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ORIGINAL RESEARCH

Comparison of Blood Inflammation Scores and Their Prognostic Value in Elderly Unresectable Esophageal Squamous Cell Carcinoma Patients Treated with Radiotherapy/Chemoradiotherapy

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Objective: To investigate the predictive value of inflammation-based prognostic scores (IBs) on overall survival (OS) in elderly unresectable esophageal squamous cell carcinoma (ESCC) patients treated with radiotherapy (RT) or chemoradiotherapy (CRT).

Methods: This retrospective study included 120 elderly ESCC patients who received RT/CRT. IBs, including neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), systemic immune-inflammation index (SII), and systemic immune response index (SIRI), were calculated within one week before treatment and within two weeks after treatment.

Results: A total of 120 patients were included. The median age was 76 years. Significant differences were found between survivors (n=29) and non-survivors (n=91) in tumor size (p=0.018), T stage (p=0.006), and pre-treatment lymphocyte count (p=0.002). At the study endpoint, 75.8% of patients (91/120) had died, and 24.2% (29/120) remained alive. The median overall survival (OS) and progression-free survival (PFS) were 18 months and 15 months, respectively. The 1-year, 3-year, and 5-year OS rates were 61.7%, 18.3%, and 5.8%, respectively, and the corresponding PFS rates were 40.8%, 7.5%, and 1.7%. Pre-treatment NLR, SIRI, and SII were associated with OS. Post-treatment NLR and PLR were also predictors. However, in multivariate analysis, only age (p=0.002) and adverse events (p=0.003) remained independent predictors of OS.

Conclusion: High NLR, SII, and SIRI before treatment, and NLR and PLR after treatment, were associated with poorer OS in elderly ESCC patients undergoing RT/CRT. However, none of these IBs remained independent predictors in multivariate analysis, suggesting that their prognostic value may be influenced by confounding factors.

Keywords: esophageal squamous cell carcinoma, chemoradiotherapy, prognostic biomarkers, inflammation, elderly patients

Introduction

Esophageal carcinoma is one of the most common gastrointestinal malignancies and ranks as the sixth leading cause of cancer-related mortality worldwide. According to 2022 global estimates (GLOBOCAN), there were approximately 510,716 new cases and 445,129 deaths annually,[1] with more than half of the cases occurring in China.[2] The predominant histological subtype in China is esophageal squamous cell carcinoma (ESCC).[3] Despite advancements in treatment, the prognosis for ESCC remains poor, particularly for elderly patients, who often present with advanced-stage disease and have limited treatment options due to age-related comorbidities and decreased treatment tolerance. Studies have shown that elderly ESCC patients have lower overall survival (OS) rates compared to younger patients, highlighting the need for improved prognostic stratification.[4–6]

Given the aggressive nature of ESCC, radiotherapy (RT) and concurrent chemoradiotherapy (CRT) are the primary treatment modalities for unresectable ESCC, offering potential survival benefits.[7] However, elderly patients frequently experience higher toxicity and treatment-related complications, making individualized treatment selection crucial.[8]

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Therefore, there is a growing interest in identifying reliable prognostic biomarkers to optimize treatment decisions and improve outcomes for this high-risk population.

Beyond traditional treatment challenges, accumulating evidence highlights the pivotal role of inflammation in cancer progression, where it modulates tumor growth, invasion, and metastasis.[9] In recent years, inflammation-based prognostic scores (IBs), including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), systemic immune-inflammation index (SII), and systemic immune response index (SIRI), have been extensively studied in various malignancies.[10] These blood-derived biomarkers reflect host immune and inflammatory status and have been associated with prognosis in ESCC.[11]

While previous studies have demonstrated the prognostic value of NLR, SII, and SIRI in ESCC, there is no comprehensive analysis comparing their predictive ability, particularly in elderly patients undergoing RT/CRT. Furthermore, the optimal cutoff values for these IBs remain inconsistent, and their independent prognostic significance in multivariate models is unclear.

Therefore, the aim of this study is to evaluate and compare the prognostic value of pre-treatment and post-treatment IBs in elderly ESCC patients undergoing RT/CRT. By identifying the most predictive IBs, this study seeks to establish a more accurate prognostic model to aid in clinical decision-making for this high-risk population.

Patients and Methods

This retrospective study analyzed elderly esophageal squamous cell carcinoma (ESCC) patients aged 70 years or older who were treated with radiotherapy (RT) or chemoradiotherapy (CRT) between October 2016 and April 2024.

Patient Eligibility

The inclusion criteria for this study were as follows: (1) histologically confirmed esophageal squamous cell carcinoma; (2) unresectable stage I–IV disease or patients who refused surgery; (3) an estimated survival time of at least three months, based on prior clinical prognostic models and physician assessment; (4) a Karnofsky Performance Status (KPS) score of 70 or higher; and (5) adequate bone marrow function, defined as a white blood cell count of at least 3.5 $\times 10^9$/L, an absolute neutrophil count of at least 1.5 $\times 10^9$/L, a platelet count of at least 100 $\times 10^9$/L, and a hemoglobin level of at least 90 g/L.

The exclusion criteria were as follows: (1) histological subtypes other than squamous cell carcinoma; (2) severe infections or uncontrolled chronic inflammatory diseases; (3) a history of other malignancies within the past five years; and (4) prior chemotherapy, radiotherapy, or surgery for esophageal cancer.

