Original Article

The value of perioperative neutrophil-to-lymphocyte ratio combined with the prognostic nutritional index for predicting anastomotic leakage after minimally invasive esophagectomy

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Background: Across the world, esophageal cancer is one of the most common malignant tumors of the digestive system. Anastomotic leakage is a severe complication after minimally invasive esophagectomy (MIE) for esophageal cancer. Research indicates that inflammation and immune system and nutritional status are linked to anastomotic leakage. Neutrophil-to-lymphocyte ratio (NLR) and prognostic nutrition index (PNI) reflect the inflammatory and nutritional status of the human body. The aim of this study is to investigate the value of perioperative NLR combined with the PNI to predict anastomotic leakage after MIE.

Methods: A retrospective analysis was conducted on 232 patients who underwent MIE in The Affiliated Lihuili Hospital of Ningbo University from January 2019 to May 2023. Patients were divided into two groups based on the presence or absence of anastomotic leakage. Clinicopathological data and perioperative peripheral blood indices of the patients were collected, and the factors associated with postoperative anastomotic leakage were analyzed via univariate and multivariate logistic regression. Moreover, the value of NLR and PNI for predicting anastomotic leakage were evaluated using receiver operating characteristic (ROC) curves.

Results: Anastomotic leakage occurred in 35 (15%) of 232 patients who underwent MIE. Multivariate logistic regression analysis identified a history of diabetes, higher NLR levels on postoperative days 3 and 5, and a lower PNI score on postoperative day 3 as independent risk factors of anastomotic leakage. ROC curve analysis indicated that NLR combined with PNI on postoperative day 3 had the best predictive value for anastomotic leakage, with an area under the curve (AUC) of 0.826, a sensitivity of 82.9%, and a specificity of 78.2%.

Conclusions: Persistently high NLR levels and persistently low PNI levels in the postoperative period correlated with the development of anastomotic leakage after MIE, and NLR combined with the PNI on postoperative day 3 had the best predictive value for anastomotic leakage after MIE.

Keywords: Neutrophil-to-lymphocyte ratio (NLR); prognostic nutrition index (PNI); minimally invasive esophagectomy (MIE); anastomotic leakage

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Introduction

Esophageal cancer remains one of the most common malignant tumors of the digestive system in the world. According to the 2020 GLOBOCAN report, the global incidence and mortality of esophageal cancer rank seventh and sixth, respectively (1,2). The present treatment strategy for patients with resectable esophageal cancer is still based on surgical resection (3). Despite significant advancements in surgical techniques and perioperative management in recent years, anastomotic leakage, a severe complication, remains unavoidable in clinical practice (4,5). The occurrence of anastomotic leakage is not only associated with prolonged hospital stays, wastage of medical resources, and increased perioperative mortality but may also leaded to tumor recurrence and a decline in long-term survival (6,7). Therefore, the early postoperative prediction of anastomotic leakage holds significant clinical value. Currently, there is a wealth of research on risk factors for anastomotic leakage after minimally invasive esophagectomy (MIE), including age, diabetes, anastomotic technique, and others (8-11). However, they failed to consider the patients' own inflammatory levels and nutritional status. The etiology of anastomotic leakage is complex and may result from the combined effects of inflammation, immune system factors, and nutritional status (12-16). In recent years, the neutrophil-to-lymphocyte ratio (NLR) has emerged as an important indicator of systemic inflammation and immune levels, garnering widespread attention (17). Previous studies have shown that NLR is associated with the prognosis of various malignant tumors and postoperative complications (18,19). Meanwhile, the prognostic nutrition index (PNI) is a nutritional marker based on serum albumin and lymphocyte levels and has been reported to be a good predictor of complications following operation on the digestive system (20-22). The NLR and PNI are relatively easy to obtain in clinical practice. Therefore, this study aimed to assess the value of perioperative NLR combined with PNI in predicting anastomotic leakage after minimally invasive resection of esophageal cancer. We present this article in accordance with the TRIPOD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-302/rc).

Highlight box

Key findings

- The combination of neutrophil-to-lymphocyte ratio (NLR) and the prognostic nutritional index (PNI) on postoperative day 3 demonstrated the best predictive value of anastomotic leakage.

What is known and what is new?

- (I) Currently, anastomotic leakage cannot be completely avoided after minimally invasive esophagectomy (MIE). (II) NLR is related to the prognosis and postoperative complications of esophageal cancer.
- (I) Patients maintain high levels of NLR and low levels of PNI after MIE. (II) The combination of NLR and PNI on postoperative day 3 demonstrated the best ability to predict anastomotic leakage.

