diabetes (+), *n* (%)	64 (8.26%)	17 (7.30%)	47 (8.67%)	0.620
CHD (+), *n* (%)	48 (6.19%)	12 (5.15%)	36 (6.64%)	0.530
Neoadjuvant (+), *n* (%)	387 (49.9%)	111 (47.6%)	276 (50.9%)	0.447
Location of tumor				0.762
Upper	57 (7.35%)	16 (6.87%)	41 (7.56%)	
Middle	364 (47.0%)	106 (45.5%)	258 (47.6%)	
Lower	354 (45.7%)	111 (47.6%)	243 (44.8%)	
Position of anastomosis				0.298
Neck	741 (95.6%)	226 (97.0%)	515 (95.0%)	
Intrathoracic	34 (4.39%)	7 (3.00%)	27 (4.98%)	
Duration of surgery (min)	320 [288; 365]	323 [289; 363]	318 [288; 367]	0.692
Blood loss (mL)	97.3 [71.0; 123]	94.5 [71.0; 121]	98.4 [71.0; 123.3]	0.200
Pathological staging				0.975
0	59 (7.61%)	18 (7.73%)	41 (7.56%)	
1	217 (28.0%)	65 (27.9%)	152 (28.0%)	
2	208 (26.8%)	66 (28.3%)	142 (26.2%)	
3	267 (34.5%)	77 (33.0%)	190 (35.1%)	
4	24 (3.10%)	7 (3.00%)	17 (3.14%)	
Number of lymph node dissection	33.0 [25.0; 42.0]	32.0 [26.0; 42.0]	33.0 [25.0; 42.0]	0.999
Vascular invasion (+), *n* (%)	153 (19.8%)	44 (18.9%)	109 (20.1%)	0.759
Nerve infiltration (+), *n* (%)	217 (28.0%)	64 (27.5%)	154 (28.4%)	0.788
Hospitalization days (day)	10.0 [8.00; 14.0]	10.0 [8.00; 14.0]	11.0 [8.00; 14.0]	0.205
Neck extubation (day)	6.00 [4.00; 8.00]	6.00 [4.00; 8.00]	6.00 [4.00; 8.00]	0.143
Surgical methods				0.832
Thoracoscope	635 (81.9%)	191 (82.0%)	444 (81.9%)	
DVSS	140 (18.1%)	42 (18.0%)	98 (18.1%)	

EGAL esophagogastric anastomotic leakage, *FEV1* forced expiratory volume in the first second, *MVV* maximum ventilatory volume, *DVSS* da Vinci Surgical System