The age threshold of 70 years was selected based on consensus definitions in geriatric oncology research[12] and clinical trial eligibility criteria. Our cohort includes 34 patients aged ≥80 years (28.3%, 34/120), providing improved statistical power for subgroup analyses. This proportion reflects real-world treatment patterns where octogenarians meeting therapeutic criteria represent a substantial subset of elderly ESCC patients, despite their higher vulnerability due to comorbidities and reduced treatment tolerance.

This study was approved by the Institutional Review Board of Peking University International Hospital (Approval No: [2024-KY-0044-01]), and informed consent was obtained from all participants.

Data Collection

Clinical and tumor-related data, including age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking and alcohol history, TNM stage, comorbidities, treatment regimen, and adverse events, were collected. TNM staging was classified according to the 8th edition of the AJCC/UICC TNM classification. Comorbidities included hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease, and chronic kidney disease. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Blood samples were collected within one week before treatment (pre-treatment IBs) and within two weeks after treatment (post-treatment IBs). The following blood parameters were analyzed: neutrophil count (N), lymphocyte count (L), monocyte count (M), platelet count (P), serum albumin (ALB), and prealbumin (PAb).

The inflammation-based prognostic scores (IBs) were calculated as follows:

① Neutrophil-to-lymphocyte ratio (NLR) = N / L

② Lymphocyte-to-monocyte ratio (LMR) = L / M

③ Platelet-to-lymphocyte ratio (PLR) = P / L

④ Systemic immune-inflammation index (SII) = P × N / L

⑤ Systemic immune response index (SIRI) = N × M / L

⑥ Prognostic nutritional index (PNI) = ALB (g/L) + 5 × L

The optimal cutoff values for IBs were determined using receiver operating characteristic (ROC) curve analysis, and patients were stratified into high and low groups based on the maximum Youden index values.

Treatment

All patients received intensity-modulated radiotherapy (IMRT). The target volume was delineated according to the International Commission on Radiological Units and Measurements (ICRU) Report 62. The total radiation dose ranged from 50.4 to 60 Gy, delivered in 28–30 fractions, once daily, five days per week, using a Varian linear accelerator.

Some patients received chemotherapy based on physician assessment of ECOG PS, renal function, and treatment tolerance. Chemotherapy regimens included Tegafur Gimeracil and Oteracil Potassium Capsules (S-1) at 40–60 mg/m² twice daily on days 1–14 every three weeks or Paclitaxel (135–175 mg/m², day 1) combined with Cisplatin (60–75 mg/m², day 1 or day 2) every three weeks.

Treatment efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Statistical Analysis

Statistical analyses were performed using SPSS™ Statistics v26.0 (IBM, NY, USA). Given the sample size of 120 patients with 34 octogenarians, post-hoc power analysis confirmed adequate statistical power (>0.80) for the primary endpoint of overall survival. The chi-square test was used to compare clinical characteristics, while the Wilcoxon rank-sum test was used to assess differences in IBs before and after treatment. The Kaplan–Meier method was applied to estimate overall survival (OS) and progression-free survival (PFS), and the Log rank test was used for survival comparisons. ROC curve analysis was performed to assess the prognostic value of IBs, with OS at one year, three years, and five years used as time-dependent endpoints. Sensitivity, specificity, and area under the curve (AUC) values were calculated for each IB. Univariate Cox regression analysis was conducted to identify factors significantly associated with OS. Variables with p-values <0.05 were included in a multivariate Cox proportional hazards model to adjust for confounders. Hazard ratios (HR) with 95% confidence intervals (CI) were reported for all prognostic factors. A two-tailed p-value ≤ 0.05 was considered statistically significant.

To address potential multicollinearity among inflammation-based scores (NLR, LMR, PLR, PNI, SII, and SIRI), we performed Pearson correlation analysis and calculated variance inflation factors (VIF). Principal component analysis (PCA) was subsequently conducted to derive orthogonal components. Additionally, stepwise regression was employed to select the most predictive markers. For the octogenarian subgroup analysis (n=34), we performed sensitivity analyses to validate the robustness of our findings in this vulnerable population.

Results

Patient Characteristics

A total of 120 elderly ESCC patients who received RT or CRT were included in this study (Figure 1). The median age was 76 years (range: 70–90 years). Among these patients, 73 (60.8%) were smokers, and 67 (55.8%) had a history of alcohol consumption. Baseline characteristics are summarized in Table 1. Among 120 patients, 29 (24.2%) survived and 91 (75.8%) died by study endpoint.

Significant differences were observed between survivors and non-survivors in multiple parameters including KPS (p=0.034), TNM stage (p=0.031), adverse events (p=0.002), BMI (p=0.023), tumor size (p=0.018), tumor differentiation (p=0.009), pre-treatment WBC (p=0.011), pre-treatment platelet count (p=0.016), and pre-treatment lymphocyte count