What is the implication, and what should change now?

- Clinicians can predict the occurrence of anastomotic leakage postoperatively by monitoring patients' NLR and PNI levels and thus take preventive measures such as prolonging fasting time, actively treating inflammation, and improving protein levels.

Methods

Patient selection

A retrospective analysis was conducted on patients who underwent minimally invasive esophageal cancer resection at the Department of Thoracic Surgery of The Affiliated Lihuili Hospital of Ningbo University from January 2019 to May 2023. A total of 232 cases were included, comprising 214 males and 18 females, with a median age of 67 years (range, 47–83 years). The inclusion criteria were as follows: (I) pathologically confirmed with primary esophageal cancer; (II) completion of minimally invasive esophageal resection; (III) availability of complete clinical and pathological data; and (IV) availability of complete perioperative peripheral blood data. Meanwhile, the exclusion criteria were as follows: (I) preoperative neoadjuvant therapy or anti-inflammatory treatment; (II) liver, kidney, or hematologic diseases; (III) patients with distant metastasis; (IV) severe lung infection within 1 week after surgery (definition of severe pneumonia: postoperative CT shows newly developed pulmonary infiltrates that are extensive in scope, such as involving multiple lung lobes or associated with lung consolidation); and (V) presence of other severe postoperative complications, such as chylothorax or cerebral infarction. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of The Affiliated Lihuili Hospital of Ningbo University (No. KY2019PJ058) and informed consent was taken from all the patients.

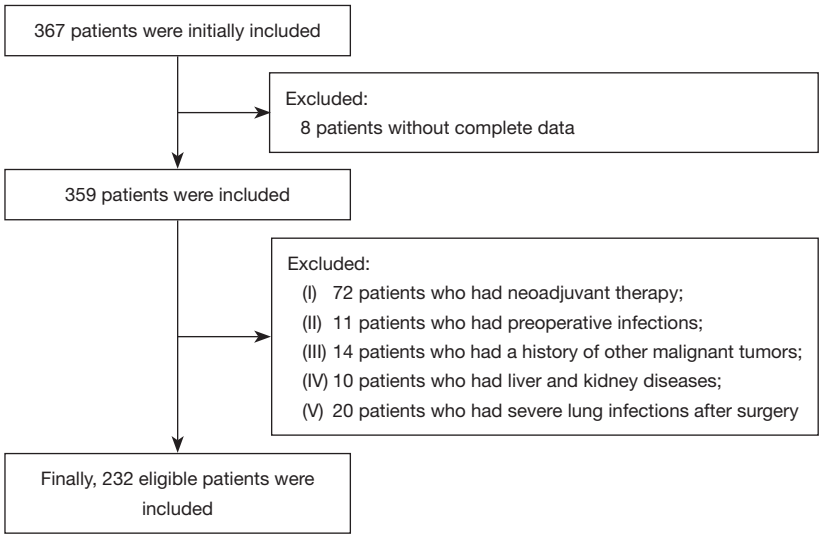

Figure 1 Flowchart of patient selection.

Data collection

The clinical and pathological characteristics of patients, including sex, age, smoking history, alcohol consumption history, history of hypertension, history of diabetes, surgical method, maximum tumor diameter, tumor location, depth of infiltration, lymph node metastasis, and routine perioperative laboratory tests, were recorded. Within 1 week before surgery, serum albumin levels, neutrophil count, lymphocyte count, platelet count, and monocyte count were collected via routine blood tests. The definitions of NLR and PNI are as follows: NLR = neutrophil count/lymphocyte count; PNI = serum albumin + 5 × lymphocyte count.

Definition and assessment of anastomotic leakage

According to the consensus of the Esophagectomy Complications Consensus Group (ECCG), in this study, anastomotic leakage was defined as a full-thickness defect involving the esophagus, anastomosis site, suture line, or tubular stomach. Postoperatively, we closely monitored patients, and postoperative anastomotic leakage was diagnosed if any of the following occurred: (I) extravasation of contrast agent on gastrointestinal contrast radiography; (II) endoscopic confirmation of anastomotic leakage; (III) computed tomography scan suggesting anastomotic leakage; and (IV) drainage tube discharge of purulent or feculent fluid.