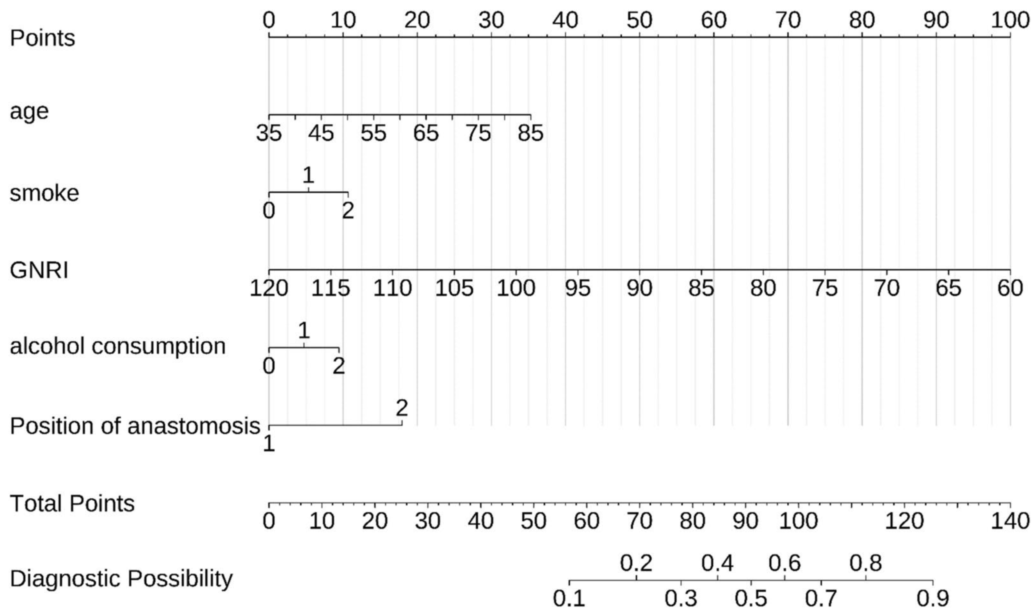

Fig. 2 A nomogram for occurrence of esophagogastric anastomotic leakage. To use the nomogram, the value for each predictor is determined by drawing a line upward to the point reference line, the points are summed, and a line is drawn downward from the total points line to find the predicted probability of node positivity

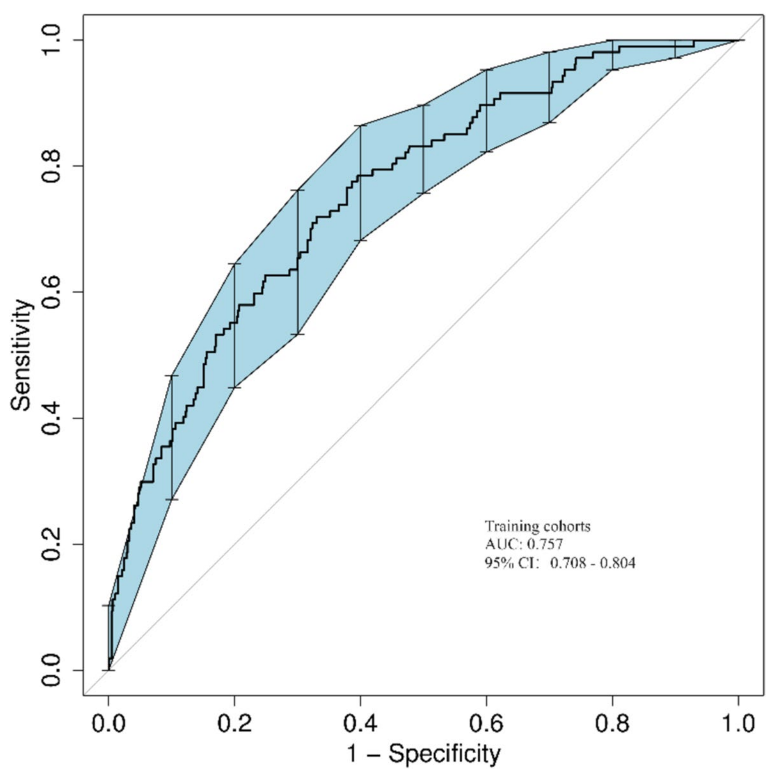

Fig. 3 Receiver operating characteristic (ROC) curves for the training group. The area under the curve (AUC) was 0.757 (95% *CI*: 0.715–0.853, *P* = 0.025)