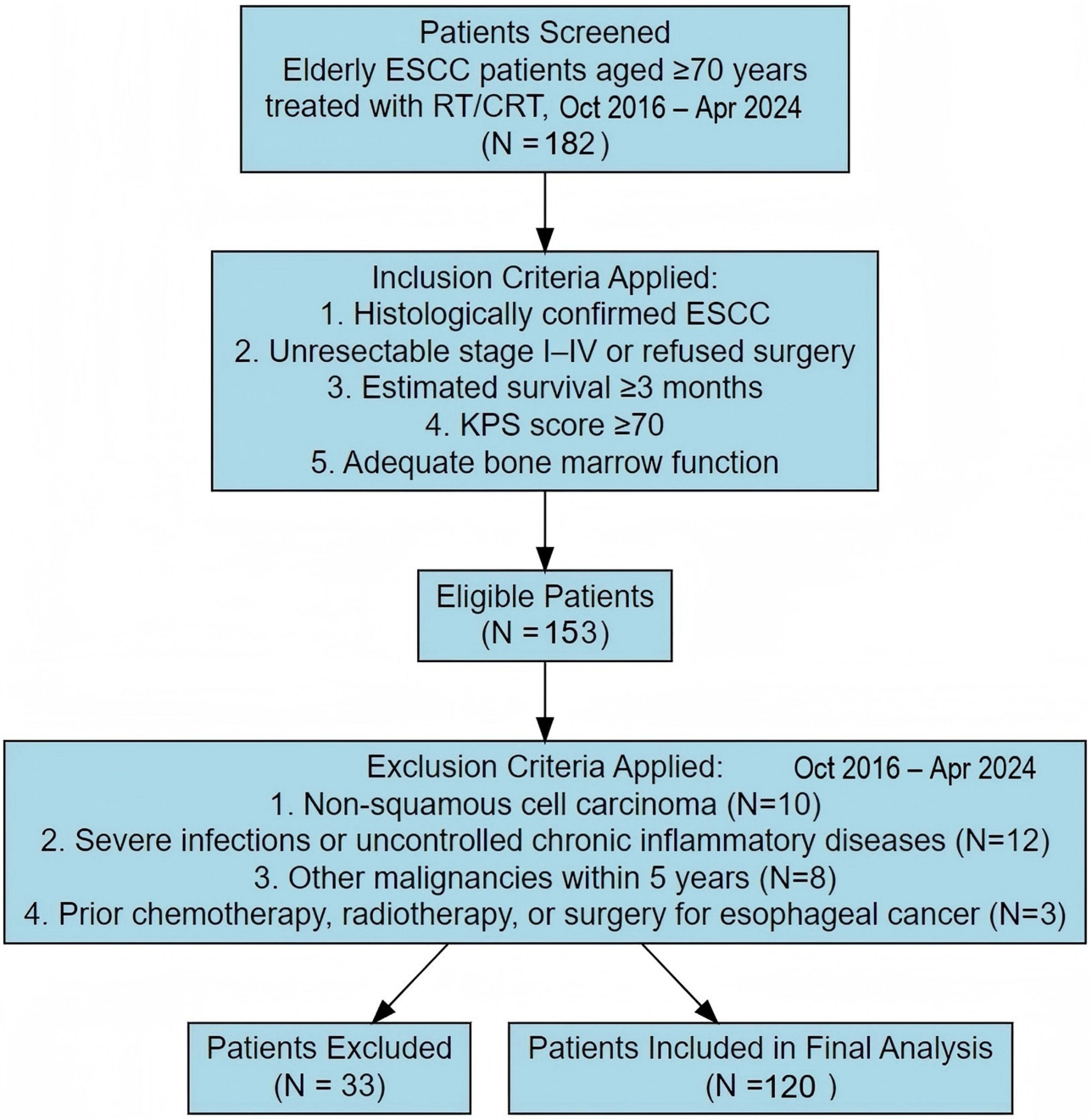

Figure 1 Flowchart illustrating the patient selection process for eligible elderly ESCC patients receiving RT/CRT. From 182 initially screened patients aged ≥70 years treated, 153 met initial inclusion criteria. Subsequently, 33 patients were excluded (10 with non-squamous cell carcinoma, 12 with severe infections or uncontrolled chronic inflammatory diseases, 8 with other malignancies within 5 years, and 3 with prior esophageal cancer treatment), resulting in 120 patients included in the final analysis.

(p=0.002). The majority of patients had stage II (n=41, 34.2%), stage III (n=35, 29.2%) or stage IV disease (n=34, 28.3%). Regarding treatment, 70 patients (58.3%) received RT alone, while 50 (41.7%) received CRT (concurrent or sequential).

The octogenarian cohort (n=34, 28.3%) provided robust comparative analysis: median OS was significantly shorter in patients aged ≥80 vs <80 years (8 vs 22 months, p=0.015), with higher rates of grade ≥3 adverse events (58.8% vs 44.9%, p=0.051) and comorbidities (88.2% vs 73.8%, p=0.092). The increased sample size allowed for meaningful subgroup analyses with adequate statistical power (Table 2).