Statistical analysis

Data analysis was performed with SPSS 26.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 10.1.2 (GraphPad Software, San Diego, CA, USA). Normally distributed continuous data are described as the mean ± standard deviation, and intergroup comparisons were made with the *t*-test. Nonnormally distributed continuous data are described as the median and interquartile range, while intergroup comparisons were made with nonparametric tests. Categorical data are expressed as frequency and percentage, and intergroup comparisons were made with the chi-square test or Fisher exact test. Univariate and multivariate logistic regression analyses were conducted to identify the risk factors of anastomotic leakage in patients with esophageal cancer. The value of NLR and PNI for predicting anastomotic leakage was assessed with receiver operating characteristic (ROC) curves. Then, NLR and PNI were combined to evaluate their predictive value for anastomotic leakage. A two-tailed P value <0.05 was considered statistically significant.

Results

Clinical and pathological characteristics

A total of 232 patients met the inclusion and exclusion criteria in this study, as shown in *Figure 1*. The clinical and pathological characteristics of 232 patients with esophageal cancer are shown in *Table 1*, including 214 males (92.2%)

Table 1 Clinicopathological characteristics and basic information of patients

Variable	Value
Age (years)	67 [47, 83]
Sex	
Male	214 (92.2)
Female	18 (7.8)
Smoking	
Yes	162 (69.8)
No	70 (30.2)
Alcohol	
Yes	168 (72.4)
No	64 (27.6)
Hypertension	
Yes	90 (38.8)
No	142 (61.2)
Diabetes	
Yes	23 (9.9)
No	209 (90.1)
Surgical procedure	
McKeown	178 (76.7)
Ivor-Lewis	54 (23.3)
Tumor maximum diameter (cm)	3.5 [2.5, 4.5]
Tumor location	
Upper	17 (7.3)
Middle	136 (58.6)
Lower	79 (34.1)
Depth of invasion	
T1	51 (22.0)
T2	45 (19.4)
T3	136 (58.6)
Lymph node metastasis	
N0	120 (51.7)
N+	112 (48.3)

Data are presented as median [interquartile range] or n (%).

and 18 females (7.8%), with a median age of 67 years (range, 47–83 years). Among them, 162 had a history of smoking (69.8%), 168 had a history of alcohol consumption (72.4%), 90 had a history of hypertension (38.8%), and 23 had a history of diabetes (9.9%). Among the cases, 178 (76.7%) underwent cervical anastomosis, while 54 (23.3%) underwent thoracic anastomosis. The tumor locations were as follows: upper, middle, and lower esophagus in 17 (7.3%), 136 (58.6%), and 79 (34.1%) cases, respectively. The median tumor maximum diameter was 3.5 cm (range, 2.5–4.5 cm). According to the eighth edition of the tumor-node-metastasis (TNM) staging system, the distribution of tumor infiltration depth among patients was as follows: T1 in 51 (22.0%) cases, T2 in 45 (19.4%) cases, and T3 in 136 (58.6%) cases. Meanwhile, N0 lymph node metastasis was observed in 120 (51.7%) cases while N+ was observed in 112 (48.3%) cases.

Univariate analysis of anastomotic leakage in patients with esophageal cancer after surgery

Patients were divided into two groups based on whether anastomotic leakage occurred postoperatively, with 35 (15.1%) cases experiencing anastomotic leakage. Among them, there were 29 (82.9%) cases of cervical anastomotic leakage and 6 (17.1%) cases of thoracic anastomotic leakage. There were 30 (85.7%) cases of anastomotic leakage occurring within 10 days after surgery. Results of the univariate analysis of the general clinical and pathological characteristics (*Table 2*) only identified a history of diabetes as being significantly associated with postoperative anastomotic leakage (P=0.003). Age, sex, smoking history, alcohol consumption history, history of hypertension, surgical method, tumor location, tumor maximum diameter, depth of infiltration, and lymph node metastasis showed no significant association with postoperative anastomotic leakage (all P values >0.05). Univariate analysis of perioperative blood indicators (*Table 3*) revealed that the factors significantly associated with postoperative anastomotic leakage were higher neutrophil levels on postoperative days 1, 3, and 5 (P=0.01, P<0.001, and P<0.001, respectively); higher platelet levels on postoperative day 1 (P=0.01); higher NLR levels on postoperative days 3 and 5 (P<0.001 and P<0.001, respectively); and lower PNI levels on postoperative days 3 and 5 (P<0.001 and P<0.001, respectively).

