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Prognostic Nutritional Index Predicts Early Recurrence After Esophagectomy for Esophageal Cancer Following Neoadjuvant Chemotherapy

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Abstract

Background/Aim: Although neoadjuvant chemotherapy (NAC) has improved oncologic outcomes in esophageal cancer, early postoperative recurrence remains a major cause of a poor prognosis. Immune-, inflammation-, and nutrition-based prognostic scores (IINBPS), such as the prognostic nutritional index (PNI), are reported prognostic markers in various malignancies; however, their ability to predict early recurrence after NAC remains unclear. This study aimed to identify the most reliable IINBPS for predicting early recurrence after esophagectomy following NAC.

Patients and Methods: We retrospectively analyzed 61 patients with esophageal cancer who underwent curative esophagectomy following NAC between January 2012 and December 2024. Early recurrence was defined as recurrence within six months after surgery. Clinicopathological factors and IINBPS before and after NAC were evaluated. Receiver operating characteristic curve analysis was used to assess predictive performance, and risk factors for early recurrence were analyzed using univariate and multivariate logistic regression analyses.

Results: Early postoperative recurrence occurred in 13 patients (21.3%). Among the evaluated IINBPS, pre-NAC PNI demonstrated the highest discriminatory ability, with an area under the receiver operating characteristic curve of 0.71. Patients with *versus* without early recurrence had significantly lower pre-NAC PNI values. Multivariate analysis identified low pre-NAC PNI as an independent predictor of early recurrence.

Conclusion: Pre-NAC PNI was the most useful IINBPS predictor of early recurrence after esophagectomy for esophageal cancer.

Keywords: Esophageal cancer, early recurrence, neoadjuvant chemotherapy, prognostic nutritional index.

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Introduction

Esophageal cancer remains one of the most lethal malignancies worldwide, with high recurrence rates and poor long-term survival (1). Neoadjuvant chemotherapy (NAC) is an established standard treatment for resectable locally advanced esophageal cancer, with improved oncologic outcomes (2). Nevertheless, early postoperative recurrence continues to limit survival benefits. Patients with early recurrence often experience aggressive disease behavior and limited responsiveness to subsequent systemic therapy, resulting in an extremely poor prognosis (3, 4).

Immune-, inflammation-, and nutrition-based prognostic scores (IINBPS), including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), prognostic nutritional index (PNI), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and C-reactive protein-to-albumin ratio (CAR), are biomarkers reflecting systemic immune-inflammatory and nutritional status. These indices correlate with oncologic outcomes in various malignancies, including esophageal cancer (5-11).

Although several studies have evaluated IINBPS in patients undergoing esophagectomy after NAC, most have focused on overall survival (OS) or disease-free survival. In contrast, comparative assessments of multiple IINBPS specifically regarding early postoperative recurrence remain limited (5, 7, 9, 10). Therefore, the present study aimed to comprehensively evaluate multiple IINBPS in patients with esophageal cancer undergoing curative resection after NAC and to identify the most reliable predictors of early postoperative recurrence.

Patients and Methods

Patients. Between January 2012 and December 2024, 105 patients underwent esophagectomy with lymph node dissection after preoperative treatment at our institution. We excluded 23 patients who received preoperative chemoradiotherapy, 13 who underwent R1 resection, and eight who received preoperative treatment at another institution or for another disease. Consequently, 61 patients who underwent R0 esophagectomy after NAC were included.

Pre-treatment evaluation routinely included upper gastrointestinal endoscopy and contrast-enhanced computed tomography (CT) from neck to pelvis. Patients clinically diagnosed with stage II or III esophageal cancer were eligible for NAC, except those aged over 80 years or with creatinine clearance <30 ml/min.

NAC regimens were selected in accordance with institutional protocols. Since 2022, eligible patients received docetaxel, cisplatin, and fluorouracil (DCF), while those unsuitable for DCF received fluorouracil plus cisplatin. All patients received two cycles of fluorouracil plus cisplatin or three cycles of DCF; none received adjuvant chemotherapy or radiotherapy. Esophagectomy was performed primarily using minimally invasive techniques, including thoracoscopic or robotic approaches, with three-field lymph node dissection. Reconstruction was mainly performed using a gastric conduit *via* the retrosternal route.

