Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Predicting Postoperative Pneumonia in ESCC After Neoadjuvant Chemo-Immunotherapy: Combined Use of ARISCAT Score and Inflammatory Biomarkers

Jiexia Ding*, Jianqiang Zhao*, Tingting Qin, Changying Liu, Yueqin Yang, Dafu Xu, Yunyun Chen*, Zhiyun Xu*

Department of Thoracic Surgery, The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, Huai'an, 223300, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhiyun Xu; Yunyun Chen, Email zhiyunxu2012@njmu.edu.cn; sarah3808@163.com

Background: Postoperative pneumonia is a common and serious complication after McKeown esophagectomy for esophageal squamous cell carcinoma (ESCC), particularly in patients receiving neoadjuvant chemo-immunotherapy. The ARISCAT score is widely used for pulmonary risk assessment in general surgery, but its predictive value in this specific oncologic setting remains unclear.

Methods: We retrospectively analyzed 312 patients with resectable ESCC who underwent two cycles of platinum-based chemotherapy plus camrelizumab followed by McKeown esophagectomy between 2018 and 2023. Preoperative ARISCAT scores, neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII) were recorded. The primary outcome was pneumonia within 30 days postoperatively, diagnosed by standardized criteria. Logistic regression identified independent predictors, and restricted cubic splines (RCS) assessed dose–response patterns. Model discrimination and calibration were evaluated using AUC, Brier score, and calibration plots.

Results: Postoperative pneumonia occurred in 86 patients (27.6%). Compared with unaffected patients, those with pneumonia had higher ARISCAT scores (53.9 vs 37.4), NLR (8.3 vs 4.9), and SII (1379.8 vs 917.2) (all $p < 0.001$). Multivariable analysis confirmed ARISCAT (OR 1.43, 95% CI 1.26–1.62), NLR (OR 1.66, 95% CI 1.31–2.10), and SII (OR 1.09, 95% CI 1.02–1.71) as independent predictors. RCS showed a linear association for ARISCAT (p_non-linearity = 0.794) and threshold effects for NLR (>≈5.0) and SII (>≈1300) (both p_non-linearity < 0.05). The combined model (ARISCAT + NLR + SII) demonstrated superior discrimination (AUC 0.962) and calibration (Brier score 0.152) compared with individual predictors.

Conclusion: In ESCC patients undergoing McKeown esophagectomy after neoadjuvant chemo-immunotherapy, the ARISCAT score independently predicts postoperative pneumonia risk. Integrating ARISCAT with inflammatory biomarkers enhances predictive performance, enabling refined preoperative risk stratification and potentially guiding targeted preventive strategies. Prospective multicenter validation is warranted.

Keywords: esophageal squamous cell carcinoma, ARISCAT score, postoperative pneumonia, neoadjuvant chemo-immunotherapy, inflammatory biomarkers, risk prediction

Introduction

Esophageal squamous cell carcinoma (ESCC) represents a major public health challenge in East Asia, particularly in China, where it accounts for a significant proportion of cancer-related morbidity and mortality.[1–3] Although the advent of minimally invasive surgical techniques and neoadjuvant multimodal therapies has improved management strategies, the overall prognosis for patients with locally advanced ESCC remains guarded.[4–6] Postoperative complications, especially pulmonary infections such as pneumonia, continue to undermine surgical success and impede long-term survival.[7–9]

Received: 7 June 2025
Accepted: 3 September 2025
Published: 16 September 2025

Postoperative pneumonia is not only common but also clinically consequential, leading to prolonged hospitalization, increased perioperative morbidity, and elevated healthcare costs.[10–12]

In recent years, neoadjuvant chemo-immunotherapy has emerged as a promising approach for treating locally advanced ESCC, enhancing pathological complete response rates and increasing the likelihood of curative resection.[13–15] However, this treatment modality may also compromise immune and nutritional reserves, thereby predisposing patients to infectious complications during the perioperative period.[16–18] The McKeown esophagectomy—although effective for complete tumor clearance—adds an additional layer of risk due to its complexity and proximity to vital respiratory structures.[19,20] These factors synergistically heighten the incidence of postoperative pneumonia, necessitating accurate risk stratification tools tailored to this high-risk population.

Currently, postoperative pneumonia is typically diagnosed based on criteria proposed by the Centers for Disease Control and Prevention (CDC) and the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA), which include new pulmonary infiltrates on imaging, signs of systemic inflammation (such as fever and leukocytosis), and respiratory symptoms (such as purulent sputum or cough with abnormal auscultation findings).[21–24] Although these criteria are widely accepted, they are usually applied retrospectively and offer limited utility in identifying high-risk individuals before surgery. This highlights the need for preoperative tools that can proactively assess pneumonia risk and guide clinical decision-making.

One such tool is the ARISCAT (Assess Respiratory Risk in Surgical Patients in Catalonia) score, which integrates key preoperative variables—including age, hemoglobin concentration, peripheral oxygen saturation, recent lower respiratory infection, and surgical characteristics—into a unified pulmonary risk model.[25–28] Its practical advantages lie in its ease of use, reliance on routinely available clinical parameters, and potential to inform perioperative management. In clinical scenarios, this score may aid in tailoring prehabilitation plans, allocating intensive care resources, and implementing preventive strategies such as pulmonary physiotherapy or prophylactic antibiotics. Despite its validation in general surgical populations, the ARISCAT score has rarely been examined in thoracic oncology, particularly in ESCC patients treated with modern neoadjuvant immunotherapy. Clarifying its predictive utility in this specific setting may help bridge a critical gap in preoperative risk stratification.

To address this, we conducted a retrospective analysis of 312 ESCC patients who received two cycles of neoadjuvant chemo-immunotherapy followed by McKeown esophagectomy. The primary objective was to assess the predictive value of the ARISCAT score for postoperative pneumonia in this specific clinical context. Additionally, we explored the interactions between ARISCAT scores, systemic inflammation indices (NLR, SII), and postoperative recovery metrics such as hospital length of stay. Through this study, we aim to refine risk stratification strategies and inform perioperative decision-making to mitigate pulmonary complications in high-risk ESCC patients.

Methods

Study Design and Population

As illustrated in Figure 1, we conducted a retrospective, single-center cohort study of consecutive patients with pathologically confirmed esophageal squamous cell carcinoma (ESCC) who underwent neoadjuvant chemo-immunotherapy followed by McKeown esophagectomy at the Affiliated Huai'an No.1 People's Hospital of Nanjing Medical University between January 2018 and December 2023. Inclusion criteria: (1) histologically proven ESCC; (2) completion of two cycles of platinum-based chemotherapy plus a PD-1 inhibitor (Camrelizumab); (3) R0 resection via McKeown approach; and (4) complete baseline, perioperative and outcome data. Exclusion criteria: (1) chronic pre-existing pulmonary disease (eg, COPD), (2) prior thoracic surgery or other active malignancies, or (3) missing key covariates required for modeling. The protocol was approved by the institutional ethics committee (Approval No. KY-2024-374-01); informed consent was waived due to the retrospective design.

