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Risk Factors for Postoperative Pneumonia in Esophageal Cancer Patients

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Purpose: Patients undergoing surgery for esophageal cancer (EC) frequently experience postoperative pneumonia (POP). POP promotes poor prognosis as well as increased medical costs and longer hospital stays. Therefore, it is desirable to prevent and strictly control high-risk cases to reduce the incidence of pneumonia. The present study aimed to determine the risk factors for POP in EC.

Patients and Methods: The subjects of this retrospective study were 151 patients with EC who underwent subtotal esophagectomy in our department between January 2012 and December 2021. Univariate and multivariate logistic regression analyses were used to evaluate the association between the incidence of POP and clinical factors.

Results: Among 151 patients, 33 cases (21.8%) developed POP. Multivariate analysis identified preoperative C-reactive protein-to-albumin ratio (CAR) $\geq$0.03 [odds ratio (OR), 2.69; $P = 0.0352$], chronic obstructive lung disease (COPD) (OR, 7.32; $P = 0.0001$), and diabetes mellitus (DM) (OR, 3.35; $P = 0.0252$) as independent risk factors for POP. In accordance with the number of risk factors, the incidence rate of POP drastically increased, and its rate in patients with 3 risk factors was 80%.

Conclusion: High CAR, COPD, and DM are independent risk factors for the development of POP in patients undergoing subtotal esophagectomy for EC. Clinicians should be aware

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of the risk factors for POP and consider more intensive preventive measures and postoperative management in patients with EC.

Key words: Esophageal cancer – Postoperative pneumonia – Risk factor – CAR

Esophagectomy with lymph node dissection for esophageal cancer (EC) is a highly invasive procedure that has high postoperative morbidity and mortality despite advances in surgical techniques and perioperative management.[1,2] Postoperative pneumonia (POP) is one of the most common complications after esophagectomy, with reported incidences ranging from 17% to 38%.[3–5] POP is associated with worse patient outcomes, including longer hospital stays and significantly higher inpatient care costs.[6–8] In addition, POP has been reported to have a negative impact on the long-term prognosis of patients with EC.[9]

In recent years, interventions such as preoperative respiratory muscle rehabilitation, oral care, and long-term administration of antibiotics have been reported to be useful in preventing POP.[10–12] Therefore, identifying risk factors or biomarkers that predict POP is important to select patients who require more intensive care and management.

Several studies demonstrated that multiple preoperative and perioperative risk factors are associated with POP, including older age, history of heavy smoking, reduced forced expiratory volume, nutritional status, preoperative definitive chemoradiotherapy, large volume of blood loss during surgery, and open thoracotomy.[13–17] Recently, preoperative inflammation and/or nutritional markers such as neutrophil-to-lymphocyte ratio (NLR), Glasgow prognostic score, and lymphocyte-C-reactive protein ratio (LCR) have also been reported as predictors of postoperative complications in patients with various cancer types.[18–20]

These measurable markers based on common blood tests are useful because they can be analyzed at any institute and objectively evaluated. However, few reports have examined the association between preoperative inflammation and/or nutritional markers and POP after surgery for EC.[15,21]

Therefore, in this study, we investigated whether preoperative factors, including preoperative inflammation and/or nutritional markers calculated from routine laboratory data, could help predict POP.

Materials and Methods

Patients and perioperative management

Between January 2012 and December 2021, 181 patients underwent esophagectomy with lymphadenectomy for esophageal or esophagogastric junction cancer at the Department of Gastrointestinal and Pediatric Surgery of Mie University Graduate School of Medicine. After the exclusion of 30 patients who did not undergo subtotal esophagectomy, 151 patients were enrolled in this study. Consent was obtained on an opt-out basis, and any patients who did not wish to provide their medical information were excluded from the study. This study was approved by the institutional review boards of Mie University Hospital. Routine preoperative screening included endoscopy and computed tomography from the neck to the pelvis. For cases clinically diagnosed as stage II or III, except for those older than 75 years or those with creatinine clearance of less than 30 mL/min, we performed esophagectomy with neoadjuvant chemotherapy using fluoropyrimidine plus platinum regimens, including fluorouracil and cisplatin, which have become the standard treatment choice in Japan.[22] Subtotal esophagectomy and dissection of the thoracic lymph nodes through a thoracoscopic approach were performed with the patient in the prone position with artificial pneumothorax but while maintaining respiratory function whenever possible. Three-field lymphadenectomy was performed in all patients except those with early EC located in the lower or abdominal esophagus. The degree of mediastinal lymph node dissection was the same in patients with superficial disease as in those with advanced cancer. The right gastric artery, right gastroepiploic artery, and branches of the left gastroepiploic arteries were preserved and provided vascular supply to the gastric wall through an arcade of peripheral vessels.