Data collection. Demographic and clinicopathological data were retrospectively collected from medical records and are listed in Table I. Tumor staging was in accordance with the International Union Against Cancer TNM Classification (8th edition). Postoperative complications were graded using the Clavien–Dindo classification.

Peripheral blood samples were collected before treatment at the initial visit (pre-NAC) and the day before surgery (post-NAC). Laboratory measurements included neutrophil, lymphocyte, monocyte, and platelet counts, as well as serum C-reactive protein (CRP) and albumin levels. IINBPS were calculated from these parameters in accordance with previously published definitions (5, 7-9). The NLR, LMR, and PLR were defined as the ratios of neutrophils, lymphocytes, and platelets to lymphocytes or monocytes, respectively. The SII was calculated as platelet count × neutrophil count/lymphocyte count, and SIRI as neutrophil count × monocyte count/lymphocyte count

Table I. *Comparison of clinicopathological characteristics between patients with and without early postoperative recurrence.*

Variables	Early recurrence (N=13)	Non-early recurrence (N=48)	*p*-Value
Age (years)	71.2±5.6	66.1±9.4	0.070
Sex (male/female)	10/2	45/8	0.080
ASA>3	0/12	2/51	0.380
B-index	1031±584	716±432	0.090
BMI	21.2±2.3	21.5±3.4	0.960
DM (yes/no)	2/10	8/45	0.890
COPD (yes/no)	3/9	24/39	0.910
Hypertension (yes/no)	7/5	27/26	0.640
Location (Ut or Mt/Lt)	5/8	27/21	0.250
cStage (III/II/I)	12/0/0	27/18/8	0.001
Postoperative pneumonia (CD grade≧2) (yes/no)	5/8	12/36	0.350
Anastomotic leakage (CDgrade≧2) (yes/no)	2/11	0/48	0.010
Pathological tumor depth after NAC (ypT ≥3 *vs.* <3)	10/3	20/28	0.020
Pathological lymph node status after NAC (ypN ≥1 *vs.* ypN0)	12/1	27/21	0.010
Histological type (SCC/Adeno)	11/2	45/3	0.320
Histological differentiation (poorly differentiated/others)	4/9	5/43	0.080
NAC regimen (DCF/FP)	1/11	7/46	0.62
Tumor regression grade (≦2/>2)	1/12	10/38	0.24

Data are presented as mean±standard deviation or number of patients. Adeno: Adenocarcinoma; ASA: American Society of Anesthesiologists physical status; BMI: body mass index; CD: Clavien–Dindo; COPD: chronic obstructive pulmonary disease; DCF: docetaxel, cisplatin, and fluorouracil; DM: diabetes mellitus; FP: fluorouracil and cisplatin; NAC: neoadjuvant chemotherapy; SCC: squamous cell carcinoma; Ut/Mt/Lt: upper thoracic esophagus/middle thoracic esophagus/lower thoracic esophagus; ypN: pathological lymph node positivity; ypT: pathological tumor depth.

(5). PNI was calculated as 10 × serum albumin (g/dl) + 0.005 × total lymphocyte count (/mm^3), and CAR as serum CRP/serum albumin (7).

Follow-up and definition of early recurrence. Postoperative follow-up was performed one month after surgery, every 2-3 months for the first two years, then every six months until death or last follow-up. Follow-up assessments comprised physical examination, routine laboratory tests, and imaging. Contrast-enhanced chest and abdominal computed tomography (CT) was routinely performed at each visit, with additional imaging, including magnetic resonance imaging or positron emission tomography-CT when recurrence was suspected.

Tumor recurrence was defined as radiologically or pathologically confirmed local or distant disease recurrence following curative resection. Radiologic recurrence was diagnosed as newly detected lesions consistent with recurrent or metastatic disease on CT, magnetic resonance imaging, or positron emission tomography-CT, with histological confirmation when necessary. Early recurrence was defined as recurrence within six months after surgery.