Treatment Regimen and Perioperative Management

All patients received a uniform neoadjuvant regimen (two cycles of platinum-based doublet plus Camrelizumab), minimizing therapeutic heterogeneity. Perioperative antibiotic prophylaxis and enhanced recovery protocols followed

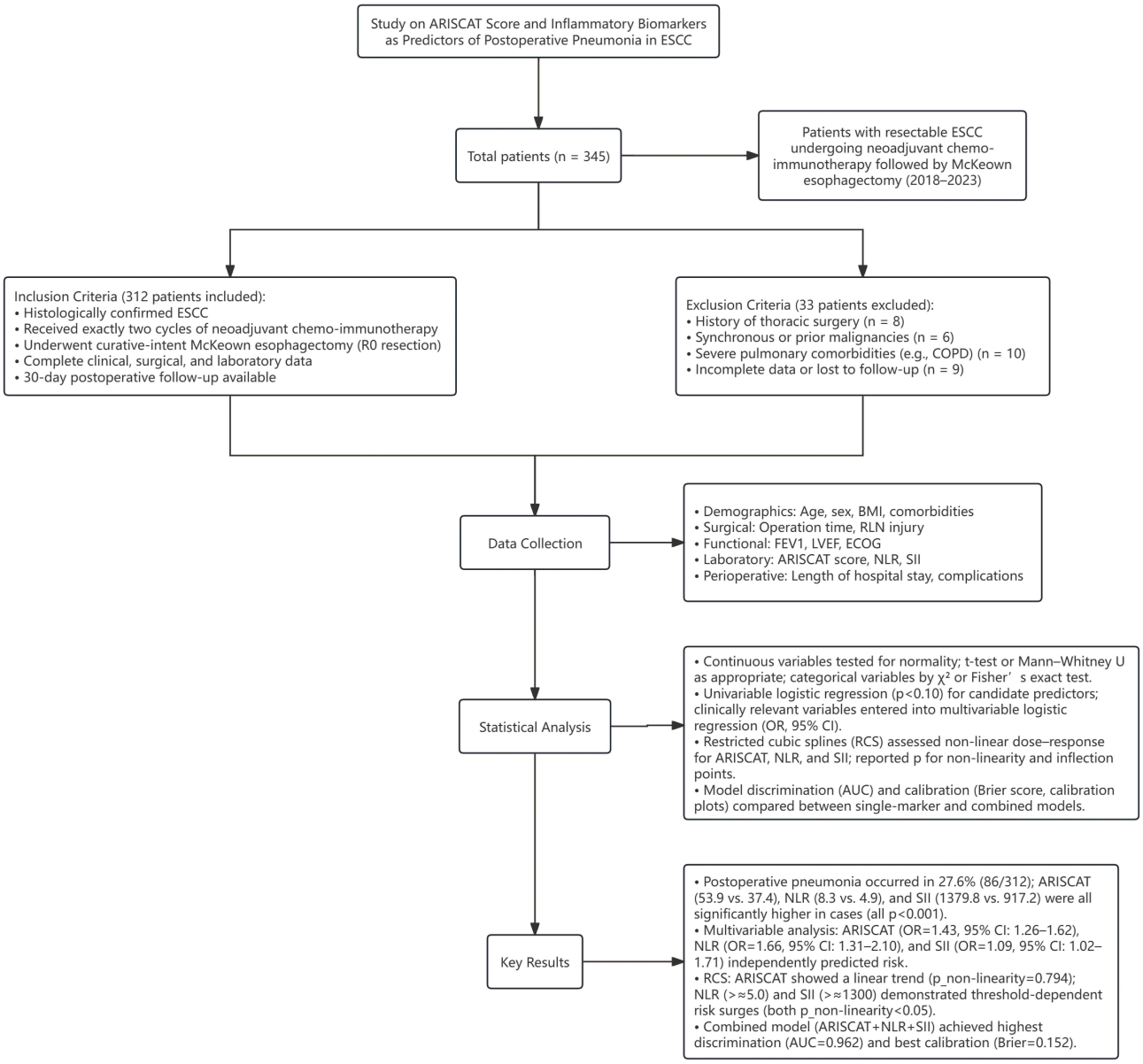

Figure 1 Flowchart of the Study Population and Analysis Framework. Patients with resectable ESCC treated with neoadjuvant chemo-immunotherapy followed by McKeown esophagectomy were retrospectively screened. After applying inclusion and exclusion criteria, 312 cases were analyzed. ARISCAT scores and inflammatory markers were evaluated preoperatively, and the occurrence of postoperative pneumonia within 30 days was assessed for predictive modeling.

institutional standards and did not differ meaningfully across patients; detailed antibiotic timing/intensity was not modeled as a covariate and is discussed as a potential source of residual confounding in the limitations.

Outcomes and Definitions

The primary outcome was postoperative pneumonia within 30 days of surgery, diagnosed per CDC/NHSN criteria: new or progressive pulmonary infiltrates on chest radiography/CT plus evidence of systemic inflammatory response (leukocytosis $>12\times10^9$/L or leukopenia $<4\times10^9$/L with fever >38 °C and/or altered mental status) and ≥2 clinical features (eg, purulent sputum, change in sputum characteristics, increased secretions requiring suctioning, or dyspnea). All suspected cases were adjudicated by two clinicians.

https://doi.org/10.2147/JIR.S545333

Data Collection and Timing of Measurements

Demographic characteristics (age, sex, BMI), comorbidities (hypertension, diabetes, coronary heart disease), lifestyle factors (smoking/drinking), cardiopulmonary function (FEV1, FEV1/FVC, LVEF, ECOG), operative variables (operative duration, recurrent laryngeal nerve palsy), and tumor features (site, length, clinical/ypTNM) were extracted from the electronic medical record by trained nurses. NLR was calculated as the ratio of absolute neutrophil count to absolute lymphocyte count. SII was calculated as platelet count × neutrophil count / lymphocyte count.

ARISCAT Calculation and Risk Strata

The ARISCAT score was calculated from seven preoperative variables (age, SpO_2, recent lower respiratory infection, hemoglobin <10 g/dL, incision site/surgical field, operative duration, and urgency) according to published algorithms. For descriptive analyses, ARISCAT was also categorized as low (0–25), intermediate (26–44), and high (≥45). Pneumonia incidence was summarized across strata to demonstrate risk gradient.

Handling of Missing Data and Data Quality

Data entry followed standardized procedures by trained staff. Records with missing key covariates required for multivariable modeling were excluded listwise. For non-critical variables with <5% missingness, we applied multiple imputation by chained equations (MICE) (20 imputations), pooling effect estimates per Rubin's rules. Variable ranges and distributions were checked to identify implausible outliers.

Statistical Analysis

Continuous variables were assessed for normality using the Shapiro–Wilk test and summarized as mean ± SD or median (IQR), as appropriate. Between-group comparisons were performed with Student's *t*-test or the Mann–Whitney *U*-test. Categorical variables were presented as counts (percentages) and compared using the χ^2-test or Fisher's exact test, as appropriate. Univariable logistic regression was first used to screen candidate predictors of postoperative pneumonia (screening threshold $p < 0.10$). Variables with clinical relevance and/or meeting the screening criterion were then entered into the multivariable logistic regression model. To avoid reverse causation, length of hospital stay (LOS) was excluded from multivariable modeling and is reported descriptively only. Categorical variables were dummy-coded with clinically sensible reference categories (eg, female sex; upper tumor location; ypTNM). Odds ratios (ORs) with 95% confidence intervals (CIs) and *p* values were reported. Potential non-linear associations for ARISCAT score, NLR, and SII were examined using restricted cubic splines (RCS). We report the *p* value for non-linearity and, where applicable, indicate approximate inflection points (eg, NLR ≈ 5.0, SII ≈ 1300). Model discrimination was evaluated using receiver operating characteristic (ROC) curves with area under the curve (AUC) and 95% CIs. Model calibration was assessed using calibration plots (observed vs predicted risk across deciles of predicted probability) and the Brier score as a global measure of prediction error. In addition, single-marker models (NLR-only, SII-only) were fitted to contextualize standalone performance relative to ARISCAT and the combined model. All statistical analyses were performed using R software (version 4.2.2), with two-sided p-values < 0.05 considered statistically significant.