Multivariate logistic regression analysis of anastomotic leakage in patients with esophageal cancer after surgery

To eliminate the influence of collinearity, a multivariate logistic regression analysis (*Table 4*) was conducted that

Table 2 Univariate analysis of general clinical and pathological characteristics

Variable	Anastomotic leakage (+)	Anastomotic leakage (–)	P value
Age, n (%)			0.06
≤67 years	23 (65.7)	96 (48.7)	
>67 years	12 (34.3)	101 (51.3)	
Sex, n (%)			0.056
Male	29 (82.9)	185 (93.9)	
Female	6 (17.1)	12 (6.1)	
Smoking, n (%)			0.57
Yes	23 (65.7)	139 (70.6)	
No	12 (34.2)	58 (29.4)	
Alcohol, n (%)			0.89
Yes	25 (71.4)	143 (72.6)	
No	10 (28.6)	54 (27.4)	
Hypertension, n (%)			0.20
Yes	17 (48.6)	73 (37.1)	
No	18 (51.4)	124 (62.9)	
Diabetes, n (%)			0.003*
Yes	9 (25.7)	17 (8.6)	
No	26 (74.3)	180 (91.4)	
Surgical procedure, n (%)			0.35
McKeown	29 (82.9)	149 (75.6)	
Ivor-Lewis	6 (17.1)	48 (24.4)	
Tumor maximum diameter, n (%)			0.40
≤3.5 cm	14 (40.0)	94 (47.7)	
>3.5 cm	21 (60.0)	103 (52.3)	
Tumor location, n (%)			0.49
Upper	2 (5.7)	15 (7.6)	
Middle	18 (51.4)	118 (59.9)	
Lower	15 (42.9)	64 (32.5)	
Depth of invasion, n (%)			0.25
T1	10 (28.6)	41 (20.8)	
T2	10 (28.6)	35 (17.8)	
T3	15 (42.8)	121 (61.4)	
Lymph node metastasis, n (%)			0.49
N0	20 (57.1)	100 (50.8)	
N+	15 (42.9)	97 (49.2)	

*, P<0.05.

Table 3 Univariate analysis of perioperative blood indicators

Variable	Group	Preoperative	Postoperative day 1	Postoperative day 3	Postoperative day 5
Neutrophils	AL (–)	3.50 (2.90, 4.29)	10.30 (8.40, 12.50)	7.20 (5.88, 8.60)	5.90 (4.60, 7.60)
	AL (+)	3.30 (2.60, 4.20)	12.00 (10.22, 13.25)	9.70 (8.15, 11.40)	7.80 (6.70, 10.40)
	P value	0.20	0.01*	<0.001*	<0.001*
Lymphocytes	AL (–)	1.65 (1.40, 1.85)	0.80 (0.54, 0.97)	0.80 (0.70, 1.00)	1.00 (0.80, 1.20)
	AL (+)	1.48 (1.20, 1.80)	0.70 (0.60, 0.95)	0.80 (0.68, 0.90)	0.90 (0.70, 1.20)
	P value	0.13	0.71	0.14	0.18
Platelets	AL (–)	237 (193, 291)	186 (162, 229)	169 (145, 206)	219 (188, 260)
	AL (+)	210 (174, 255)	229 (180, 254)	188 (148, 227)	220 (171, 254)
	P value	0.057	0.01*	0.10	0.62
RBC	AL (–)	4.23 (4.03, 4.59)	4.08±0.51	3.63±0.51	3.67±0.52
	AL (+)	4.28 (4.00, 4.65)	4.11±0.45	3.62±0.56	3.55±0.50
	P value	0.84	0.80	0.97	0.19
Hemoglobin	AL (–)	135 (125, 147)	131 (119, 141)	114.46±15.41	115.66±15.44
	AL (+)	138 (129, 147)	132 (120, 141)	113.77±18.72	112.23±16.94
	P value	0.57	0.64	0.82	0.23
NLR	AL (–)	2.32 (1.71, 3.13)	14.82 (10.67, 19.90)	8.45 (6.57, 10.70)	5.90 (4.63, 7.25)
	AL (+)	2.31 (1.66, 3.13)	14.42 (11.44, 18.33)	12.4 (10.87, 15.07)	10.00 (6.82, 12.31)
	P value	0.96	0.44	<0.001*	<0.001*
PNI	AL (–)	49.1 (46.4, 51.5)	38.5 (35.9, 40.6)	37.4 (34.8, 39.9)	39.1 (36.5, 42.1)
	AL (+)	48.2 (44.7, 51.6)	38.3 (35.7, 41.7)	34.5 (32.7, 35.9)	36.2 (33.5, 38.6)
	P value	0.47	0.62	<0.001*	<0.001*

Data are presented as median (interquartile range) or mean ± standard deviation. *, P<0.05. AL, anastomotic leakage; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; RBC, red blood cell.