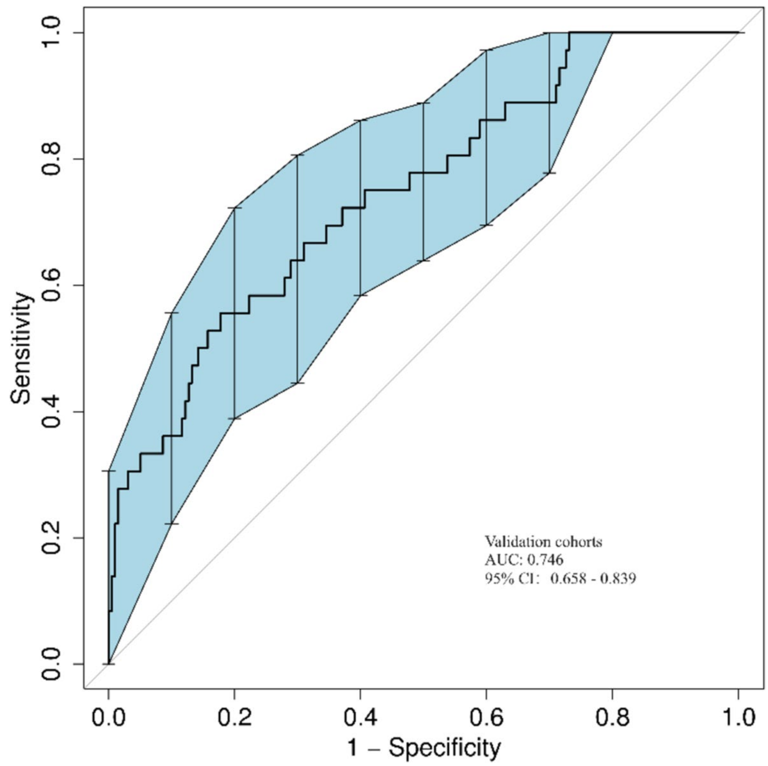

Fig. 4 Receiver operating characteristic (ROC) curves for the validation group. The area under the curve (AUC) was 0.746 (95% *CI*: 0.6588–0.839, *P* = 0.045)