Patients were transferred to the intensive care unit after surgery and returned to the ward on the basis of extubation the next morning. A feeding jejunostomy was placed routinely and enteral feeding was started from postoperative day 1. Antibiotics were administered 30 minutes before the surgery and then every 3 hours during the surgery.

Perioperative data collection

We recorded patient characteristics including demographic data [sex, age, body mass index, American Society of Anesthesiologists classification, comorbidities including diabetes mellitus (DM), history of smoking, and past medical history], tumor-specific data (tumor location and pathological stage) according to the Japanese classification of EC (11th ed),[23] surgery-related factors [estimated blood loss, duration of surgery, and approach used for abdominal surgery (laparoscopic or open laparotomy)], and postoperative complications (surgical site infection, anastomotic leak, and recurrent laryngeal nerve paralysis). Patients' blood samples were obtained within 3 days before surgery. Neutrophil and lymphocyte counts, as well as C-reactive protein (CRP) and albumin levels, were measured. All patients underwent pulmonary function testing before surgery, and chronic obstructive lung disease (COPD) was defined as a 1-second rate of less than 70%.

Definition of postoperative pneumonia

We defined POP as pneumonia that developed within 30 days after surgery, and pneumonia that was characterized by a fever of 38 degrees or higher, elevation of inflammatory markers (white blood cells and CRP), and infiltrative shadows on X-ray or computed tomography.

Definition of inflammation and/or nutritional markers

The inflammation and/or nutrition-based markers examined in this study were as follows: C-reactive protein-to-albumin ratio (CAR),[24] NLR,[25] LCR,[20] and prognostic nutritional index (PNI), which was calculated by the formula 10 $\times$ albumin (g/dL) + 0.005 $\times$ lymphocyte count/μL.[26]

The Youden index was calculated by receiver operating characteristic (ROC) analysis to determine an optimal cutoff value for POP in esophagectomy in association with each inflammatory factor (CAR, NLR, LCR, and PNI).

Measurements and statistical analysis

To compare clinical parameters between the groups with and without POP, the χ^2 test was used for categorical variables and the Wilcoxon signed-rank test was used for continuous variables. Values are shown as mean ± SD. ROC curves were established for 4 inflammatory and/or nutritional markers, and their area under the curve (AUC) values were compared. Cutoff values in the logistic regression analysis were tested using ROC for CAR, LCR, NLR, and PNI. Cutoff values of the Brinkman index were defined according to the median value. Risk factors of POP were examined using univariate and multivariate logistic regression models. Risk stratification of POP by 3 risk factors was estimated by logistic regression analysis.

A 2-sided *P* value of <0.05 was considered statistically significant. Statistical analyses were conducted with the JMP 13.1 software program (SAS Inc, Cary, North Carolina).

Table 1 Patients' characteristics

	N = 151
Age (y)	67.4 ± 8.80
Gender (male, %)	133 (88.1)
BMI (kg/m^2)	21.8 ± 3.4
ASA classification ≧3, n (%)	7 (4.6)
Diabetes mellitus, n (%)	27 (17.8)
Dementia, n (%)	5 (3.3)
Brinkman Index	719 ± 538.4
COPD, n (%)	32 (21.2)
Cardiovascular disease, n (%)	75 (49.6)
Stage (0/I/II/III/IV)	18/49/35/38/11
Tumor location (Ce/Ut/Mt/Lt)	2/10/66/73
Neoadjuvant chemotherapy, n (%)	52 (34.4)
Thoracoscopy, n (%)	144 (95.3)
Laparoscopy, n (%)	64 (42.3)
Three-field lymphadenectomy, n (%)	66 (43.7)
Estimated blood loss (g)	425.7 ± 414.8
Duration of surgery (min)	584 ± 125.5

ASA, American Society of Anesthesiologists; BMI, body mass index; Ce, cervical esophagus; Lt, lower thoracic esophagus; Mt, middle thoracic esophagus; Ut, upper thoracic esophagus.