Results

Patient Characteristics

Among the 312 patients with resectable esophageal squamous cell carcinoma who received neoadjuvant chemoimmunotherapy followed by McKeown esophagectomy, 86 (27.6%) developed postoperative pneumonia within 30 days after surgery. Table 1 summarizes the baseline characteristics of the entire cohort, stratified by pneumonia occurrence. There were no statistically significant differences between the pneumonia and non-pneumonia groups in terms of gender (p = 0.587), age (66.0 ± 6.4 vs 66.0 ± 6.7 years, p = 0.937), BMI (22.5 ± 2.6 vs 22.7 ± 2.3 kg/m², p = 0.438), smoking history (p = 0.603), or common comorbidities such as hypertension (p = 0.478), diabetes (p = 0.266), and coronary artery disease (p = 0.331). However, significant differences emerged in several perioperative and inflammatory parameters. The pneumonia group had markedly higher preoperative ARISCAT scores (53.9 ± 10.6 vs 37.4 ± 5.2, p < 0.001), suggesting a higher baseline risk for

Table 1 Baseline Clinical Characteristics of ESCC Patients Undergoing Neoadjuvant Chemo-Immunotherapy Followed by McKeown Esophagectomy Stratified by Postoperative Pneumonia Status

Variables	Total (n = 312)	Postoperative Pneumonia Status		p
		No (n = 226)	Yes (n = 86)	
Gender, n (%)				0.587
Female	141 (45.2)	100 (44.2)	41 (47.7)	
Male	171 (54.8)	126 (55.8)	45 (52.3)	
Age (years), Mean ± SD	66.0 ± 6.6	66.0 ± 6.7	66.0 ± 6.4	0.937
BMI (kg/m^2), Mean ± SD	22.7 ± 2.4	22.7 ± 2.3	22.5 ± 2.6	0.438
FEV1 (%), Mean ± SD	92.2 ± 19.6	92.4 ± 20.6	91.4 ± 16.7	0.679
FEV1/FVC (%), Mean ± SD	105.1 ± 12.6	104.7 ± 11.5	106.2 ± 15.1	0.354
LVEF (%), Mean ± SD	66.1 ± 2.2	66.2 ± 2.2	65.6 ± 2.2	0.071
Hypertension, n (%)				0.478
No	164 (52.6)	116 (51.3)	48 (55.8)	
Yes	148 (47.4)	110 (48.7)	38 (44.2)	
Diabetes Mellitus, n (%)				0.266
No	262 (84.0)	193 (85.4)	69 (80.2)	
Yes	50 (16.0)	33 (14.6)	17 (19.8)	
Coronary Heart Disease, n (%)				0.331
No	197 (63.1)	139 (61.5)	58 (67.4)	
Yes	115 (36.9)	87 (38.5)	28 (32.6)	
Smoking, n (%)				0.603
No	203 (65.1)	149 (65.9)	54 (62.8)	
Yes	109 (34.9)	77 (34.1)	32 (37.2)	
Drinking, n (%)				0.4
No	210 (67.3)	149 (65.9)	61 (70.9)	
Yes	102 (32.7)	77 (34.1)	25 (29.1)	
ECOG, n (%)				0.811
0	177 (56.7)	127 (56.2)	50 (58.1)	
1	126 (40.4)	93 (41.2)	33 (38.4)	
2	9 (2.9)	6 (2.7)	3 (3.5)	
NLR, Mean ± SD	5.8 ± 2.9	4.9 ± 2.1	8.3 ± 3.1	< 0.001
SII, Mean ± SD	1044.8 ± 488.7	917.2 ± 397.2	1379.8 ± 547.3	< 0.001
ARISCAT Score, Mean ± SD	42.0 ± 10.2	37.4 ± 5.2	53.9 ± 10.6	< 0.001
Operative duration (minutes), Mean ± SD	281.5 ± 41.3	278.0 ± 39.7	290.9 ± 44.2	0.061
Recurrent laryngeal nerve paralysis, n (%)				0.389
No	275 (88.1)	197 (87.2)	78 (90.7)	
Yes	37 (11.9)	29 (12.8)	8 (9.3)	
Tumor location, n (%)				0.526
Upper	76 (24.4)	58 (25.7)	18 (20.9)	
Middle	154 (49.4)	112 (49.6)	42 (48.8)	
Low	82 (26.3)	56 (24.8)	26 (30.2)	
cTNM, n (%)				0.484
II	184 (59.0)	136 (60.2)	48 (55.8)	
III	128 (41.0)	90 (39.8)	38 (44.2)	
ypT, n (%)				0.055
ypT0	96 (30.8)	78 (34.5)	18 (20.9)	
ypT1	133 (42.6)	93 (41.2)	40 (46.5)	
ypT2	64 (20.5)	45 (19.9)	19 (22.1)	
ypT3	19 (6.1)	10 (4.4)	9 (10.5)	
ypN, n (%)				0.219
ypN0	252 (80.8)	187 (82.7)	65 (75.6)	

(*Continued*)

https://doi.org/10.2147/JIR.S545333

Table 1 (Continued).

Variables	Total (n = 312)	Postoperative Pneumonia Status		p
		No (n = 226)	Yes (n = 86)	
ypN1	58 (18.6)	37 (16.4)	21 (24.4)	
ypN2	2 (0.6)	2 (0.9)	0 (0)	
ypTNM, n (%)				0.108
0	234 (75.0)	177 (78.3)	57 (66.3)	
I	18 (5.8)	10 (4.4)	8 (9.3)	
II	56 (17.9)	36 (15.9)	20 (23.3)	
III	4 (1.3)	3 (1.3)	1 (1.2)	
Length of hospital stay (days), Mean ± SD	14.8 ± 3.0	13.7 ± 2.3	17.7 ± 2.8	< 0.001

respiratory complications. Inflammatory markers were also notably elevated: neutrophil-to-lymphocyte ratio (NLR: 8.3 ± 3.1 vs 4.9 ± 2.1, $p < 0.001$) and systemic immune-inflammation index (SII: 1379.8 ± 547.3 vs 917.2 ± 397.2, $p < 0.001$). Moreover, patients with pneumonia experienced significantly prolonged hospital stays (17.7 ± 2.8 vs 13.7 ± 2.3 days, $p < 0.001$).

Discrimination and Calibration

As shown in Figure 2, the combined model integrating ARISCAT, NLR, and SII achieved the highest discriminatory performance for predicting postoperative pneumonia, with an AUC of 0.962 (95% CI: 0.916–0.992), outperforming ARISCAT alone (AUC = 0.935, 95% CI: 0.884–0.977), NLR alone (AUC = 0.812, 95% CI: 0.732–0.876), and SII alone (AUC = 0.781, 95% CI: 0.659–0.881). Calibration plots (Figure 3) demonstrated acceptable agreement between predicted