Table 4 Multivariate logistic regression analysis

Variable	OR	95% CI	P value
Diabetes	3.125	1.018–9.593	0.047*
NLR on POD 3	1.111	1.000–1.235	0.048*
NLR on POD 5	1.195	1.043–1.368	0.01*
PNI on POD 3	0.824	0.699–0.971	0.02*
PNI on POD 5	0.991	0.856–1.148	0.91

*, P<0.05. CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; POD, postoperative day; PNI, prognostic nutritional index.

included a history of diabetes, NLR levels on postoperative days 3 and 5, PLR levels on postoperative day 3, and PNI levels on postoperative days 3 and 5. The results showed that the independent influencing factors for postoperative anastomotic leakage were a history of diabetes (P=0.047), higher NLR levels on postoperative days 3 and 5 (P=0.048

Table 5 Efficacy of NLR and PNI in predicting anastomotic leakage

Variable	AUC (95% CI)	P value	Cutoff	Sensitivity	Specificity
Postoperative day 3					
NLR	0.801 (0.724–0.878)	<0.001*	10.715	0.829	0.756
PNI	0.737 (0.668–0.807)	<0.001*	36.875	0.886	0.548
NLR + PNI	0.826 (0.754–0.898)	<0.001*	0.152	0.829	0.782
Postoperative day 5					
NLR	0.772 (0.677–0.868)	<0.001*	7.960	0.629	0.853
PNI	0.727 (0.635–0.819)	<0.001*	34.225	0.429	0.898
NLR + PNI	0.777 (0.681–0.873)	<0.001*	0.150	0.743	0.766

*, P<0.05. AUC, area under the curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index.

and P=0.01, respectively), and lower PNI levels on postoperative day 3 (P=0.02).

Efficacy of NLR and PNI in predicting the development of anastomotic leakage in patients with esophageal cancer after surgery

Patients who developed anastomotic leakage after esophageal cancer surgery often exhibit persistently elevated NLR levels and persistently decreased PNI levels postoperatively. To further characterize the efficacy of NLR and PNI in predicting postoperative anastomotic leakage, we established ROC curves. The analysis results showed that at a cutoff value of 10.715, the area under the curve (AUC) of NLR on postoperative day 3 was 0.801, with a sensitivity and specificity of 0.829 and 0.756, respectively. At a cutoff value of 36.875, the AUC of PNI on postoperative day 3 was 0.737, with a sensitivity and specificity of 0.886 and 0.548, respectively. When NLR and PNI were combined, the AUC was 0.826 on postoperative day 3, with a sensitivity and specificity of 0.829 and 0.782, respectively, indicating a higher predictive efficacy when these two indicators were combined on postoperative day 3. At a cutoff value of 7.960, the AUC of NLR on postoperative day 5 was 0.772, with a sensitivity and specificity of 0.629 and 0.853, respectively. At a cutoff value of 34.225, the AUC of PNI on postoperative day 5 was 0.727, with a sensitivity and specificity of 0.429 and 0.898, respectively. When NLR and PNI were combined, the AUC was 0.777 [95% confidence interval (CI): 0.681–0.873] on postoperative day 5, with a sensitivity and specificity of 0.743 and 0.766, respectively, the AUC was 0.826 (95% CI: 0.754–0.898) on postoperative day 3, with a sensitivity and specificity of 0.829 and 0.782. See *Table 5* and *Figure 2* for further details.

Discussion

Minimally invasive esophageal cancer resection is the primary treatment modality for patients with esophageal cancer. Although surgical techniques are continuously evolving, the incidence of anastomotic leakage after surgery remains relatively high, ranging from 10% to 20%. In our study, the incidence of anastomotic leakage after esophageal cancer surgery was 15.1%, which is consistent with the literature (23,24). Anastomotic leakage, as one of the most serious postoperative complications of esophageal cancer surgery, may lead to fever, abscess formation, sepsis, or septic shock (25). This can result in prolonged hospital stays, higher hospitalization costs, and even secondary surgeries, thereby increasing perioperative mortality rates (26,27). Therefore, the early prediction of postoperative anastomotic leakage in patients is of significant clinical value.

According to a relevant study, anastomotic leakage is pathophysiologically associated with ischemia, hypoxia, infection, and inflammation (28). The main risk factors include advanced age, obesity, anastomotic site and technique, hypoalbuminemia, and a history of diabetes (29). Multifactorial logistic regression analysis in our study revealed that a history of diabetes, elevated NLR levels on postoperative days 3 and 5, and decreased PNI levels on postoperative day 3 were independent risk factors for anastomotic leakage. Diabetes, as a chronic debilitating disease, can lead to immunodeficiency in patients due to long-term metabolic disturbances, increasing the risk of anastomotic infection. Additionally, diabetes can slow down blood flow, impairing tissue-healing capabilities (30).