Statistical analysis. Continuous variables are expressed as mean±standard deviation and compared using the Wilcoxon rank-sum test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Patients were classified into early- and non-early recurrence groups. The non-early recurrence group comprised patients without recurrence and those who developed recurrence >6 months after surgery. To identify risk factors for early recurrence, univariate analyses were performed, followed by multivariate logistic regression analysis using variables that were significant in the univariate analyses.

NLR, LMR, PLR, SII, SIRI, PNI, and CAR were calculated in accordance with previously reported definitions (5, 7-9). Variables significantly associated with early recurrence were further evaluated using receiver operating characteristic (ROC) curve analysis. Optimal cut-off values were determined using Youden's index, and predictive performance was assessed by the area under the ROC curve.

OS was defined as the time from surgery to death from any cause or last follow-up, and disease-free survival as the time from surgery to first recurrence or death. Survival curves were estimated using the Kaplan–Meier method and compared with the log-rank test. For the survival analyses, patients were stratified into high and low groups by the optimal cut-off value of the prognostic score most strongly associated with early recurrence. Patients without events were censored at the date of the last follow-up. All statistical analyses were two-sided, with $p<0.05$ considered statistically significant. Analyses were performed using JMP software (SAS Institute Inc., Cary, NC, USA).

Results

Patients' characteristics. Early postoperative recurrence within six months after surgery was observed in 13/61 patients (21.3%); the remaining 48 patients comprised the non-early recurrence group (Table I). All patients in the early recurrence group were classified as clinical stage III, resulting in a significantly higher proportion of cStage III disease compared with the non-early recurrence group (p=0.001).

Baseline clinicopathological characteristics, including age, sex, tumor location, histological type, NAC regimen, and major postoperative complications (Clavien–Dindo grade ≥2 pneumonia and anastomotic leakage), were comparable between the groups. Advanced pathological tumor depth (≥pT3) and pathological lymph node metastasis (≥pN1) were significantly more frequent in the early *versus* non-early recurrence groups (p=0.02 and p=0.01, respectively). No significant difference was observed in pathological response to NAC.

Timing of early recurrence. The median time to recurrence was 3.9 months (range=1.4-6 months) in the early recurrence group. No patients experienced locoregional recurrence at the primary tumor site. In the early recurrence group, distant metastases were observed in nine patients, extra-regional lymph node recurrence in three patients, and intra-regional lymph node recurrence in one patient. Regarding distant metastases, the liver was the most frequent site (n=5), followed by lymph nodes (n=3), bone (n=1), and brain (n=1), with some patients exhibiting multiple metastatic sites.

Comparison of IINBPS between groups. Baseline IINBPS were compared between the early- and non-early recurrence groups. Pre-NAC PNI was significantly lower in the early- *versus* non-early recurrence groups (p=0.02). No significant differences were observed between the groups in the other pre-NAC IINBPS. Post-NAC IINBPS were also compared between the groups, with no significant association with early postoperative recurrence (Table II).

Predictive performance of pre-NAC PNI for early recurrence. In the univariate analysis (Table II), pre-NAC PNI was the only inflammation-based prognostic index showing a significant difference between the early- and non-early recurrence groups. Therefore, ROC curve analysis was performed exclusively for pre-NAC PNI to evaluate its diagnostic performance for predicting early postoperative recurrence.

ROC analysis demonstrated that pre-NAC PNI had an area under the curve of 0.71, with a sensitivity of 0.77 and a specificity of 0.74 at an optimal cut-off value of 45.5 (Figure 1A). Using this cut-off value, patients were subsequently stratified into high- and low-PNI groups for further analyses.

Kaplan–Meier analysis demonstrated that patients with a low *versus* high pre-NAC PNI had significantly worse OS (p=0.01, log-rank test) (Figure 1B). Disease-free survival was also significantly shorter in the low *versus* high pre-NAC PNI groups (p=0.002, log-rank test) (Figure 1C).