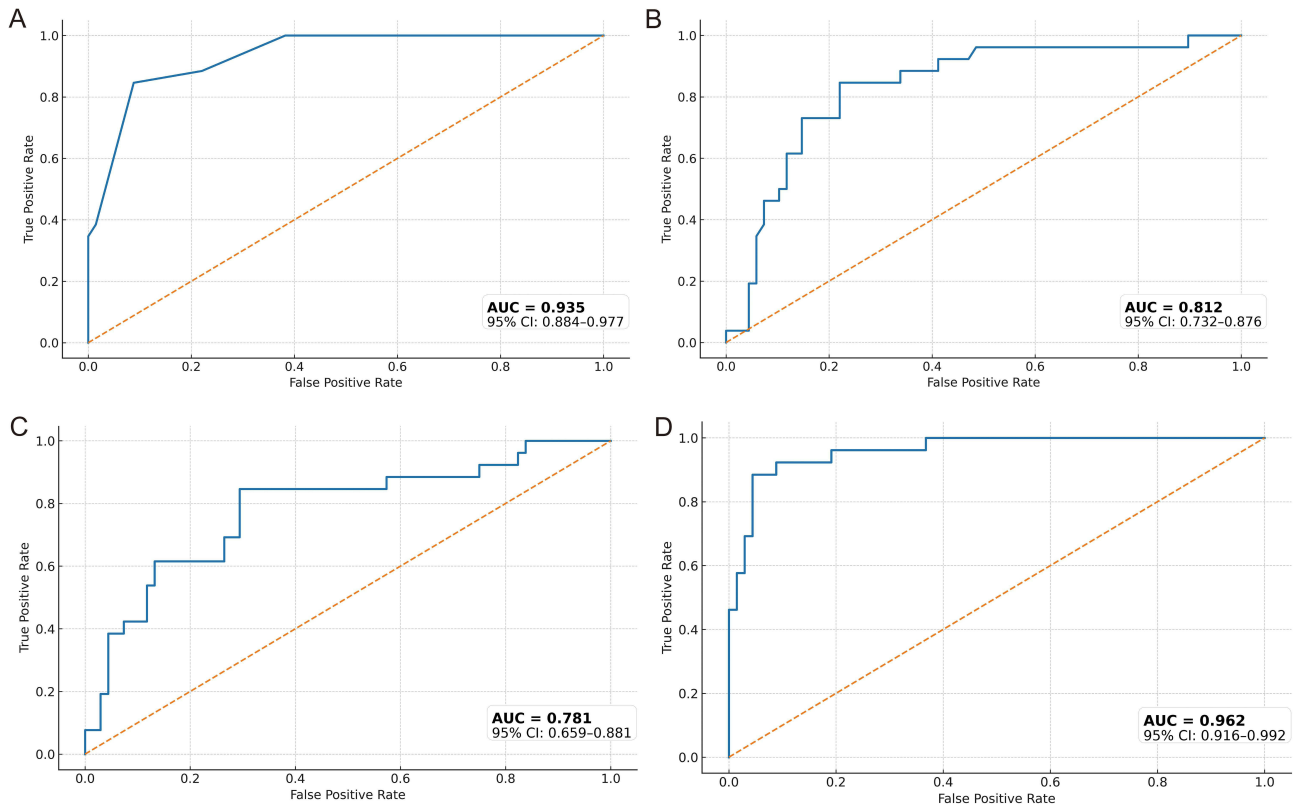

Figure 2 Receiver operating characteristic (ROC) curves for predicting postoperative pneumonia in ESCC patients after neoadjuvant chemo-immunotherapy and McKeown esophagectomy. (**A**) ARISCAT score; (**B**) NLR; (**C**) SII; (**D**) Combined model incorporating ARISCAT, NLR, and SII. The area under the curve (AUC) with 95% confidence intervals (CI) is shown for each model, demonstrating that the combined model achieved the highest discriminative ability.

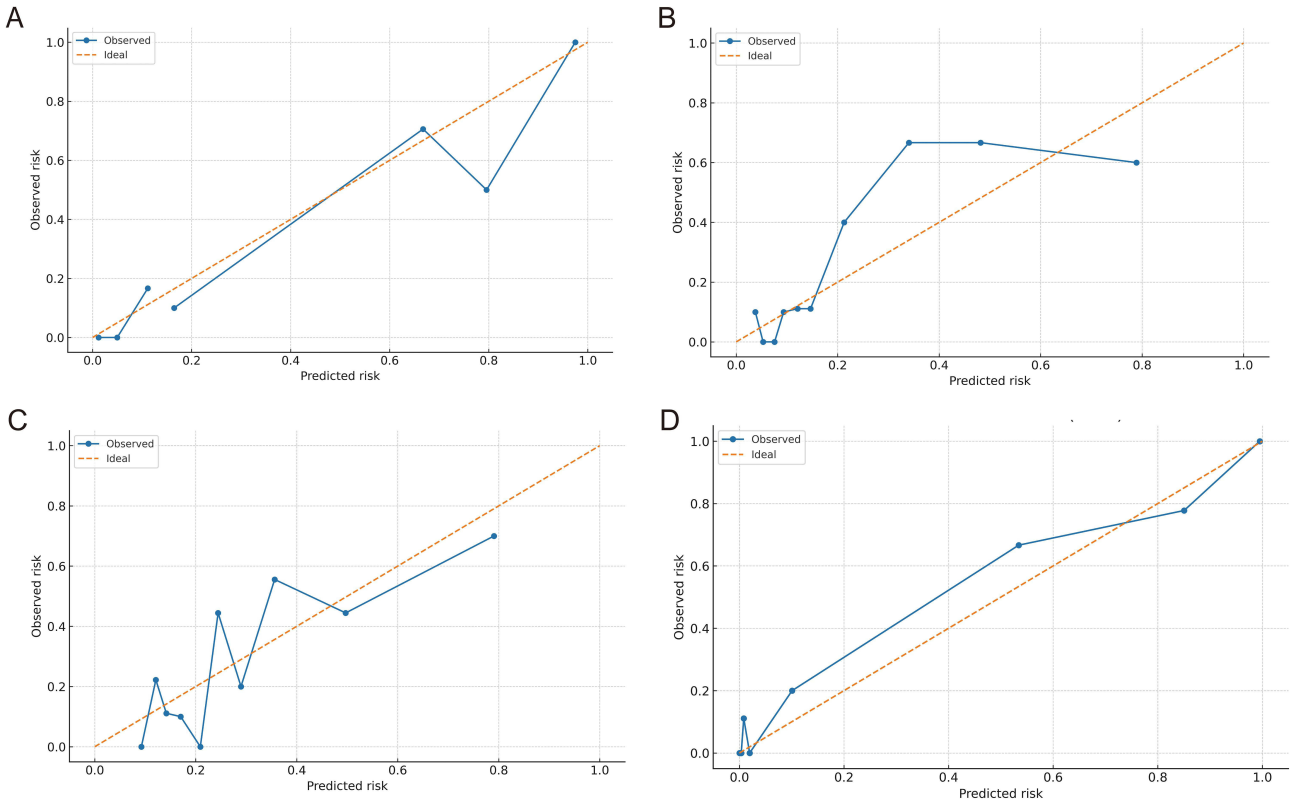

Figure 3 Calibration plots assessing the agreement between predicted and observed risk of postoperative pneumonia. (**A**) ARISCAT score; (**B**) NLR; (**C**) SII; (**D**) Combined model. The solid line represents model predictions, the dashed diagonal line represents perfect calibration, and shaded areas indicate 95% confidence intervals. All models demonstrated acceptable calibration, with the combined model exhibiting the closest fit to the ideal line. Model performance metrics were as follows: ARISCAT score: Brier score = 0.168, Hosmer–Lemeshow p = 0.421; NLR: Brier score = 0.174, Hosmer–Lemeshow p = 0.387; SII: Brier score = 0.182, Hosmer–Lemeshow p = 0.359; Combined model: Brier score = 0.152, Hosmer–Lemeshow p = 0.628.

and observed risks for all models, with the combined model showing the closest alignment to the ideal 45° reference line. Quantitatively, model performance metrics were as follows: ARISCAT—Brier score = 0.168, Hosmer–Lemeshow p = 0.421; NLR—Brier score = 0.174, Hosmer–Lemeshow p = 0.387; SII—Brier score = 0.182, Hosmer–Lemeshow p = 0.359; combined model—Brier score = 0.152, Hosmer–Lemeshow p = 0.628. Collectively, these findings indicate that the combined model not only provided superior discrimination but also achieved the lowest overall prediction error and the most accurate risk estimation among all models assessed.

Univariable and Multivariable Analyses

Univariable logistic regression identified several variables associated with postoperative pneumonia ($p<0.10$; Table 2). To avoid reverse causality, length of hospital stay (LOS) was excluded from the multivariable analysis. In the final adjusted model, ARISCAT score (OR = 1.43, 95% CI: 1.26–1.62, $p<0.001$), NLR (OR = 1.66, 95% CI: 1.31–2.10, $p<0.001$), and SII (OR = 1.09, 95% CI: 1.02–1.71, p = 0.010) remained independent predictors. NLR demonstrated the most robust effect size, whereas the effect size for SII—although statistically significant—was close to the lower bound of clinical relevance, suggesting its value lies primarily in combination with structured scores like ARISCAT.