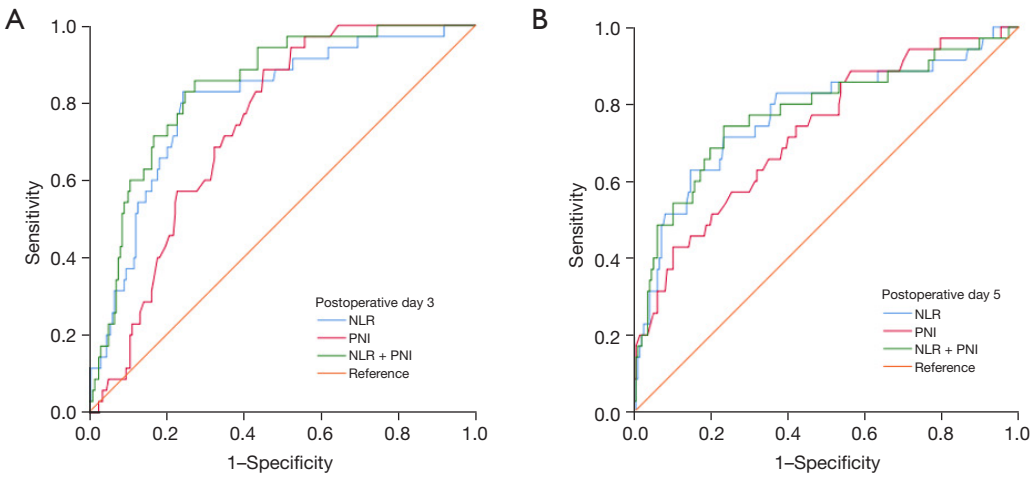

Figure 2 ROC curves of NLR and PNI in predicting anastomotic leakage after minimally invasive esophagectomy. (A) Postoperative day 3. (B) Postoperative day 5. NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; ROC, receiver operating characteristic.

NLR is recognized as an inflammatory response marker associated with the activation and regulation of the body's inflammatory response (31,32). Neutrophils, as key cellular components of the innate immune system, recruit, activate, and modulate other immune cells during early inflammation, secreting a series of proinflammatory cytokines, regulatory cytokines, and chemokines, thereby triggering a cascade of inflammatory reactions. Meanwhile, lymphocytes, as the main components of the adaptive immune system, suppress the body's inflammatory response by secreting anti-inflammatory factors. Neutrophils and lymphocytes interact to maintain immune system balance. Previous studies have demonstrated a correlation between NLR and the occurrence of anastomotic leakage after gastrointestinal surgery. In a retrospective study by Radulescu *et al.* of 204 patients undergoing gastric cancer resection, there was a significant correlation between high preoperative NLR levels and anastomotic leakage, with preoperative NLR >3.54 being an independent risk factor for anastomotic leakage (33). However, in our study, there was no correlation between preoperative NLR levels and anastomotic leakage (P=0.96), suggesting that the correlation between preoperative NLR levels and postoperative anastomotic leakage still needs to be verified by multicenter studies. In a study by Paliogiannis *et al.*, the optimal cutoff value for NLR on postoperative day 4 was 7.1, representing the best predictive ability for anastomotic leakage, with the maximum AUC being 0.744 (34). In our study, the NLR levels of patients who developed anastomotic leakage after surgery were basically the same as those who did not develop anastomotic leakage on the first day, but thereafter, the NLR levels declined slowly but remained elevated. We found that high NLR levels were mainly due to high neutrophil counts and not decreased lymphocyte counts, which may be attributed to neutrophils primarily relying on glycolysis and thus consuming more oxygen, thereby exacerbating tissue hypoxia at the anastomotic site.

Due to prolonged dietary restrictions, most patients with esophageal cancer have poor nutritional status. Studies have shown that patients' nutritional status is associated with cancer prognosis and postoperative complications. Onodera *et al.* first proposed the concept of the PNI in 1984 (21). PNI, based on serum albumin and lymphocyte levels, has been proven to be a good predictor of complications after gastrointestinal surgery. Our findings indicated that patients who developed anastomotic leakage had consistently low PNI levels postoperatively, and low PNI levels on postoperative day 3 were an independent risk factor for anastomotic leakage. To further investigate the predictive value of NLR and PNI for postoperative anastomotic leakage in esophageal cancer, we established ROC prediction models. The ROC models showed that NLR on postoperative day 3 had good predictive value for anastomotic leakage, with an AUC of 0.801, a sensitivity of 82.9%, and a specificity of 75.6%. Furthermore, when NLR was combined with PNI on postoperative day 3, the AUC was 0.826, with a sensitivity of 82.9% and a specificity of 78.2%, indicating higher predictive value than NLR alone. The results on postoperative day 5 were similar to those on postoperative day 3, with the combined NLR and PNI showing better predictive value for anastomotic leakage.