Risk factors for early recurrence. Univariate logistic regression analysis identified several factors

Table II. *Inflammation-based prognostic scores before and after neoadjuvant chemotherapy.*

IINBPS	Early recurrence	Non-early recurrence	*p*-Value
Pre-NAC			
NLR	3.6±1.7	2.6±1.2	0.12
LMR	3±1.3	3.9±1.7	0.06
PLR	194.1±82.4	161.9±72.2	0.14
SII	901±533	684±445	0.12
SIRI	1.93±1.22	1.27±0.75	0.15
PNI	44.6±4.8	48.3±5.7	0.02
CAR	0.21±0.26	0.16±0.35	0.13
Post-NAC			
NLR	3.2±2.1	2.3±1.3	0.11
LMR	5.7±9.0	3.4±1.5	0.36
PLR	198.5±128.5	171.5±215.1	0.27
SII	810±771	514±447	0.11
SIRI	1.73±1.58	1.17±0.86	0.12
PNI	45.6±6.5	47.5±7.2	0.36
CAR	0.08±0.13	0.09±0.15	0.82

Data are presented as mean±standard deviation. Pre-NAC values were obtained at the initial visit before treatment initiation, and post-NAC values immediately before surgery. NAC: Neoadjuvant chemotherapy; IINBPS: immune-, inflammation-, and nutrition-based prognostic scores; NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; PNI: prognostic nutritional index; CAR: C-reactive protein-to-albumin ratio.

significantly associated with early postoperative recurrence (Table III). Advanced pathological tumor depth (ypT3-4) [odds ratio (OR)=4.66, 95% confidence interval (CI)=1.24-22.8, *p*=0.02], pathological lymph node positivity (ypN1-3) (OR=9.33, 95% CI=1.63-176.8, *p*=0.01), and pre-NAC low PNI (OR=6.18, 95% CI=1.69-26.5, *p*=0.01) were significantly associated with early recurrence. The remaining clinicopathological variables were not significantly associated with early recurrence.

In the multivariate analysis, low pre-NAC PNI remained an independent predictor of early postoperative recurrence (OR=5.13, 95% CI=1.33-22.8, *p*=0.02). Pathological lymph node positivity showed a marginal association with early recurrence (OR=6.21, 95% CI=0.98-121, *p*=0.052) (Table IV).

Discussion

In this retrospective study, we demonstrated that pre-NAC PNI was the most reliable predictor of early postoperative recurrence within six months after esophagectomy. Among the evaluated IINBPS, pre-NAC PNI showed the highest discriminatory ability and remained independently associated with early recurrence even after adjustment for pathological lymph node status.

Early postoperative recurrence is a clinically critical event in esophageal cancer because it is associated with extremely poor survival after recurrence (3, 4). Previous studies have reported pathological predictors of early recurrence after esophagectomy, such as advanced tumor depth, lymph node metastasis, lymphovascular invasion, and poor histological differentiation (12-18). However, most of these factors are evaluable only after surgery, limiting their utility for pre-treatment decision-making.

Yoshida *et al.* reported that elevated pre-NAC CRP was a risk factor for early recurrence after esophagectomy following NAC (14), supporting the importance of evaluating systemic inflammatory and nutritional status before treatment initiation. Our findings are consistent with this concept, as PNI comprises serum albumin and peripheral lymphocyte count, reflecting both nutritional status and immune competence (19).

Recent studies have further emphasized the clinical relevance of immunonutritional markers in esophageal cancer. Deterioration of nutritional status during NAC has been associated with worse postoperative outcomes (20), and composite indices such as HALP (21) and GINI (22), as well as other inflammation-based assessment tools (23), have been reported as independent predictors of long-term survival after curative treatment. However, most of these investigations focused on overall or recurrence-free survival rather than very early postoperative recurrence. In contrast, our study specifically addressed recurrence within six months after esophagectomy, which may reflect pre-existing occult systemic disease at the time of treatment initiation.