Age, Brinkman index, estimated blood loss, and duration of surgery data are shown as median ± SD.

Results

Patients' characteristics

The patients' demographic and pre- and perioperative characteristics are presented in Table 1. The median ± SD age was 67.4 ± 8.8 years, and the male ratio was 88.1%. Presence of DM, dementia, COPD, and cardiovascular disease was 17.8%, 3.3%, 2.2%, and 49.6%, respectively. The most frequent tumor location was the lower thoracic esophagus.

Preoperative clinical staging classified 18, 49, 35, 38, and 11 patients with TNM stages 0, I, II, III, and IV, respectively. Neoadjuvant treatment was administered to 52 (34.4%) patients. Thoracoscopic and laparoscopic procedures were performed in 95.3%

Table 2 Relationship between postoperative pneumonia and preoperative factors

Category	All (N = 151)	POP (−) (n = 118)	POP (+) (n = 33)	*P* value
Age (y)	67.4 ± 8.80	66.9 ± 9.23	69.4 ± 6.83	0.15
Gender				
Male	133	102	31	0.21
Female	18	16	2	
BMI (kg/m^2)	21.8 ± 3.4	22.03 ± 3.59	21.04 ± 2.5	0.23
ASA classification				
2>	144	114	30	0.21
3≦	7	4	3	
Tumor location (Ut)	11 (7.3)	8/110	3/30	0.66
Stage (I / II,III,IV)		64/54	20/13	0.51
Neoadjuvant chemotherapy				0.17
Non	99	81	18	
Fluoropyrimidine plus platinum	52	37	15	
Diabetes mellitus, n (%)	27 (17.8)	16 (13.6)	11 (33.3)	**0.013**
Dementia, n (%)	5 (3.3)	3 (2.5)	2 (6.1)	0.35
Brinkman Index	719 ± 538.4	638.8 ± 514	997.9 ± 534	**0.002**
COPD, n (%)	32 (21.2)	15 (12.7)	17 (51.5)	**<0.0001**
Cardiovascular disease, n (%)	75 (49.6)	61 (51.7)	15 (45.5)	0.53
CAR	0.12 ± 0.36	0.09 ± 0.28	0.23 ± 0.55	**0.004**
LCR	32887.3 ± 70425.4	37984.8 ± 78534.2	14968 ± 18670	**0.006**
NLR	2.61 ± 1.61	2.50 ± 1.61	2.97 ± 1.54	**0.03**
PNI	50 ± 7.82	50.5 ± 8.35	48.0 ± 5.15	**0.02**

Bold values indicate statistical significance. Data are presented as mean ± SD.

ASA, American Society of Anesthesiologists; BMI, body mass index; CAR, C-reactive protein-to-albumin ratio; LCR, lymphocyte-to-C-reactive protein ratio; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; POP postoperative pneumonia; Ut, upper thoracic esophagus.

and 42.3% of cases, respectively. Surgical duration and estimated blood loss were 584 ± 125.5 minutes and 425.7 ± 414.8 g, respectively.

Relationship between postoperative pneumonia and preoperative factors

POP developed in 33 patients (21.8%). In terms of preoperative factors, patients with POP had a significantly higher prevalence of COPD and DM; a greater Brinkman index; higher preoperative CAR, NLR, and LCR; and lower preoperative PNI compared with patients without POP. In contrast, sex, age, American Society of Anesthesiologists classification, clinical stage, and the presence or absence of preoperative chemotherapy did not differ between the groups (Table 2).

In terms of intraoperative and postoperative factors, there were no significant differences between both groups in operation time, estimate of blood loss, tumor location, extent of dissection (2 or 3 fields), surgical site infection, anastomotic leakage, or recurrent laryngeal nerve paralysis. However, patients with POP had significantly longer hospital stay after surgery (Table 3).