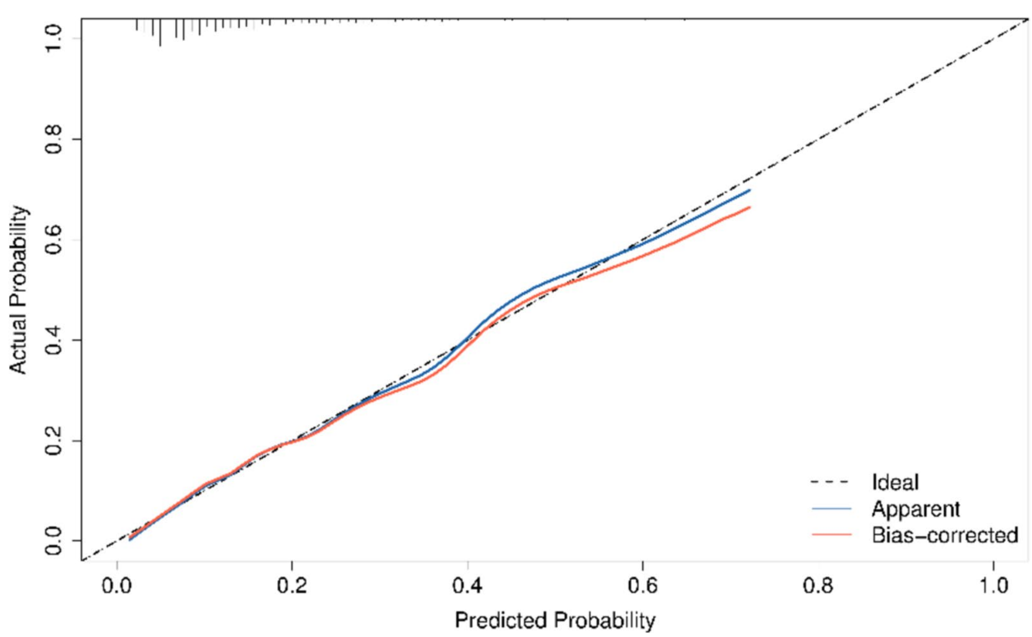

Fig. 5 Calibration curves for the training group, respectively

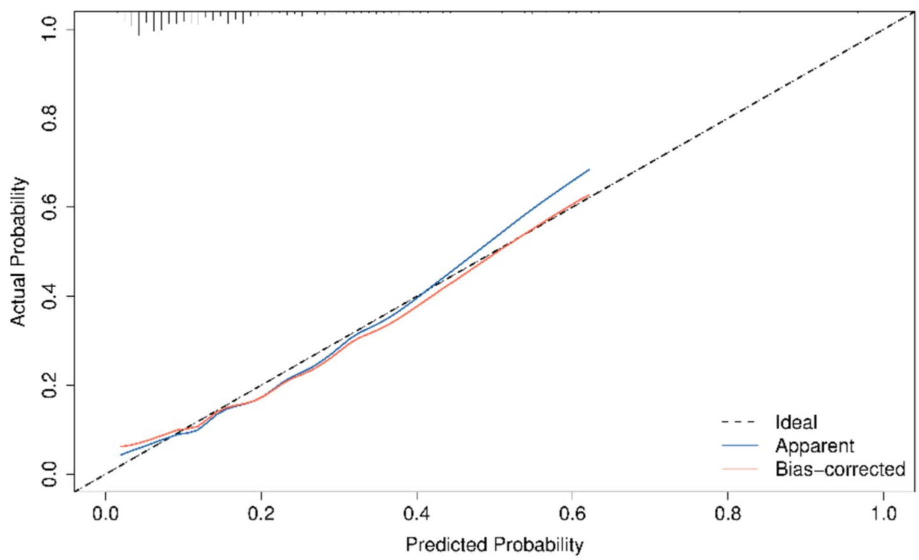

Fig. 6 Calibration curves for the validation group, respectively

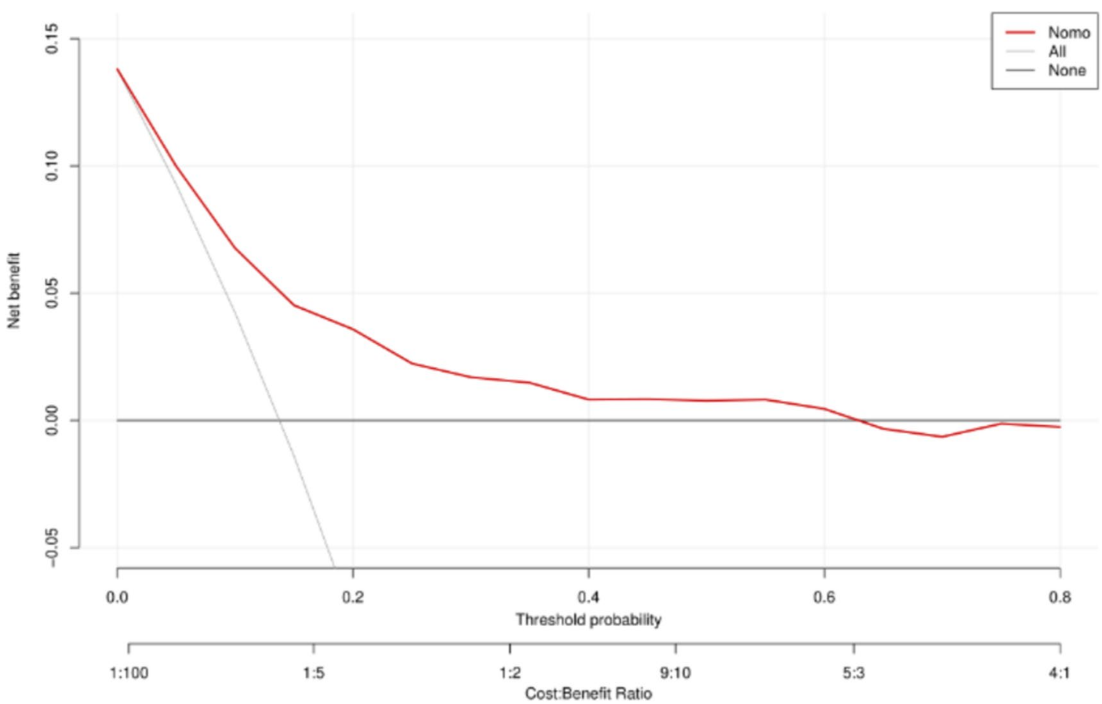

Fig. 7 The decision curve analysis (DCA) curve for the training group, respectively