Dose–Response Patterns From Restricted Cubic Splines

Restricted cubic spline modeling revealed distinct dose–response patterns for the three predictors (Figures 4–6). For the ARISCAT score, a linear association with postoperative pneumonia risk was observed across the entire range, with no evidence of non-linearity (p for non-linearity = 0.794), indicating a steady risk increase with higher scores. In contrast, both NLR and SII demonstrated threshold-dependent non-linear relationships. Pneumonia risk began to rise sharply when

https://doi.org/10.2147/JIR.S545333

Table 2 Univariate and Multivariate Logistic Regression Analyses of Risk Factors for Postoperative Pneumonia in ESCC Patients After Neoadjuvant Chemo-Immunotherapy and McKeown Esophagectomy

Variable	crude.OR (95% CI)	crude.P value	adj.OR (95% CI)	adj.P value
Gender				
Female	Ref			
Male	0.87 (0.53~1.43)	0.587		
Age	1 (0.96~1.04)	0.937		
BMI	0.96 (0.86~1.07)	0.437		
FEV1	1 (0.98~1.01)	0.677		
FEV1/FVC	1.01 (0.99~1.03)	0.353		
LVEF	0.88 (0.78~1.18)	0.072		
Hypertension				
No	Ref			
Yes	0.83 (0.51~1.38)	0.478		
Diabetes Mellitus				
No				
Yes	1.44 (0.75~2.75)	0.268		
Coronary Heart Disease				
No	Ref			
Yes	0.77 (0.46~1.3)	0.332		
Smoking				
No	Ref			
Yes	1.15 (0.68~1.92)	0.603		
Drinking				
No	Ref			
Yes	0.79 (0.46~1.36)	0.401		
ECOG				
0	Ref			
1	0.9 (0.54~1.51)	0.692		
2	1.27 (0.31~5.28)	0.742		
NLR	1.67 (1.46~1.91)	<0.001	1.66 (1.31~2.1)	<0.001
SII	1.12 (1.03~1.98)	<0.001	1.09 (1.02~1.71)	0.01
ARISCAT Score	1.41 (1.3~1.53)	<0.001	1.43 (1.26~1.62)	<0.001
Operative duration	1.12 (0.95~1.97)	0.064		
Recurrent laryngeal nerve paralysis1				
No	Ref			
Yes	0.7 (0.31~1.59)	0.391		
Anastomotic leak				
No	Ref			
Yes	1.45 (0.56~3.77)	0.444		
Length of hospital stay	1.78 (1.55~2.04)	<0.001	1.61 (1.27~2.05)	<0.001
Tumor location				
Upper	Ref			
Middle	1.21 (0.64~2.28)	0.56		
Low	1.5 (0.74~3.03)	0.262		
ypTNM				
0	Ref			
I	2.48 (0.94~6.6)	0.068		
II	1.73 (0.93~3.22)	0.086		
III	1.04 (0.11~10.15)	0.976		

NLR exceeded approximately 5.0 (p for non-linearity < 0.05), while for SII, a similar inflection occurred at around 1300 (p for non-linearity < 0.05). These findings suggest that while ARISCAT operates as a consistent linear predictor, NLR and SII may confer disproportionate increases in risk beyond specific biomarker thresholds.

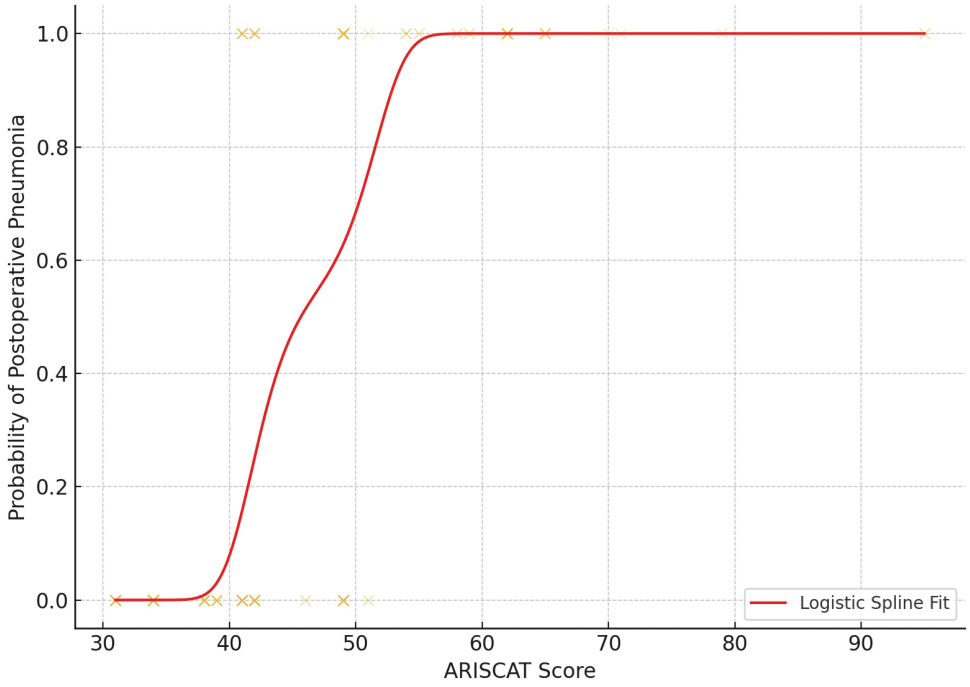

Figure 4 Restricted cubic spline illustrating the association between ARISCAT score and postoperative pneumonia risk in ESCC patients undergoing McKeown esophagectomy after neoadjuvant chemo-immunotherapy. A linear dose-response trend was observed (p for non-linearity = 0.794), with risk increasing steadily at higher ARISCAT scores. No distinct inflection point was detected across the observed range.

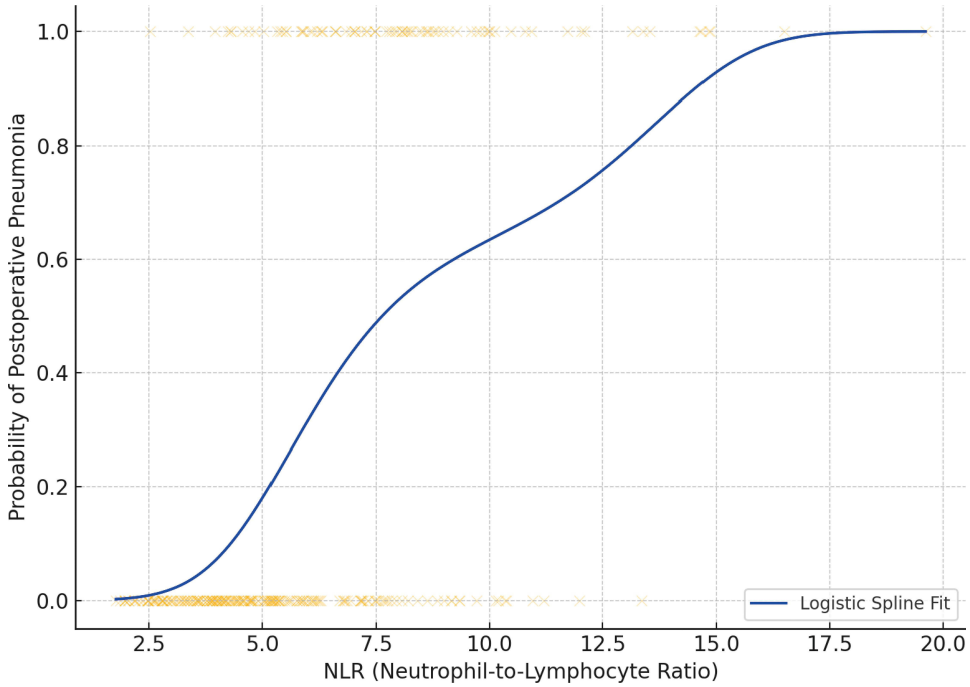

Figure 5 Restricted cubic spline showing the relationship between NLR and postoperative pneumonia risk in ESCC patients treated with neoadjuvant chemo-immunotherapy followed by McKeown esophagectomy. A nonlinear association was observed (p for non-linearity < 0.05), with a marked increase in pneumonia risk when NLR exceeded approximately 5.0, suggesting a potential threshold effect.