Cutoff value of CAR, NLR, LCR, and PNI calculated by ROC curve analysis

We performed ROC analyses to define the optimal cutoff values of preoperative CAR, NLR, LCR, and PNI for POP after esophagectomy. In addition, we compared the AUC values of 4 biomarkers for predicting POP (Fig. 1). As a result, CAR demonstrated the highest AUC value of 0.66667, suggesting its potential as a candidate marker for POP in esophagectomy.

Multivariate analyses of factors associated with POP

Using the preoperative factors that were significantly associated with POP, we performed multivariate logistic regression analysis to investigate independent risk factors. DM, COPD, and high CAR were shown to be independent risk factors for POP after subtotal esophagectomy, as shown in Table 4.

Risk stratification of POP using a combination of DM, COPD, and high CAR

The number of risk factors was significantly associated with an increased risk of POP ($P < 0.001$). The combination of specific preoperative clinical factors

Table 3 Relationship between postoperative pneumonia and surgical factors

Category	POP (−) (n = 118)	POP (+) (n = 33)	*P* value
Duration of surgery (min)	610.6 ± 119.8	611.5 ± 150.3	0.54
Estimated blood loss (g)	419.6 ± 437.1	447.6 ± 327.9	0.15
Approach (laparotomy / laparoscopic)	65/53	11/22	0.23
Lymphadectomy (3-field/2-field)	52/66	14/19	0.94
Surgical site infection, n (%)	7 (5.9)	1 (3.0)	0.48
Anastomotic leakage, n (%)	6 (5.1)	4 (12.1)	0.18
Recurrent nerve paralysis, n (%)	17 (14.4)	7 (21.2)	0.37
Duration of hospital stay (d)	27.88 ± 14.7	35.9 ± 14.4	**0.002**

Bold value indicates statistical significance. Data are presented as mean ± SD.
POP, postoperative pneumonia.

improved prediction of POP in EC. We performed combined ROC analysis using independent preoperative predictors COPD, DM, and high CAR to determine whether this approach can improve the predictive accuracy for POP in EC. The combination of these 3 risk factors successfully identified patients harboring POP, with a high AUC value of 0.77337 (sensitivity, 51.5%; specificity, 89.8%) and an optimal cutoff score of 2 (Fig. 2). Compared with the overall population, patients with 1 or fewer risk factors had a lower risk, and patients with 2 or more risk factors had a significantly higher risk. The risk of POP was 13.8% in patients with 0 to 1 risk factor [odds ratio (OR), 0.12; 95% confidence interval (CI), 0.04–0.29], 52.2% in patients with 2 risk factors (OR, 5.56; 95% CI, 2.16–14.5), and 80.0% in patients with 3 risk factors (OR, 16.13; 95% CI, 1.73–149.8). The association between the number of risk factors and the incidence of POP is shown in Table 5.

Discussion

We evaluated preoperative and surgery-related factors correlated with POP after subtotal esophagectomy. COPD, DM, and high CAR (>0.03) were identified as independent predictors of POP. In our study, 33 (21.9%) patients developed POP after subtotal esophagectomy; this incidence rate was similar to that of several previous studies.[3–5]

There are various reports on the risk factors of POP in EC. As in the present study, it is well documented that low lung function, especially decrease in forced expiratory volume 1.0%, and DM are risk factors.

In general, patients with pulmonary diseases such as COPD and restrictive lung disease have a higher rate of POP than those without pulmonary diseases. Both Takahashi *et al*[14] and Kinugasa *et al*[9] demonstrated that low forced expiratory volume and COPD are independent risk factors for POP in patients undergoing esophagectomy. COPD is a disease characterized by compromised airway defenses, increasing susceptibility to pneumonia, and is difficult to cure. Therefore, in COPD cases, efforts are made to prevent pneumonia through physical therapy and postoperative pulmonary exercise.[27] Furthermore, in terms of prophylactic agents, a prospective study is ongoing to investigate the efficacy of inhaled drugs in EC patients with COPD using the incidence of postoperative pneumonia as an endpoint.[28]

DM has also been reported as a risk factor for POP in various cancers. This increased risk might be associated with immunosuppression caused by DM. Miki *et al*[29] demonstrated that DM increased the risk of postoperative pneumonia by 2.46-fold in patients with gastric cancer after gastrectomy, and Ma *et al*[30] showed in a study of 43,174 inpatients with surgery that the incidence of POP and mortality was higher in patients with DM than in non-DM patients. Strict control of blood glucose levels using an intensive perioperative protocol has been reported to reduce the incidence of surgical site infection.[31] However, it is not clear whether control of blood glucose can reduce the incidence of POP, and further investigations are required.