Although dynamic changes in nutritional markers during NAC may be clinically relevant, exploratory

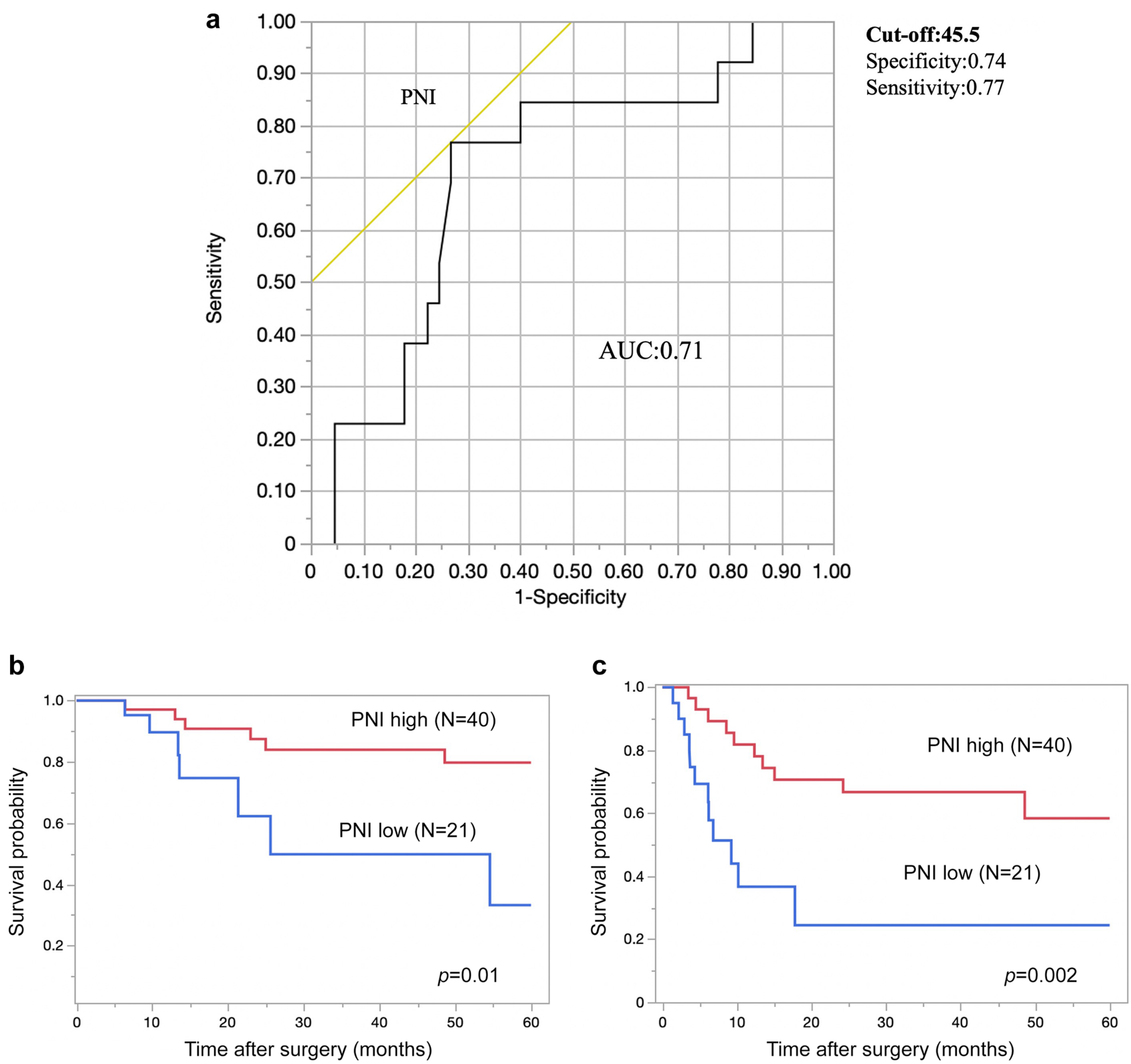

Figure 1. *Predictive value of pre-neoadjuvant chemotherapy (NAC) prognostic nutritional index (PNI) and its association with survival. (a) Receiver operating characteristic curve of pre-NAC PNI for predicting early postoperative recurrence within six months after esophagectomy. The optimal cut-off value was determined using Youden's index. (b) Kaplan–Meier overall survival (OS) curves stratified by pre-NAC PNI (high versus low). (c) Kaplan–Meier disease-free survival (DFS) curves stratified by pre-treatment PNI (high versus low). AUC: Area under the curve.*

analyses in our cohort did not demonstrate a clear association between peri-treatment changes in PNI and early recurrence. This observation suggests that baseline host immunonutritional status, rather than treatment-related fluctuation, may play a more decisive role in determining rapid relapse.