https://doi.org/10.2147/JIR.S545333

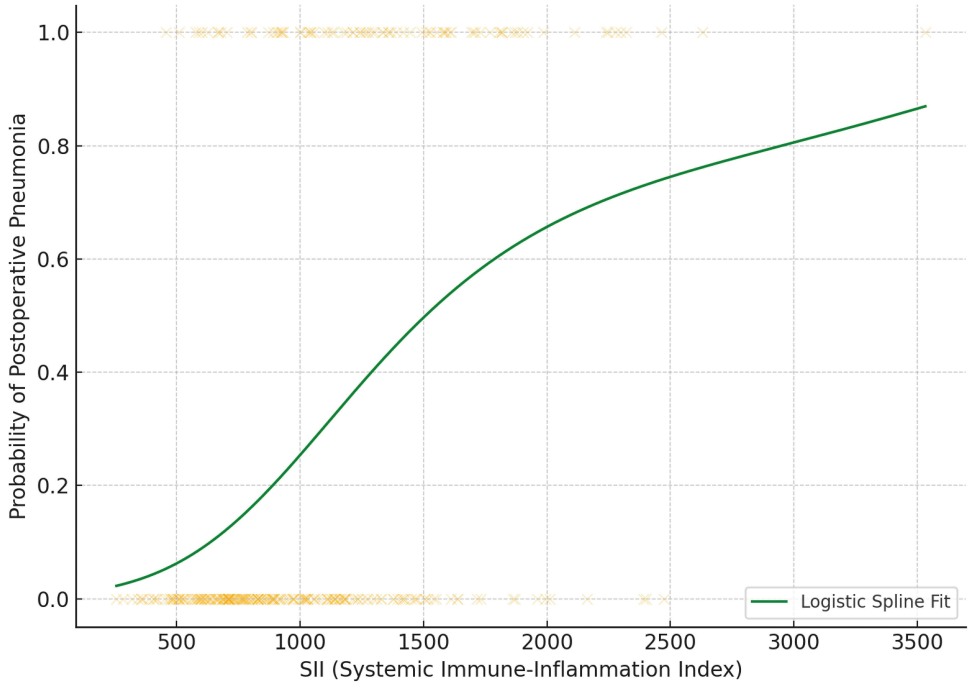

Figure 6 Restricted cubic spline depicting the association between SII and postoperative pneumonia risk following McKeown esophagectomy in ESCC patients who received neoadjuvant chemo-immunotherapy. A threshold-dependent nonlinear pattern was noted (p for non-linearity < 0.05), with pneumonia risk rising sharply when SII exceeded approximately 1300.

Discussion

This retrospective cohort study demonstrates that the ARISCAT score is an independent and clinically meaningful predictor of postoperative pneumonia in patients with resectable ESCC undergoing McKeown esophagectomy after neoadjuvant chemo-immunotherapy. In multivariable analyses that excluded length of stay to avoid reverse causality, ARISCAT, the neutrophil-to-lymphocyte ratio (NLR), and the systemic immune-inflammation index (SII) remained significant risk factors. Importantly, a combined model integrating ARISCAT, NLR, and SII achieved superior discrimination (AUC 0.804; 95% CI 0.756–0.852) and the lowest prediction error (Brier 0.152) with acceptable calibration, outperforming each component alone. Restricted cubic spline analyses further clarified risk dynamics: ARISCAT showed a linear dose–response across the observed range (p for non-linearity = 0.794), whereas NLR and SII exhibited threshold-dependent surges in risk at approximately 5.0 and 1300, respectively (both p for non-linearity < 0.05). Together, these findings underscore the multifactorial nature of postoperative pneumonia and support combining a structured clinical score with readily available inflammatory biomarkers to refine preoperative risk stratification in this high-risk population.

To our knowledge, this is the first study to validate the ARISCAT score in a cohort of ESCC patients treated with modern neoadjuvant chemo-immunotherapy, a regimen that is increasingly adopted as standard care. While the ARISCAT model has been widely evaluated in general surgical settings, evidence for its applicability in thoracic oncology—particularly after combined chemo-immunotherapy—has been lacking. Our findings confirm its strong predictive value in this immunologically and surgically complex context, addressing an important gap in the literature and underscoring its clinical relevance in the current treatment era.

Mechanistically, the ARISCAT score captures several biologically relevant domains that synergistically contribute to postoperative pulmonary vulnerability.[29] Advanced age is associated with progressive decline in respiratory muscle strength, reduced mucociliary clearance, and immunosenescence—factors that collectively diminish the ability to clear pulmonary pathogens and recover from surgical stress.[30] Preoperative anemia, as included in the ARISCAT scoring system, compromises systemic oxygen-carrying capacity, which can exacerbate tissue hypoxia and impair wound healing and immune responses.[31] Low peripheral SpO_2 may reflect baseline pulmonary dysfunction or subclinical cardiopulmonary disease, further compounding intraoperative and postoperative respiratory compromise.[32] Moreover, a recent history of lower respiratory tract infection

suggests a primed pro-inflammatory milieu in the lungs, potentially increasing susceptibility to nosocomial pathogens post-surgery.[33] Importantly, the duration and complexity of McKeown esophagectomy—characterized by three-field lymphadenectomy, bilateral thoracic manipulation, and intrathoracic anastomosis—intensify these risks.[34] The procedure leads to substantial operative trauma, extensive exposure of mediastinal structures, fluid shifts, and prolonged mechanical ventilation, all of which contribute to increased incidence of atelectasis, pleural effusion, and ventilator-associated infections.

Furthermore, neoadjuvant chemo-immunotherapy introduces immunologic and metabolic perturbations that further complicate the perioperative course.[35] Immune checkpoint inhibitors (ICIs), particularly anti–PD-1/PD-L1 agents, while enhancing anti-tumor immunity, may disrupt immune homeostasis by promoting autoimmune-like inflammation or depleting regulatory T-cell populations critical for mucosal tolerance.[36] These alterations have been associated with increased risks of immune-related adverse events, including pneumonitis and opportunistic infections in other oncologic settings.[37] Concurrent cytotoxic chemotherapy, such as platinum-based doublets, impairs bone marrow function, suppresses mucosal barrier integrity, and depletes neutrophil reserves, thereby reducing microbial defense capacity.[38] When these therapeutic effects are superimposed on the tumor-driven immune suppression frequently observed in ESCC—marked by high myeloid-derived suppressor cell (MDSC) activity and T-cell exhaustion—the result is a profoundly immunocompromised state. Additionally, malnutrition and sarcopenia, prevalent in ESCC patients due to dysphagia and catabolic tumor burden, further impair both innate and adaptive immune responses.[39] Collectively, this complex interplay of oncologic treatment, tumor biology, and surgical trauma creates a "perfect storm" for the development of postoperative pneumonia.