high-risk malnourished patients, preoperative nutritional and exercise therapy may need to be considered, even if surgery must be delayed based on disease severity. Studies have shown that nutritional risk screening tools, such as the GNRI, are effective in identifying patients who require nutritional support and improving their postoperative outcomes (Turrentine et al. 2015). However, there is no specific nutritional assessment tool for preoperative patients with esophageal cancer. Nutrition risk screening (NRS 2002), a nutritional screening tool for hospitalized patients recommended by the guidelines of the European Society for Parenteral and Enteral Nutrition (ESPEN), is the first evidence-based nutritional risk screening tool in the world (Kondrup et al. 2002). Since the 1970s, there

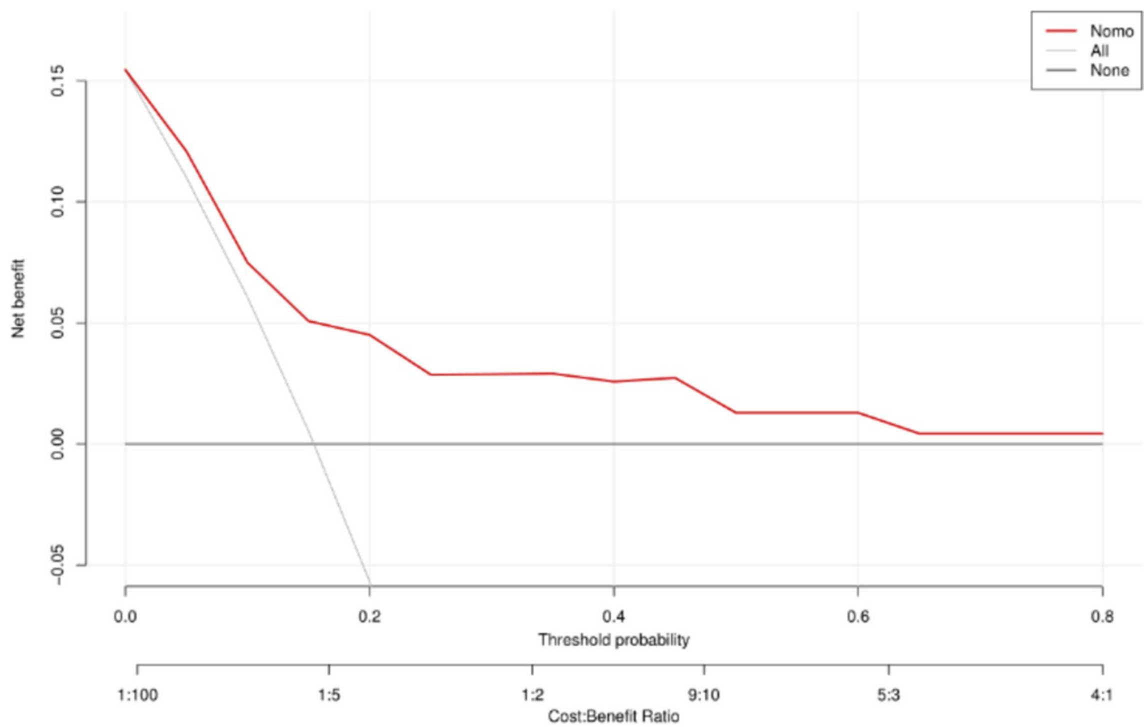

Fig. 8 The decision curve analysis (DCA) curve for the validation group, respectively

have been a variety of nutritional assessment methods such as the Mini Nutritional Assessment (MNA) (Rubenstein et al. 2001) and Malnutrition Universal Screening Tool (MUST) (Stratton et al. 2004). However, these nutritional assessment tools have certain limitations, and cannot avoid the interference of subjective assessment. Therefore, the GNRI, a nutritional assessment tool based on objective indicators, can more accurately reflect the nutritional status of patients (Yamada et al. 2008). Yamana et al. reported the effectiveness of the GNRI in screening for respiratory complications after radical resection of esophageal cancer (Yamana et al. 2015). Bo et al. reported the efficacy of the GNRI in predicting the prognosis of patients older than 60 years with esophageal squamous cell carcinoma who received radiotherapy (Bo et al. 2016). In this study, the GNRI was found to be an independent risk factor for EGAL, which also suggested that preoperative improvement in nutritional status in patients with esophageal cancer can improve the incidence of EGAL.