Few studies have revealed a relationship between inflammation and/or nutrition-related markers and POP in patients with EC. Zhang *et al*[21] reported that NLR is a predictor of POP in patients with EC treated with neoadjuvant therapy. Baba *et al*[15] also reported that PNI is a predictor of POP in general and digestive surgery including esophagectomy. However, these reports did not refer to CAR as a risk factor for POP. In our study, we investigated 4 inflammation and/or nutrition-related markers, NLR, LCR, CAR, and PNI, each of which was

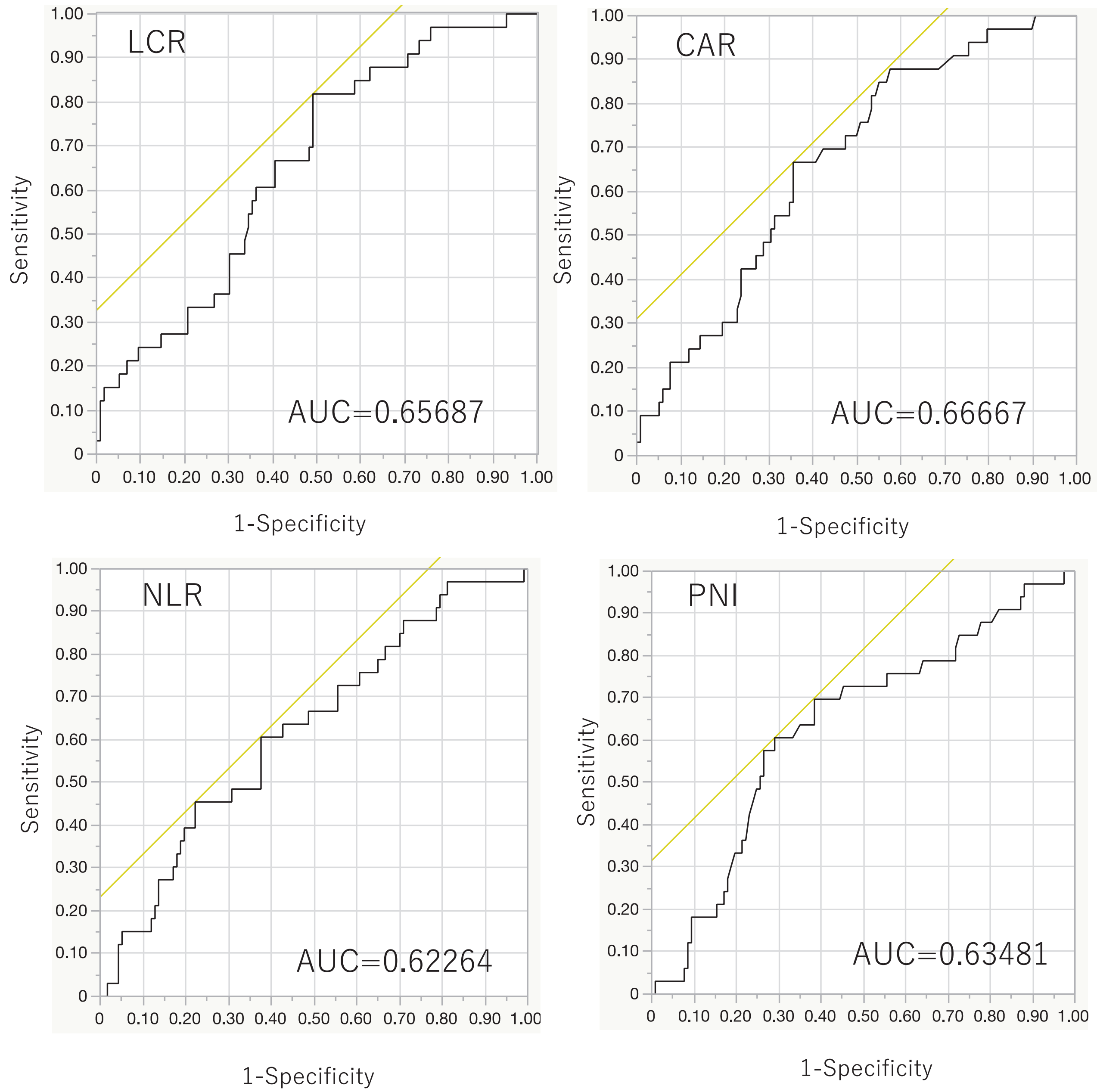

Fig. 1 ROC curve analysis to evaluate the predictive values of 4 inflammatory and/or nutritional biomarkers for POP. CAR had the highest AUC value (0.66667).

significantly associated with POP. Therefore, we determined which inflammation- and/or nutritional-related markers were best in predicting the incidence of POP by ROC analyses, and revealed that CAR was the most potent biomarker among them.

Albumin is used as a simple nutritional marker in gastrointestinal surgeries. Patients with EC are at risk of malnutrition and systemic inflammation because of several factors such as cancer-induced higher metabolism, reduced dietary intake by obstruction due to stricture caused by the tumor, protein turnover, and cachexia.[32] Malnutrition leads to reduced performance status and weak respiratory muscles, and is associated with a high risk of POP. The presence of systemic inflammation, as indicated by a high CRP level, is also associated with weight loss in patients with various solid tumor types.[33–35] Therefore, both high CRP and low albumin levels

Table 4 Multivariate analyses of risk factors for postoperative pneumonia

	OR (95% CI)	*P* value
Diabetes mellitus	3.35 (1.16–9.70)	**0.03**
COPD	7.32 (2.63–20.4)	**<0.001**
High CAR	2.69 (1.07–6.78)	**0.04**
B-index ≧ 710	1.21 (0.44–3.26)	0.71

Bold values indicate statistical significance.

B-index, Brinkman index; CAR, C-reactive protein albumin ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

(which can equate to high CAR) might be linked to malnutrition followed by postoperative POP.