Table 1 Patient Information (N=120)

Characteristics	Total N=120 (%)	Survivors (n=29)	Non-Survivors (n=91)	P value
Age				0.125
<80 years old	86 (71.7%)	22 (75.9%)	64 (70.3%)	
≥80 years old	34 (28.3%)	7 (24.1%)	27 (29.7%)	
Gender				0.683
Male	92 (76.7%)	22 (75.9%)	70 (76.9%)	
Female	28 (23.3%)	7 (24.1%)	21 (23.1%)	
KPS				0.034
90–100	82 (68.3%)	23 (79.3%)	59 (64.8%)	
70–80	38 (31.7%)	6 (20.7%)	32 (35.2%)	
Location				0.438
Upper thoracic	33 (27.5%)	9 (31.0%)	24 (26.4%)	
Middle thoracic	52 (43.3%)	12 (41.4%)	40 (44.0%)	
Lower thoracic	35 (29.2%)	8 (27.6%)	27 (29.7%)	
TNM stage				0.031
I	10 (8.3%)	4 (13.8%)	6 (6.6%)	
II	41 (34.2%)	13 (44.8%)	28 (30.8%)	
III	35 (29.2%)	9 (31.0%)	26 (28.6%)	
IV	34 (28.3%)	3 (10.3%)	31 (34.1%)	
Treatment				0.118
RT alone	70 (58.3%)	18 (62.1%)	52 (57.1%)	
CCRT	17 (14.2%)	4 (13.8%)	13 (14.3%)	
SCRT	33 (27.5%)	7 (24.1%)	26 (28.6%)	
Radiation dose				0.432
<60Gy	17 (14.2%)	5 (17.2%)	12 (13.2%)	
≥60Gy	103 (85.8%)	24 (82.8%)	79 (86.8%)	
Smoking				0.794
Yes	73 (60.8%)	18 (62.1%)	55 (60.4%)	
No	47 (39.2%)	11 (37.9%)	36 (39.6%)	
Alcohol				0.589
Yes	67 (55.8%)	16 (55.2%)	51 (56.0%)	
No	53 (44.2%)	13 (44.8%)	40 (44.0%)	
Comorbidities				0.572
Yes	85 (70.8%)	20 (69.0%)	65 (71.4%)	
No	35 (29.2%)	9 (31.0%)	26 (28.6%)	
Adverse Events				0.002
≥grade 3	59 (49.2%)	8 (27.6%)	51 (56.0%)	
<grade 3	61 (50.8%)	21 (72.4%)	40 (44.0%)	
BMI (kg/m^2)	24.5 ± 3.2	25.8 ± 2.6	24.0 ± 3.3	0.023
Tumor size (cm)	5.2 ± 2.1	4.1 ± 1.5	5.6 ± 2.2	0.018
Tumor differentiation				0.009
Well/Moderate	60 (50.0%)	19 (65.5%)	41 (45.1%)	
Poor	60 (50.0%)	10 (34.5%)	50 (54.9%)	
Pre-treatment WBC ($\times 10^9/L$)	7.8 ± 2.4	6.9 ± 1.8	8.1 ± 2.5	0.011
Pre-treatment Platelet ($\times 10^9/L$)	220 ± 65	245 ± 60	210 ± 66	0.016
Pre-treatment Lymphocyte ($\times 10^9/L$)	1.2 ± 0.5	1.6 ± 0.4	1.0 ± 0.5	0.002

Survival Status and Analysis

The final follow-up was conducted on October 1, 2024, with a median follow-up duration of 38.5 months. The median OS and PFS were 18 months and 15 months, respectively. The 1-year, 3-year, and 5-year OS rates were 61.7% (74/120), 18.3% (22/120), and 5.8% (7/120), respectively. Corresponding PFS rates were 40.8% (49/120), 7.5% (9/120), and 1.7% (2/120). Among the 91 deceased patients, causes of death were categorized as follows: 7 (7.7%) due to complications

Table 2 Comparison of Clinical Characteristics Between Age Groups

Characteristics	≥80 Years Group (n=34)	<80 Years Group (n=86)	p-value
Median OS (months)	8	22	0.015
≥Grade 3 adverse events (%)	58.8 (20/34)	44.9 (39/86)	0.051
Medical comorbidities (%)	88.2 (30/34)	73.8 (63/86)	0.092

such as bleeding and pneumonia, 46 (50.5%) due to comorbidities including cardiovascular, renal, and pulmonary diseases, 11 (12.1%) due to local and regional lymph node progression, and 27 (29.7%) due to distant metastases.

Treatment-Related Adverse Events

The detailed distribution of treatment-related adverse events is shown in Table 3. The most common any-grade adverse events were esophagitis (54/120, 45.0%) and fatigue (45/120, 37.5%). Grade ≥3 toxicities predominantly included esophagitis (41/120, 34.2%) and pneumonia (5/120, 4.2%).

IBs of Different Treatment Times and Optimal Cutoff Values

Pre-treatment IBs included NLRpre, LMRpre, PLRpre, PNIpre, SIRIpre, and SIIpre, while post-treatment IBs included NLRpost, LMRpost, PLRpost, PNIpost, SIRIpost, and SIIpost. After treatment, there was a significant decrease in LMR, PNI, and PAb, whereas NLR, PLR, SIRI, and SII increased significantly. Wilcoxon rank-sum test confirmed these differences were statistically significant ($p < 0.001$, Table 4). Survivors exhibited significantly lower post-treatment NLR (p=0.007) and PLR (p=0.021) compared to non-survivors (Figure 2 and Table 4).