Markers such as NLR and SII serve as easily obtainable yet biologically meaningful surrogates for systemic inflammatory and immunologic status.[40] Elevated NLR is indicative of a neutrophil-predominant pro-inflammatory state coupled with lymphopenia-mediated immunosuppression—a profile associated with impaired pathogen clearance and poor surgical outcomes in multiple solid tumor types.[41] Recent meta-analyses have established NLR as a prognostic biomarker not only for postoperative infection but also for survival in ESCC, further highlighting its clinical relevance.[42] Similarly, the SII, calculated as platelet count × neutrophil count / lymphocyte count, reflects both innate immune activation and thrombopoietic response to systemic inflammation.[43,44] Platelets play a non-trivial role in pulmonary host defense and tissue remodeling but can also promote microvascular thrombosis and immune dysregulation.[45] Our finding that both NLR and SII were independently associated with pneumonia risk—and displayed non-linear dose-response curves—underscores their value as integrative, dynamic indicators of perioperative immune competence. These markers may prove especially valuable in resource-limited settings where advanced immunophenotyping is not feasible, offering a pragmatic approach to individualized risk stratification and early intervention.[46] However, it is noteworthy that the adjusted odds ratio for SII in our multivariate model was 1.09, with a 95% confidence interval ranging from 1.02 to 1.71. While statistically significant, this effect size approaches the lower bound of clinical relevance. This suggests that SII alone may have limited predictive power when used in isolation. Accordingly, SII should be interpreted as a complementary marker rather than a standalone predictor, particularly when combined with structured clinical tools such as the ARISCAT score.

This study benefits from a relatively large, homogeneous cohort, contemporary treatment protocol, and rigorous statistical analysis. The integration of traditional logistic regression with RCS modeling allowed for a more granular understanding of risk factor behavior. However, limitations remain. The retrospective design precludes causal inference and may be subject to residual confounding. Additionally, factors such as perioperative antibiotic regimens, chest physiotherapy, and fluid management were not standardized or accounted for. Our single-center experience may limit generalizability, and survival outcomes were not assessed. Despite these limitations, our findings strongly support the clinical utility of the ARISCAT score in thoracic oncology. By combining it with inflammation-based markers and recovery metrics, a more robust and individualized risk model can be established to guide preoperative counseling, enhance perioperative care, and potentially reduce postoperative morbidity.

Conclusion

In this retrospective study of patients with resectable ESCC undergoing McKeown esophagectomy after neoadjuvant chemo-immunotherapy, the preoperative ARISCAT score, neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII) were identified as independent predictors of postoperative pneumonia. ARISCAT demonstrated a linear association with risk, whereas NLR (>5.0) and SII (>1300) showed threshold-dependent surges. A combined model incorporating these

variables achieved superior discrimination and calibration, representing a practical and cost-effective tool for individualized perioperative risk assessment and targeted preventive strategies. Prospective multicenter studies are needed for validation.

Data Sharing Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request. Researchers or institutions seeking access to the datasets are invited to reach out to the corresponding author for comprehensive information regarding data sharing conditions and procedures.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki and received ethical approval from the Ethics Committee of Nanjing Medical University. All procedures were carried out in compliance with relevant institutional and national regulations. Given the retrospective nature of the study, the Ethics Committee granted a waiver of informed consent after confirming that the study met the criteria for exemption upon thorough evaluation of the study protocol.

Furthermore, as patient consent to review their medical records was not required, all patient data were handled with the utmost confidentiality in accordance with applicable data protection regulations. Identifiable information was anonymized to ensure privacy and security throughout the research process.

Author Contributions

Jiexia Ding and Jianqiang Zhao contributed equally to this work and share first authorship. Yunyun Chen and Zhiyun Xu contributed equally to this work and share corresponding authorship.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Nanjing Medical University Science and Technology Development Fund (NMUB20230112) and Jiangsu Provincial Medical Key Discipline Cultivation Unit (JSDW202233).

Disclosure

The authors declare that they have no competing interests.

References

1. Shang X, Xie Y, Yu J, et al. A prospective study of neoadjuvant pembrolizumab plus chemotherapy for resectable esophageal squamous cell carcinoma: the Keystone-001 trial. *Cancer Cell*. 2024;42:1747–1763.e1747. doi:10.1016/j.ccell.2024.09.008
2. Yue P, Bie F, Zhu J, et al. Minimal residual disease profiling predicts pathological complete response in esophageal squamous cell carcinoma. *Mol Cancer*. 2024;23:96. doi:10.1186/s12943-024-02006-x
3. Yang H, Wang F, Hallemeier CL, et al. Oesophageal cancer. *Lancet*. 2024;404(10466):1991–2005. doi:10.1016/S0140-6736(24)02226-8
4. Liu Z, Zhang Y, Ma N, et al. Progenitor-like exhausted SPRY1(+)CD8(+) T cells potentiate responsiveness to neoadjuvant PD-1 blockade in esophageal squamous cell carcinoma. *Cancer Cell*. 2023;41:1852–1870.e1859. doi:10.1016/j.ccell.2023.09.011
5. Puhr HC, Prager GW, Ilhan-Mutlu A. How we treat esophageal squamous cell carcinoma. *ESMO Open*. 2023;8:100789. doi:10.1016/j.esmoop.2023.100789
6. Wen J, Fang S, Hu Y, et al. Impacts of neoadjuvant chemoradiotherapy on the immune landscape of esophageal squamous cell carcinoma. *EBioMedicine*. 2022;86:104371. doi:10.1016/j.ebiom.2022.104371
7. Liang Z, Luo K, Wang Y, et al. Clinical and dosimetric predictors for postoperative cardiopulmonary complications in esophageal squamous cell carcinoma patients receiving neoadjuvant chemoradiotherapy and surgery. *Ann Surg Oncol*. 2023;30:529–538. doi:10.1245/s10434-022-12526-9
8. Zou W, Kuang W, Cai C, Qian Y. Prognostic nutritional index as a prognostic indicator for the occurrence of postoperative complications in patients with esophageal squamous cell carcinoma following neoadjuvant immunochemotherapy. *Cancer Manag Res*. 2024;16:643–650. doi:10.2147/CMAR.S465501