In addition, this study revealed that age is an independent risk factor for AL, and older patients are more prone to AL. It is speculated that older patients have poor physical condition, often with underlying disease, and weakened organ function, body compensation, and tissue repair function, which not only increases the risk of surgery but also increases the likelihood of postoperative complications (Schlottmann et al. 2018). In terms of sex, Gao C. (Gao et al. 2019) and Goense L. (Goense et al. 2017a) reported that EGAL was related to sex, and the incidence of EGAL in males was significantly greater than that in females. They believed that male sex was usually associated with poor living habits such as smoking and drinking. However, this study revealed no significant relationship between anastomotic leakage and sex. It is speculated that this may be related to the different living habits of people in different regions, which may be one of the reasons why the results of our study are different from those of other studies, but the details still need to be further explored.

Smoking is considered to be a risk factor for EGAL (Cooke et al. 2009), which is similar to the results of this study. However, the mechanism by which smoking affects EGAL is not fully understood. Previous studies have shown that smoking can cause tissue hypoxia and affect blood perfusion (Babayan 2012). In addition, long-term drinking invasion of the digestive tract can cause gastrointestinal mucosal ulcers, erosion, bleeding, and other injuries, and postoperative anastomotic infection can easily delay tissue healing (Goense et al. 2017b). Due to the adverse effects of smoking and drinking on perioperative patients, patients should be encouraged to quit smoking and drinking at any time.

Table 2 Differential analysis and multivariate logistic regression analysis of the result of anastomotic leak and clinical candidate predictors in the training set

	Differential analysis		Multivariate analysis	
	OR	***P***	**OR (95% *CI*)**	***P***
Sex (male/female)	1.21 [0.74; 1.94]	0.512		
Age (years)	1.04 [1.01; 1.07]	0.004	1.036 (1.003–1.071)	0.034
Smoking history		< 0.001	1.420 (1.096–1.841)	0.008
None	-			
Moderate	0.66 [0.31; 1.30]			
Lots	2.19 [1.40; 3.45]			
BMI (kg/m^2)	0.98 [0.91; 1.05]	0.538		
Weight (kg)	0.99 [0.97; 1.01]	0.368		
GNRI	0.89 [0.87; 0.92]	< 0.001	0.901 (0.873–0.931)	0.000
FEV1 (kg/m^2)	0.70 [0.51; 0.97]	0.040	0.913 (0.611–1.363)	0.656
MVV (L)	0.99 [0.97; 1.00]	0.006	0.991 (0.977–1.005)	0.185
Alcohol consumption:		< 0.001	1.385 (1.075–1.785)	0.012
None	-			
Moderate	0.70 [0.23; 1.65]			
Lots	2.37 [1.52; 3.67]			
Hypertension (no/yes)	1.21 [0.73; 1.96]	0.534		
Diabetes (no/yes)	1.19 [0.55; 2.32]	0.802		
CHD (no/yes)	1.09 [0.43; 2.36]	1.000		
Neoadjuvant (no/yes)	1.27 [0.85; 1.93]	0.291		
Location of tumor		0.270		
Upper	-			
Middle	1.33 [0.61; 3.38]			
Lower	0.95 [0.42; 2.43]			
Position of anastomosis		0.018	3.253 (1.381–7.664)	0.007
Neck	-			
Intrathoracic	2.79 [1.23; 5.88]			
Duration of surgery (min)	1.00 [1.00; 1.00]	0.493		
Blood loss (ml)	1.00 [1.00; 1.00]	0.978		
Pathological staging		0.322		
0	-			
1	0.51 [0.24; 1.12]			
2	0.73 [0.36; 1.59]			
3	0.55 [0.27; 1.19]			
4	0.80 [0.20; 2.67]			
Number of lymph node dissection	0.99 [0.97; 1.00]	0.098		
Vascular invasion (no/yes)	1.06 [0.63; 1.74]	0.927		
Nerve infiltration (no/yes)	1.173 [0.752–1.829]	0.556		
Hospitalization days (day)	1.14 [1.11; 1.16]	< 0.001		
Neck extubation (day)	1.10 [1.06; 1.14]	0.001		
Surgical methods		0.751		
Thoracoscope	-			
DVSS	1.13 [0.66; 1.87]			