To predict OS at 1-year, 3-year, and 5-year timepoints, ROC curve analysis was performed. The AUC values for 1-year OS prediction were ranked as follows: NLRpre (0.718), SIRIpre (0.692), PLRpost (0.665), NLRpost (0.662), and SIIpre (0.657). Sensitivity, specificity, and AUC values are detailed in Table 5. The optimal cutoff values, determined using the maximum Youden index, were as follows: NLRpre (2.95, Sensitivity: 69.8%, Specificity: 71.2%), SIRIpre

Table 3 Treatment-Related Adverse Events

Item	Any Grade (1–2)	≥ Grade 3
Leukopenia	26	3
Anemia	21	4
Thrombocytopenia	6	1
Hypoproteinemia	43	0
Nausea	8	0
Fatigue	45	1
Esophagitis	54	41
Pneumonia	7	5
Fever	3	1

Table 4 Comparison of IBs Before and After Treatment

IBs	Pre-Treatment	Post-Treatment	P value	Survivors vs Non-Survivors (Post-Treatment)
NLR	3.52 ± 1.84	8.87 ± 4.25	<0.001	6.5 vs 9.8 (p=0.007)
LMR	3.48 ± 1.52	2.05 ± 0.86	<0.001	2.6 vs 1.9 (p=0.015)
PLR	189.23 ± 78.54	438.60 ± 186.32	<0.001	312.5 vs 485.3 (p=0.021)
PNI	45.28 ± 8.92	37.85 ± 7.43	<0.001	41.3 vs 36.2 (p=0.012)
SIRI	1.75 ± 0.92	3.42 ± 1.68	<0.001	2.2 vs 3.9 (p=0.028)
SII	792.45 ± 352.18	1498.36 ± 645.72	<0.001	1085.2 vs 1625.8 (p=0.095)

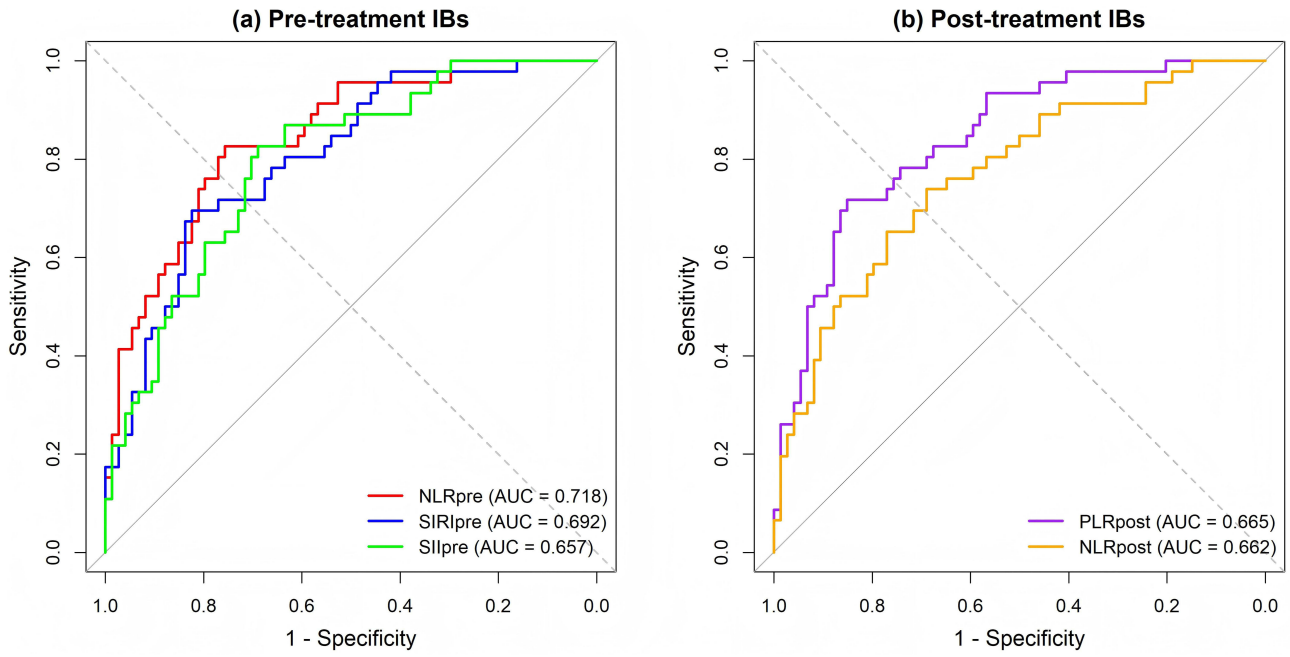

Figure 2 ROC curves demonstrating the predictive performance of inflammatory biomarkers (**a**) pre-treatment and (**b**) post-treatment for 1-year overall survival. Pre-treatment NLRpre showed the highest AUC value (0.718), followed by SIRIpre (0.692).

(0.89, Sensitivity: 65.3%, Specificity: 73.1%), PLRpost (388.20, Sensitivity: 61.9%, Specificity: 67.5%), NLRpost (7.92, Sensitivity: 63.2%, Specificity: 68.7%), and SIIpre (365.30, Sensitivity: 59.1%, Specificity: 65.8%).

Correlations of IBs with Clinical Traits and Survival Outcomes

The relationship between IBs and clinical characteristics is summarized in Table 6. Patients in the low IBs groups (NLRpre <2.95, SIRIpre <0.89, etc.) had significantly longer median OS (26 vs 11 months, p=0.002) and PFS (19 vs 9 months, p=0.003) compared to high IBs groups (Figure 3). SIIpre was significantly associated with adverse events (p = 0.005). PLRpost correlated with TNM stage (p = 0.048), smoking (p = 0.002), and comorbidities (p = 0.003). NLRpost was associated with age (p = 0.022).