To our knowledge, few studies have examined the correlation between inflammatory-nutritional markers such as NLR and PNI and postoperative anastomotic leakage after MIE. Therefore, our study has important clinical value and can inform the management of patients with esophageal cancer after surgery. Clinicians can predict the occurrence of anastomotic leakage postoperatively by monitoring patients' NLR and PNI levels and then implement preventive measures such as prolonging fasting time, actively treating inflammation, and improving protein levels. In summary, persistently high NLR levels and persistently low PNI levels after surgery have certain predictive value for postoperative anastomotic leakage in patients with esophageal cancer. The combination of NLR and PNI on postoperative day 3 demonstrated the best predictive value, and postoperative NLR and PNI indicators are simple and easy to obtain, supporting there applicability in clinical practice.

It should be noted that our study involved certain limitations, including its single-center, retrospective design and a relatively small sample size, which inevitably introduced selection bias. Therefore, further large-scale, multicenter, prospective studies are needed to verify the results. What's more, given that all surgeries were performed by the same team, the anastomotic technique remained nearly consistent. We used a circular stapler for esophago-tubular gastric end-side anastomosis, with manual interrupted sutures applied to reinforce the anastomosis. Looking forward, we hope to collaborate with other centers to explore the impact of different anastomotic techniques on anastomotic leakage in future studies.