Biologically, a low PNI may reflect an unfavorable systemic condition characterized by ongoing inflammation

Table III. *Univariate analysis of risk factors for early postoperative recurrence after esophagectomy following neoadjuvant chemotherapy.*

Variables	OR	95% CI	*p*-Value
Age (≧70/<70)	2.24	0.65-8.38	0.21
Sex (male/female)	0.78	0.15-5.86	0.78
cStage (III/others)	2	0.52-9.79	0.32
ypT (pT3-4/pT0-2)	4.66	1.24-22.8	0.02
ypN (pN1-3/pN0)	9.33	1.63-176.8	0.01
Lymphatic invasion (yes /no)	2.92	0.84-11.1	0.09
Vessel invasion (yes /no)	1.94	0.56-6.93	0.29
Tumor regression grade (≦2/>2)	2.26	0.51-15.8	0.29
PNI (low *vs.* high)	6.18	1.69-26.5	0.01

Values are presented as odds ratios (ORs) with 95% confidence intervals (CIs). High- and low pre-NAC PNI groups were defined using the optimal cut-off value determined by receiver operating characteristic curve analysis. ypT: Pathological tumor depth; ypN: pathological lymph node positivity; NAC: neoadjuvant chemotherapy; PNI: prognostic nutritional index.

Table IV. *Multivariate analysis of independent predictors of early postoperative recurrence after esophagectomy following neoadjuvant chemotherapy.*

Variables	OR	95% CI	*p*-Value
ypN (pN1-3/pN0)	6.21	0.98-121	0.052
PNI (low *vs.* high)	5.13	1.33-22.8	0.02

Values are presented as odds ratios (ORs) with 95% confidence intervals (CIs). High- and low pre-NAC PNI groups were defined using the optimal cut-off value determined by receiver operating characteristic curve analysis. ypN: pathological lymph node positivity; PNI: prognostic nutritional index.

and impaired host immune status rather than malnutrition alone (24). Proinflammatory cytokines, such as interleukin-6, have been associated with reduced serum albumin levels and altered lymphocyte dynamics and may contribute to tumor progression and early relapse (25). Although cytokine levels were not assessed in the current study, the consistent tendency across inflammation-based scores supports a role of systemic inflammation in early recurrence.

Patients with early cancer recurrence frequently develop distant metastases (3, 4). Therefore, alternative strategies emphasizing systemic disease control may merit consideration. Recent trials have explored intensified neoadjuvant approaches, including triplet chemotherapy and neoadjuvant chemoimmunotherapy, with the JCOG1109 (NExT) trial demonstrating improved survival with DCF compared with conventional doublet regimens (2, 26). However, most patients in the current study received fluorouracil plus cisplatin-based regimens, and the interaction between host-related risk factors warrants further investigation.

Pre-treatment PNI alone is insufficient to justify treatment modification because early recurrence rates remain limited even in high-risk groups (27). Integrating host-related biomarkers with tumor response and nodal treatment effects may improve risk stratification. Given the retrospective design and small sample size, our findings should be interpreted cautiously.

Conclusion

Low pre-NAC PNI was significantly associated with early recurrence after esophagectomy. Pre-NAC PNI represents a simple and readily available biomarker that may help identify patients at increased risk of early postoperative recurrence.

Conflicts of Interest

The Authors declare that they have no conflicts of interest related to this study.

Authors' Contributions

Conceptualization: HY, YT; Methodology: HY, S Yoshiyama, MO; Data curation: HY, RU, MS, TI; Formal analysis: HY, S Yamashita; Investigation: HY, RU, S Yoshiyama, MO, HI; Resources: TK, Y Okugawa; Writing – original draft: HY; Writing – review & editing: YT, TS, MK, Y Okita; Supervision: YT; Project administration: YT. All Authors read and approved the final manuscript.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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