Matsui *et al*[36] demonstrated that the sputum culture on the first postoperative day after esophagectomy was an independent risk factor for POP. In addition, Yoshida *et al*[37] showed that the sputum in the respiratory tract on preoperative computed tomography is a novel predictor of POP in patients with esophagectomy. These results may indicate that micro intratracheal infections without clinical symptoms from before surgery could be important risk factors for inducing POP. In our study, CAR was significantly higher in patients who required preoperative decompression for esophageal strictures (data not shown). Therefore, high CAR levels may reflect not only the effects of cancer-induced systemic inflammation but also bacterial infection from silent aspiration before surgery, suggesting that patients with high CAR levels have a higher risk of developing POP.

Both CRP and albumin are routinely ordered in blood screening panels, and although they certainly do have merit in isolation, they can be combined as a tool for risk stratification of POP. In the present study, we determined the optimal cutoff of CAR to be 0.03; values equal to or higher than this were associated with a 2.69-fold increased risk of POP. This is a high-magnitude association, suggesting its promising role for predicting POP. However, the diagnostic accuracy of each single parameter of COPD, DM, and high CAR was underpowered. Therefore, we performed a combined ROC analysis using the identified independent clinical risk factors to evaluate whether the diagnostic accuracy of POP can be increased. As expected, combining independent risk factors could increase diagnostic accuracy (AUC = 0.77337) with 51.5% sensitivity and 89.8% specificity. In addition, risk stratification suggested that patients with 1 risk factor or fewer were found to be less likely to develop POP than the remaining population. Conversely, patients with 2 or more risk factors were more likely to develop POP. This risk stratification provides a simple method to identify high-risk patients with POP. Using this method, patients who are at significantly greater