Conclusions

Persistently high NLR levels and persistently low PNI levels in the postoperative period following MIE correlated with the development of anastomotic leakage, and NLR combined with PNI on postoperative day 3 demonstrated the best ability to predict anastomotic leakage after this procedure.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-302/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-302/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-302/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of The Affiliated Lihuili Hospital of Ningbo University (No. KY2019PJ058) and informed consent was taken from all the patients.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Demarest CT, Chang AC. The Landmark Series: Multimodal Therapy for Esophageal Cancer. Ann Surg Oncol 2021;28:3375-82.
3. 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;36:2796-803.
4. van der Werf LR, Busweiler LAD, van Sandick JW, et al. Reporting National Outcomes After Esophagectomy and Gastrectomy According to the Esophageal Complications Consensus Group (ECCG). Ann Surg 2020;271:1095-101.
5. van de Beld JJ, Crull D, Mikhal J, et al. Complication Prediction after Esophagectomy with Machine Learning. Diagnostics (Basel) 2024;14:439.
6. Hua X, Qian R, Shi K, et al. Effectiveness and safety of bovine pericardium patch repair for cervical anastomotic leakage after oesophagectomy for cancer. J Thorac Dis 2019;11:3808-13.
7. Zhu J, Tao T, Zhang G, et al. Predictive factors for intrathoracic anastomotic leakage and postoperative mortality after esophageal cancer resection. BMC Surg 2024;24:260.
8. Tan H, Levi E, Nisa EL. Determinants of malignancy in paediatric neck lymphadenopathy—emphasis on the neutrophil-to-lymphocyte ratio. Aust J Otolaryngol 2025;8:10.
9. Chen Y, Huang S, Chen R, et al. Predicting prognosis of locally advanced esophageal squamous cell carcinoma through early changes in neutrophil-to-lymphocyte ratio following neoadjuvant immunochemotherapy. J Thorac Dis 2024;16:8230-9.
10. An N, Li J, Li M. Role of systemic inflammation response index and prognostic nutritional index in the prediction of moderate-to-severe bronchopulmonary dysplasia in very preterm infants. Transl Pediatr 2025;14:52-60.
11. Wu M, Zhu Y, Chen X, et al. Prognostic nutritional index predicts the prognosis of patients with advanced esophageal cancer treated with immune checkpoint inhibitors: a retrospective cohort study. J Gastrointest Oncol 2023;14:54-63.
12. Liesenfeld LF, Sauer P, Diener MK, et al. Prognostic value of inflammatory markers for detecting anastomotic leakage after esophageal resection. BMC Surg 2020;20:324.
13. Wang P, Li Y, Sun H, et al. Predictive Value of Body Mass Index for Short-Term Outcomes of Patients with Esophageal Cancer After Esophagectomy: A Meta-analysis. Ann Surg Oncol 2019;26:2090-103.
14. Yonis G, Cabalag CS, Link E, et al. Utility of routine oral contrast study for detecting postesophagectomy anastomotic leak - a systematic review and meta-analysis. Dis Esophagus 2019;32:doz011.
15. Wang YJ, Xie XF, He YQ, et al. Impact of perioperative decreased serum albumin level on anastomotic leakage in esophageal squamous cell carcinoma patients treated with neoadjuvant chemotherapy followed by minimally invasive esophagectomy. BMC Cancer 2023;23:1212.
16. Takahashi N, Okamura A, Kuriyama K, et al. Early Postoperative Serum Lactate Levels Predict Anastomotic Leakage After Minimally Invasive Esophagectomy. Ann Surg Oncol 2025;32:834-40.
17. Van Daele E, Vanommeslaeghe H, Peirsman L, et al. Early postoperative systemic inflammatory response as predictor of anastomotic leakage after esophagectomy: a systematic review and meta-analysis. J Gastrointest Surg 2024;28:757-65.
18. Wang C, Zhao K, Hu S, et al. A predictive model for treatment response in patients with locally advanced esophageal squamous cell carcinoma after concurrent chemoradiotherapy: based on SUVmean and NLR. BMC Cancer 2020;20:544.
19. Sun Y, Zhang L. The clinical use of pretreatment NLR, PLR, and LMR in patients with esophageal squamous cell carcinoma: evidence from a meta-analysis. Cancer Manag Res 2018;10:6167-79.
20. Watanabe M, Iwatsuki M, Iwagami S, et al. Prognostic nutritional index predicts outcomes of gastrectomy in the elderly. World J Surg 2012;36:1632-9.
21. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai Zasshi 1984;85:1001-5.
22. Mohri Y, Inoue Y, Tanaka K, et al. Prognostic nutritional index predicts postoperative outcome in colorectal cancer. World J Surg 2013;37:2688-92.
23. Markar S, Gronnier C, Duhamel A, et al. The Impact of Severe Anastomotic Leak on Long-term Survival and Cancer Recurrence After Surgical Resection for Esophageal Malignancy. Ann Surg 2015;262:972-80.
24. Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking Complications Associated with Esophagectomy. Ann Surg 2019;269:291-8.
25. Zheng X, Yang X, Lei S. Chylous leakage after esophagectomy for esophageal cancer: a systematic review. J Cardiothorac Surg 2024;19:240.
26. Rates of Anastomotic Complications and Their Management Following Esophagectomy: Results of the Oesophago-Gastric Anastomosis Audit (OGAA). Ann Surg 2022;275:e382-91.
27. Rutegård M, Lagergren P, Rouvelas I, et al. Intrathoracic

anastomotic leakage and mortality after esophageal cancer resection: a population-based study. Ann Surg Oncol 2012;19:99-103.
28. Ishida H, Fukutomi T, Taniyama Y, et al. Serum C-reactive protein and procalcitonin levels in patients with pneumonia and anastomotic leakage in the postoperative period after esophagectomy. Gen Thorac Cardiovasc Surg 2024;72:746-51.
29. Raymond DP, Seder CW, Wright CD, et al. Predictors of Major Morbidity or Mortality After Resection for Esophageal Cancer: A Society of Thoracic Surgeons General Thoracic Surgery Database Risk Adjustment Model. Ann Thorac Surg 2016;102:207-14.
30. Hagens ERC, Reijntjes MA, Anderegg MCJ, et al. Risk Factors and Consequences of Anastomotic Leakage After Esophagectomy for Cancer. Ann Thorac Surg 2021;112:255-63.
31. Greten FR, Grivennikov SI. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. Immunity 2019;51:27-41.
32. Yang X, Huang Y, Feng JF, et al. Prognostic significance of neutrophil-to- lymphocyte ratio in esophageal cancer: a meta-analysis. Onco Targets Ther 2015;8:789-94.
33. Radulescu D, Baleanu VD, Padureanu V, et al. Neutrophil/Lymphocyte Ratio as Predictor of Anastomotic Leak after Gastric Cancer Surgery. Diagnostics (Basel) 2020;10:799.
34. Paliogiannis P, Deidda S, Maslyankov S, et al. Blood cell count indexes as predictors of anastomotic leakage in elective colorectal surgery: a multicenter study on 1432 patients. World J Surg Oncol 2020;18:89.

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