Univariate and Multivariate Regression Analysis

Univariate Cox regression analysis identified age (p = 0.001), adverse events (p = 0.002), NLRpre (p = 0.032), SIRIpre (p = 0.014), PLRpost (p = 0.026), NLRpost (p = 0.009), treatment modality (p = 0.004), TNM stage (p < 0.05), ALB before treatment (<35 g/L vs ≥35 g/L, HR: 1.987, 95% CI: 1.152–3.425, p = 0.015), and combined with other systemic infections (yes/no, HR: 0.248, 95% CI: 0.115–0.534, p = 0.001) as significant prognostic factors for OS (Table 7). In multivariate analysis, only age (HR: 0.236, 95% CI: 0.123–0.452, p = 0.002), adverse events (HR: 0.425, 95% CI: 0.242–0.747, p = 0.003), and combined with other systemic infections (HR: 0.398, 95% CI: 0.227–0.698, p = 0.004) remained independent predictors of OS.

Table 5 ROC Curve Results for OS Prediction

IB	Timepoint	AUC	Sensitivity (%)	Specificity (%)	Cutoff Value
NLRpre	1-year	0.718	69.8	71.2	2.95
SIRIpre	1-year	0.692	65.3	73.1	0.89
PLRpost	1-year	0.665	61.9	67.5	388.20
NLRpost	1-year	0.662	63.2	68.7	7.92
SIIpre	1-year	0.657	59.1	65.8	365.30

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Table 6 Correlations of IBs with Clinical Traits

Variables	NLRpre			SIRIpre			SIIpre			PLRpost			NLRpost		
	Low (n=65)	High (n=55)	P value	Low (n=32)	High (n=88)	P value	Low (n=24)	High (n=96)	P value	Low (n=68)	High (n=52)	P value	Low (n=71)	High (n=49)	P value
Age			0.428			0.106			0.435			0.095			0.022
<80 years old	50	36		28	58		19	67		53	33		57	29	
≥80 years old	15	19		4	30		5	29		15	19		14	20	
Gender			0.677			0.821			0.672			0.103			0.614
Male	48	44		24	68		17	75		56	36		55	37	
Female	17	11		8	20		7	21		12	16		16	12	
TNM stage			0.342			0.296			0.162			0.048			0.064
I/II	29	22		15	36		12	39		33	18		33	18	
III/IV	36	33		17	52		12	57		35	34		38	31	
Smoking			0.794			0.697			0.659			0.002			0.178
Yes	40	33		20	53		14	59		33	40		47	26	
No	25	22		12	35		10	37		35	12		24	23	
Comorbidities			0.572			0.383			0.273			0.003			0.286
Yes	47	38		24	61		18	67		42	43		52	33	
No	18	17		8	27		6	29		26	9		19	16	
Adverse Events			0.098			0.105			0.005			0.154			0.101
≥grade 3	28	31		13	46		5	54		30	29		31	28	
<grade 3	37	24		19	42		19	42		38	23		40	21	