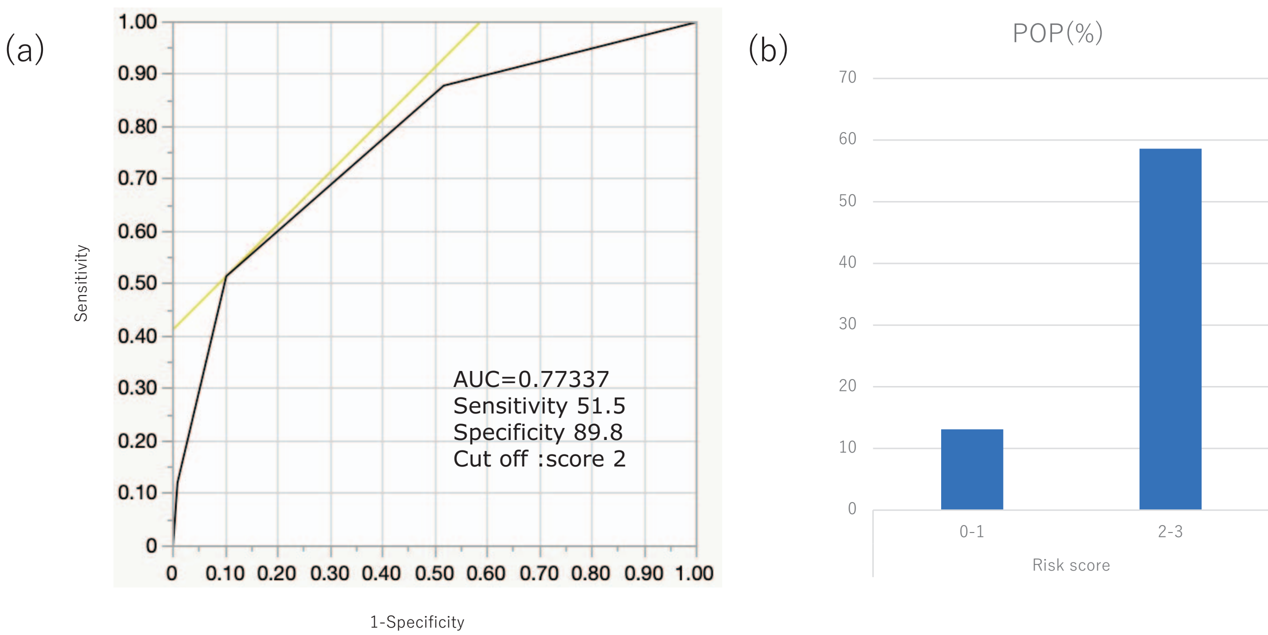

Fig. 2 (a) Predictive value of the combination of COPD, DM, and high CAR for POP. (b) Percentage of POP cases classified as having more and less than 2 preoperative risk factors (COPD, DM, and high CAR).

Table 5 Association between the number of risk factors and the incidence of postoperative pneumonia

Risk factors	All	0–1	2	3	*P* value
Number of patients	151	123	23	5	
Incidence of POP (%)	21.8	13.8	52.2	80	**<0.0001**
OR (95% CI)	1	0.12 (0.04–0.29)	5.55 (2.16–14.2)	16.13 (1.73–149.8)	

Bold value indicates statistical significance.
CI, confidence interval; OR, odds ratio; POP, postoperative pneumonia.

risk could benefit from more frequent monitoring and access effective preventive interventions and timely responses.

We acknowledge several potential limitations of this study. First, it was a retrospective study at a single institution with a small sample size. However, the surgical procedures (R0 resection plus subtotal esophagectomy with lymphadenectomy), laboratory examinations, and follow-up were uniform throughout the entire study period. Another limitation is the heterogeneity in the patients' pre- and postsurgical treatments, especially their adjuvant chemotherapy. Third, we identified DM as a risk factor for pneumonia, but in individual cases we could not go so far as to examine whether blood sugar control had been properly performed. We believe that future studies are needed to determine whether the control of blood glucose can be used to prevent POP. Finally, the cutoff value of CAR in this study is likely to be biased because it was selected using ROC analysis. Therefore, independent studies are needed to confirm our results.

Conclusion

We show that the combination of COPD, DM, and preoperative high CAR serves as a significant predictor of POP for patients with EC undergoing subtotal esophagectomy. Active medical intervention for the prevention of POP in patients with multiple risk factors may improve the postoperative quality of life for patients with EC.

Acknowledgments

The authors declare that they have no competing interests. Informed consent was obtained on an opt-out basis, and any patients who did not wish to provide their medical information were excluded from the study. This study was approved by the institutional review board of Mie University Hospital (Registration Number: 2023–132).

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