9. Wang H, Tang H, Fang Y, et al. Morbidity and mortality of patients who underwent minimally invasive esophagectomy after neoadjuvant chemoradiotherapy vs neoadjuvant chemotherapy for locally advanced esophageal squamous cell carcinoma: a randomized clinical trial. *JAMA Surg*. 2021;156:444–451. doi:10.1001/jamasurg.2021.0133
10. Xu L, Wei XF, Li CJ, et al. Pathologic responses and surgical outcomes after neoadjuvant immunochemotherapy versus neoadjuvant chemoradiotherapy in patients with locally advanced esophageal squamous cell carcinoma. *Front Immunol*. 2022;13:1052542. doi:10.3389/fimmu.2022.1052542
11. Xu Z, Chen C, Zhao J, et al. The CALLY index as a predictive tool for postoperative pneumonia in esophageal squamous cell carcinoma: a retrospective cohort study. *J Inflamm Res*. 2025;18:5463–5475. doi:10.2147/JIR.S517074
12. Hong Z, Xu J, Chen Z, et al. Additional neoadjuvant immunotherapy does not increase the risk of anastomotic leakage after esophagectomy for esophageal squamous cell carcinoma: a multicenter retrospective cohort study. *Int J Surg*. 2023;109:2168–2178. doi:10.1097/JS9.0000000000000487
13. Wu C, Zhang G, Wang L, et al. Spatial proteomic profiling elucidates immune determinants of neoadjuvant chemo-immunotherapy in esophageal squamous cell carcinoma. *Oncogene*. 2024;43:2751–2767. doi:10.1038/s41388-024-03123-z
14. Li Y, Ji Y, Shen L, et al. Clinical efficacy of combination therapy of an immune checkpoint inhibitor with taxane plus platinum versus an immune checkpoint inhibitor with fluorouracil plus platinum in the first-line treatment of patients with locally advanced, metastatic, or recurrent esophageal squamous cell carcinoma. *Front Oncol*. 2022;12:1015302. doi:10.3389/fonc.2022.1015302
15. Liu F, Wang D, Rong Y, et al. Safety and efficacy of neoadjuvant toripalimab plus chemotherapy followed by chemoradiotherapy for locally advanced esophageal squamous cell carcinoma in China (GASTO 1071): a non-randomised, two-cohort, Phase 2 trial. *EClinicalMedicine*. 2025;82:103184. doi:10.1016/j.eclinm.2025.103184
16. Zhang H, Lin J, Huang Y, Chen Y. The systemic immune-inflammation index as an independent predictor of survival in patients with locally advanced esophageal squamous cell carcinoma undergoing neoadjuvant radiotherapy. *J Inflamm Res*. 2024;17:4575–4586. doi:10.2147/JIR.S463163
17. Ma X, Guo Z, Wei X, et al. Spatial distribution and predictive significance of dendritic cells and macrophages in esophageal cancer treated with combined chemoradiotherapy and PD-1 blockade. *Front Immunol*. 2021;12:786429. doi:10.3389/fimmu.2021.786429
18. Yuan Y, Luo S, Wang X, et al. Efficacy and safety of concurrent programmed cell death protein 1 inhibitor and definitive radiotherapy with immunonutrition support in esophageal squamous cell cancer: a Phase II multicenter clinical trial. *Radiat Oncol*. 2025;20:58. doi:10.1186/s13014-025-02604-z
19. Yang H, Liu H, Chen Y, et al. Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus (NEOCRTEC5010): a phase III multicenter, randomized, open-label clinical trial. *J Clin Oncol*. 2018;36:2796–2803. doi:10.1200/JCO.2018.79.1483
20. Xu Z, Wang Q, Zhang Z, et al. Association between preoperative diagnosis of sarcopenia and postoperative pneumonia in resectable esophageal squamous cell carcinoma patients: a retrospective cohort study. *Front Oncol*. 2023;13:1144516. doi:10.3389/fonc.2023.1144516
21. Huai Q, Luo C, Song P, et al. Peripheral blood inflammatory biomarkers dynamics reflect treatment response and predict prognosis in non-small cell lung cancer patients with neoadjuvant immunotherapy. *Cancer Sci*. 2023;114:4484–4498. doi:10.1111/cas.15964
22. Asano Y, Hayashi K, Takeuchi A, et al. Combining dynamics of serum inflammatory and nutritional indicators as novel biomarkers in immune checkpoint inhibitor treatment of non-small-cell lung cancer with bone metastases. *Int Immunopharmacol*. 2024;136:112276. doi:10.1016/j.intimp.2024.112276
23. Taylor M, Evison M, Michael S, et al. Pre-Operative Measures Of Systemic Inflammation Predict Survival After Surgery For Primary Lung Cancer. *Clin Lung Cancer*. 2024;25:460–467.e467. doi:10.1016/j.cllc.2024.04.018
24. Mahiat C, Bihin B, Duplaquet F, et al. Systemic inflammation/nutritional status scores are prognostic but not predictive in metastatic non-small-cell lung cancer treated with first-line immune checkpoint inhibitors. *Int J Mol Sci*. 2023;25:24. doi:10.3390/ijms25010024
25. Dorland G, Saadat W, van Meenen DMP, et al. Association of preoperative smoking with the occurrence of postoperative pulmonary complications: a post hoc analysis of an observational study in 29 countries. *J Clin Anesth*. 2025;104:111856. doi:10.1016/j.jclinane.2025.111856
26. Fernandez-Bustamante A, Parker RA, Frendl G, et al. Perioperative lung expansion and pulmonary outcomes after open abdominal surgery versus usual care in the USA (PRIME-AIR): a multicentre, randomised, controlled, Phase 3 trial. *Lancet Respir Med*. 2025;13:447–459. doi:10.1016/S2213-2600(25)00040-2
27. Zhou Y, Wang H, Lu D, et al. Development and validation of a nomogram for predicting postoperative pulmonary complications in older patients undergoing noncardiac thoracic surgery: a prospective, bicentric cohort study. *BMC Geriatr*. 2025;25:169. doi:10.1186/s12877-025-05791-2
28. Li P, Gao S, Wang Y, et al. Utilising intraoperative respiratory dynamic features for developing and validating an explainable machine learning model for postoperative pulmonary complications. *Br J Anaesth*. 2024;132:1315–1326. doi:10.1016/j.bja.2024.02.025
29. Smetana GW, Lawrence VA, Cornell JE. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American college of physicians. *Ann Intern Med*. 2006;144:581–595. doi:10.7326/0003-4819-144-8-200604180-00009
30. Baer ET. Iatrogenic meningitis: the case for face masks. *Clin Infect Dis*. 2000;31:519–521. doi:10.1086/313991
31. Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet*. 2011;378:1396–1407. doi:10.1016/S0140-6736(11)61381-0
32. Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology*. 2010;113:1338–1350. doi:10.1097/ALN.0b013e3181fc6e0a
33. Qaseem A, Snow V, Fitterman N, et al. Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: a guideline from the American College of Physicians. *Ann Intern Med*. 2006;144:575–580. doi:10.7326/0003-4819-144-8-200604180-00008
34. Marti S, Devant M, Amatayakul-Chantler S, et al. Effect of anti-gonadotropin-releasing factor vaccine and band castration on indicators of welfare in beef cattle. *J Anim Sci*. 2015;93:1581–1591. doi:10.2527/jas.2014-8346
35. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. *J Clin Oncol*. 2017;35:56–62. doi:10.1200/JCO.2016.69.1378
36. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. *N Engl J Med*. 2018;378:158–168. doi:10.1056/NEJMra1703481
37. van Hest R, Baars H, Kik S, et al. Hepatotoxicity of rifampin-pyrazinamide and isoniazid preventive therapy and tuberculosis treatment. *Clin Infect Dis*. 2004;39:488–496. doi:10.1086/422645

38. Youn JI, Gabrilovich DI. The biology of myeloid-derived suppressor cells: the blessing and the curse of morphological and functional heterogeneity. *Eur J Immunol*. 2010;40:2969–2975. doi:10.1002/eji.201040895
39. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cancer cachexia: understanding the molecular basis. *Nat Rev Cancer*. 2014;14:754–762. doi:10.1038/nrc3829
40. Abais-Battad JM, Lund H, Fehrenbach DJ, et al. Parental dietary protein source and the role of CMKLR1 in determining the severity of dahl salt-sensitive hypertension. *Hypertension*. 2019;73:440–448. doi:10.1161/HYPERTENSIONAHA.118.11994
41. Xu J, Li Y, Fan Q, et al. Clinical and biomarker analyses of sintilimab versus chemotherapy as second-line therapy for advanced or metastatic esophageal squamous cell carcinoma: a randomized, open-label phase 2 study (ORIENT-2). *Nat Commun*. 2022;13:857. doi:10.1038/s41467-022-28408-3
42. Wu X, Han R, Zhong Y, et al. Post treatment NLR is a predictor of response to immune checkpoint inhibitor therapy in patients with esophageal squamous cell carcinoma. *Cancer Cell Int*. 2021;21:356. doi:10.1186/s12935-021-02072-x
43. Ni X, Gao Y, Wu Z, et al. Functional human induced hepatocytes (hiHeps) with bile acid synthesis and transport capacities: a novel in vitro cholestatic model. *Sci Rep*. 2016;6:38694. doi:10.1038/srep38694
44. Zhang X, Gari A, Li M, et al. Combining serum inflammation indexes at baseline and post treatment could predict pathological efficacy to anti-PD-1 combined with neoadjuvant chemotherapy in esophageal squamous cell carcinoma. *J Transl Med*. 2022;20:61. doi:10.1186/s12967-022-03252-7
45. Sun X, Liu B, Zhao XD, et al. MicroRNA-221 accelerates the proliferation of laryngeal cancer cell line Hep-2 by suppressing Apaf-1. *Oncol Rep*. 2015;33:1221–1226. doi:10.3892/or.2015.3714
46. Zhang Z, Yang L, Wang D, et al. Retrospective study of the combination of TP and PF regimens with or without immune checkpoint inhibitors for the first-line treatment of locally advanced or advanced esophageal squamous cell carcinoma. *Ther Adv Med Oncol*. 2023;15:17588359231169981. doi:10.1177/17588359231169981