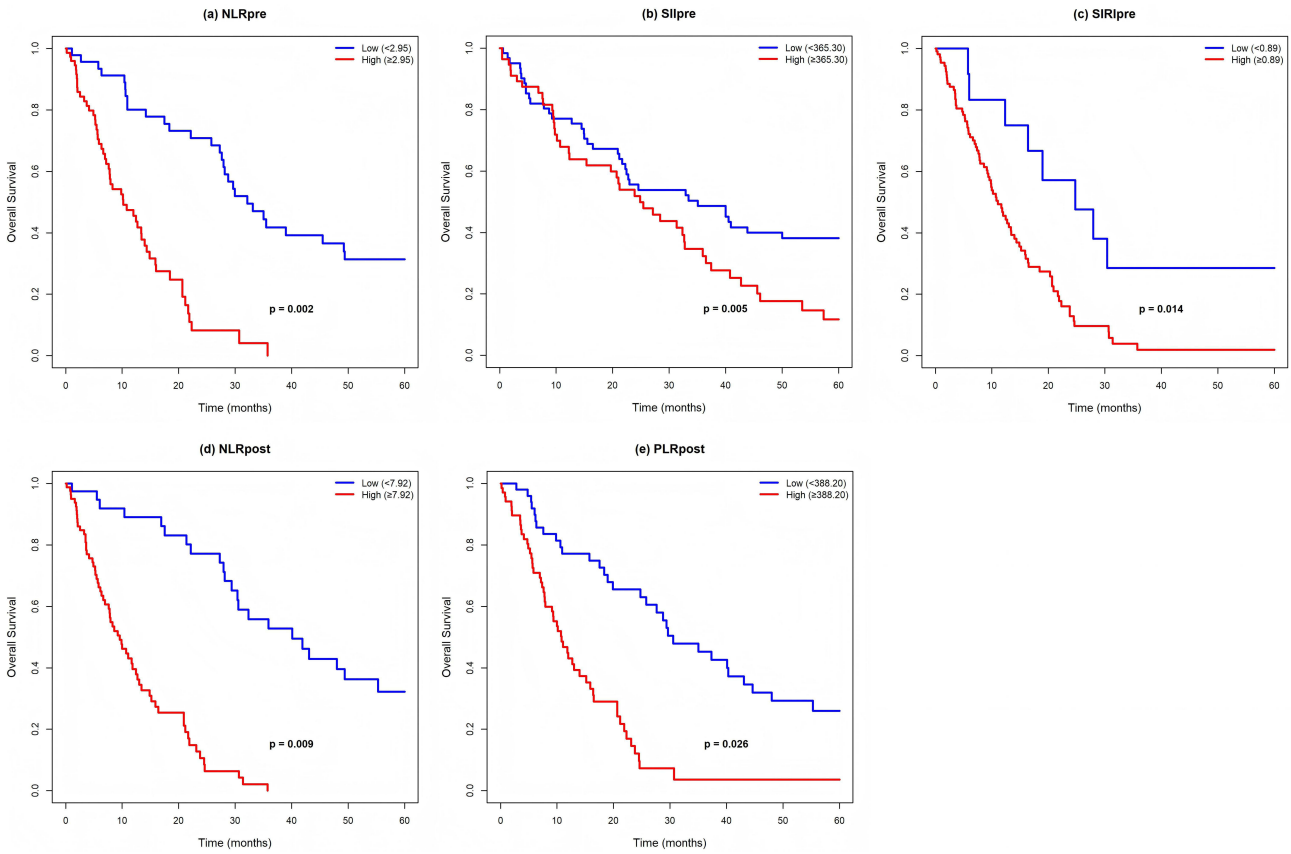

Figure 3 Kaplan-Meier survival analysis showing overall survival stratified by (**a**) pre-treatment NLR, (**b**) pre-treatment SII, (**c**) pre-treatment SIRI, (**d**) post-treatment NLR, and (**e**) post-treatment PLR, with Log rank test comparisons between high and low groups. All inflammatory biomarkers showed significant stratification of survival outcomes (all $p < 0.05$).

Correlation and Multicollinearity Analysis

Significant correlations were observed between pre-treatment markers, particularly NLRpre-SIIpre ($r=0.843$, $p<0.001$) and PLRpre-SIIpre ($r=0.806$, $p<0.001$) (Table 8). VIF analysis confirmed multicollinearity (SIIpre VIF=10.42). PCA extracted two principal components (PC1: 36.2% variance, dominated by NLRpre/SIIpre; PC2: 27.8% variance, primarily NLRpost) (Table 9). Stepwise regression identified NLR and SII as the most robust predictors.

Table 7 Univariable and Multivariable Analyses of Covariables Associated with OS

Covariables	Univariate Analysis HR (95% CI)	P value	Multivariate Analysis HR (95% CI)	P value
Age (<80 vs ≥80years)	0.218 (0.121–0.394)	0.001	0.236 (0.123–0.452)	0.002
Gender (male vs female)	0.724 (0.385–1.362)	0.298		
TNM stage				
I	I			
II	0.058 (0.008–0.445)	0.007		
III	0.412 (0.209–0.812)	0.010		
IV	0.565 (0.325–0.982)	0.039		
Treatment (RT vs CCRT/SCRT)	2.156 (1.302–3.572)	0.004		
Smoking (YES vs No)	1.248 (0.739–2.108)	0.445		
Alcohol (YES vs No)	0.968 (0.595–1.574)	0.868		
Comorbidities (YES vs No)	0.982 (0.595–1.621)	0.917		

(*Continued*)

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Table 7 (Continued).

Covariables	Univariate Analysis HR (95% CI)	P value	Multivariate Analysis HR (95% CI)	P value
Adverse Events (<stage 3 vs ≥stage 3)	0.392 (0.239–0.643)	0.002	0.425 (0.242–0.747)	0.003
SIIpre (<365.30 vs ≥365.30)	1.685 (0.835–3.398)	0.165		
NLRpre (<2.95 vs ≥2.95)	0.592 (0.368–0.952)	0.032		
SIRIpre (<0.89 vs ≥0.89)	0.472 (0.261–0.854)	0.014		
NLRpost (<7.92 vs ≥7.92)	0.528 (0.327–0.853)	0.009		
PLRpost (<388.20 vs ≥388.20)	0.578 (0.359–0.931)	0.026		
ALB before treatment (<35 g/L vs ≥35g/L)	1.987 (1.152–3.425)	0.015		
Combined with other systemic infections (yes/no)	0.248 (0.115–0.534)	0.001	0.398 (0.227–0.698)	0.004
Absolute lymphocyte count before treatment (<1×10^9/L vs ≥1×10^9/L)	1.382 (0.823–2.321)	0.251		

Table 8 Correlation Analysis

Item	NLRpre		LMRpre		PLRpre		PNIpre		SIIpre		SIRIpre	
	r	p	r	p	r	p	r	p	r	p	r	p
NLRpre	1	–	0.768	<0.001	0.702	<0.001	0.451	<0.001	0.843	<0.001	0.825	<0.001
LMRpre	0.768	<0.001	1	–	0.608	<0.001	0.478	<0.001	0.705	<0.001	0.882	<0.001
PLRpre	0.702	<0.001	0.608	<0.001	1	–	0.442	<0.001	0.806	<0.001	0.486	<0.001
PNIpre	0.451	<0.001	0.478	<0.001	0.442	<0.001	1	–	0.342	0.003	0.351	0.002
SIIpre	0.843	<0.001	0.705	<0.001	0.806	<0.001	0.342	0.003	1	–	0.819	<0.001
SIRIpre	0.825	<0.001	0.882	<0.001	0.486	<0.001	0.351	0.002	0.819	<0.001	1	–