It has been well established that cervical anastomosis is more likely to cause EGAL than thoracic anastomosis. A meta-analysis involving 13 centers revealed a significant increase in the incidence of EGAL in the cervical anastomosis group (Markar et al. 2013), and another meta-analysis involving four experiments reported similar results (Biere et al. 2011). Importantly, reasons are that the cervical anastomosis requires a longer tubular stomach, poor blood perfusion around the anastomosis, and the greater tension of the cervical anastomosis, and the superficial position of the neck increases the susceptibility of the anastomosis site to compression and ischemia. Although cervical anastomosis has a greater incidence of EGAL, because of the superficial position of cervical anastomosis, it is easy to detect EGAL earlier and treat it in quickly. In addition, this study revealed that neoadjuvant therapy was not a risk factor for EGAL. Kumagai et al. also reported that neoadjuvant therapy did not increase the incidence of EGAL (Kumagai et al. 2014). However, the timing of surgery after neoadjuvant therapy can affect the occurrence of EGAL and the long-term survival rate (Tsang et al. 2017). Whether neoadjuvant therapy increases the incidence of postoperative complications in patients with esophageal cancer still needs further study. The nomogram suggested that for patients with advanced age, long-term smoking, heavy drinking, malnutrition, and cervical anastomosis, we should pay attention to the possibility of anastomotic leakage after surgery. Preoperative respiratory rehabilitation has been shown to improve lung function and reduce postoperative complications in patients undergoing thoracic surgery and may benefit high-risk patients (Morano et al. 2013). Furthermore, for patients at high risk, implementing preoperative nutritional support and exercise interventions could reduce the likelihood of leakage and enhance recovery (Kondrup et al. 2002). In the event of anastomotic leakage, timely imaging and endoscopic diagnosis, as well as targeted treatment strategies, are critical to minimizing adverse outcomes (Table 2) (Goense et al. 2017b).

Limitations

There are several limitations in this study. First, this was a single-center retrospective study, which may introduce potential bias. Second, because external validation could not be performed, we performed internal validation only on the established nomograms. Third, since the purpose of this study was to predict postoperative anastomotic leakage, postoperative parameters, such as complications such as pneumonia, were not included. We will further verify the relationship between these parameters and anastomotic leakage in other studies.

Conclusion

Preoperative malnutrition is an independent risk factor for EGAL. A diagnostic model was developed based on age, anastomotic location, and smoking and drinking history. This model is a reliable noninvasive tool that can timely predict the occurrence of AL and aid in clinical decision-making on treatment selection to improve patient outcomes.

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Authors' contributions
Jiang-Shan Huang and Li-tao Yang and designed the study, performed the statistical analysis, participated in the operation. Jiang-Shan Huang was a major contributor in writing the manuscript. Jia-fu Zhu, Qi-hong Zhong and Fei-long Guo collected the clinical data. Zhen-yang Zhang and Jiang-bo Lin directed the design and statistical analysis and revised the writing of the manuscript. All authors read and approved the final manuscript.

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No.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The present study was approved by the ethics committee of Fujian Medical University Union Hospital and adhered to the tenets of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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