Table 9 Principal Component Analysis

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	4.346	36.215	36.215	4.346	36.215	36.215
2	3.341	27.834	64.049	3.341	27.834	64.049
3	0.979	8.156	72.205	0.979	8.156	72.205
4	0.816	6.803	79.008			
5	0.678	5.652	84.660			
6	0.592	4.936	89.596			
7	0.448	3.732	93.328			
8	0.286	2.382	95.710			
9	0.262	2.185	97.895			
10	0.157	1.308	99.203			
11	0.058	0.482	99.685			
12	0.038	0.315	100.000			

Discussion

Clinical management of ESCC presents significant challenges. The aging population is leading to an increasing number of elderly cancer patients, who are at a higher risk of mortality and disease progression compared to younger patients and have a lower tolerance to radiotherapy and chemotherapy.[13–15] Our study of 120 elderly ESCC patients provides robust evidence for prognostic biomarker evaluation. In our cohort, 28.3% (34/120) of the patients were over 80 years old, offering adequate statistical power for octogenarian subgroup analyses. Additionally, 70.8% (85/120) had varying

degrees of comorbidities (such as hypertension, diabetes, renal disease, and pulmonary disease), and 31.7% (38/120) had Karnofsky performance scores of 70–80, indicating an overall poor condition. These characteristics highlight the unique challenges in treating this patient population and underscore the need for accurate prognostic markers to guide treatment decisions.

This study explored the predictive value of different IBs in predicting overall survival (OS) in elderly ESCC patients receiving radiotherapy (RT) or chemoradiotherapy (CRT), which is not commonly addressed in previous studies. Previous studies have indicated that elderly patients with esophageal carcinoma may experience more toxicities and complications during treatment, thus limiting their ability to tolerate extensive diagnostic procedures.[16] Moreover, treatment-related adverse events significantly impact survival in elderly patients, emphasizing the need for risk stratification tools. Blood biomarker tests, however, offer a convenient and rapid means of real-time monitoring at various stages of treatment, providing a widely applicable prognostic tool for clinical practice and enabling better understanding of the inflammatory changes and treatment responses in elderly ESCC patients. More importantly, for this patient population, the selection of individualized treatment intensity is crucial, as different choices may directly impact their quality of life and survival. This necessitates more refined subgroup stratification of elderly patients during clinical treatment. However, there is currently no mature biomarker available to predict treatment efficacy and survival in this subgroup of patients undergoing radiotherapy (with or without chemotherapy).

The tumor microenvironment plays a pivotal role in cancer progression.[17] Inflammatory cells, including neutrophils and monocytes, are integral components of the tumor microenvironment, exerting functional effects at various stages of cancer progression. These cells can either promote or inhibit tumor progression, depending on multiple factors, such as their phenotypes and the factors they secrete. For instance, an increase in neutrophils can lead to the release of inflammatory factors like vascular endothelial growth factor (VEGF) and interleukins, as well as a series of proteases.[18] Lymphocytes play a crucial role in tumor defense by inducing cytotoxic cell death, inhibiting tumor cell proliferation, and migration.[19] ATP released from tumor-associated platelets in the blood facilitates tumor metastasis by relaxing endothelial barrier function.[20] These cells can also influence tumor development by modulating immune responses.[21] Given this inflammatory influence, IBs have been increasingly explored as prognostic markers across different cancer types, including ESCC.

Meta-analyses have shown that in patients with small cell lung cancer receiving chemotherapy, a high NLR is associated with poorer OS and progression-free survival (PFS). The PLR does not significantly impact OS overall but may have prognostic value in specific subgroups.[22] In our study, post-treatment NLR, PLR, and SIRI were significantly elevated, while PNI and LMR were reduced compared to pre-treatment levels, with all changes reaching statistical significance (p-values < 0.01). These findings align with prior research, reinforcing the hypothesis that systemic inflammation increases following anti-tumor treatment, while immunity and nutritional status decline.[17,23–25]

Compared to other IBs, NLR, SII, and SIRI before treatment, as well as NLR and PLR after treatment, were significantly related to survival with higher area under the curve (AUC) values. Based on their cutoff values, these five indicators were divided into low and high groups. In the survival curves, we observed that an increase in IBs was associated with poorer OS, with the low group showing significantly better OS than the high group. Additionally, our analysis demonstrated significant associations between specific IBs and clinical factors. Patients with a higher PLRpost were more likely to have an advanced TNM stage, more comorbidities, and a smoking history, while a high SIIpre was more likely to be associated with severe adverse events (≥stage 3), and a high NLRpost was correlated with older age (≥80 years). These findings reveal an association between post-treatment inflammation markers and clinical outcomes, including tumor progression, treatment response, and prognosis.

In univariate analysis, IBs, including NLR and SIRI before treatment and NLR and PLR after treatment, were significantly associated with OS (all p-values < 0.001), confirming the prognostic value of IBs in ESCC patients. However, in the multivariate analysis, none of the IBs remained independent predictors of OS, with only age and adverse events (≥grade 3) being significant. This finding differs from some previous studies that suggested IBs as independent prognostic markers, indicating potential confounding factors affecting our results. It is possible that in elderly ESCC patients, treatment-related toxicities play a more dominant role in survival outcomes than inflammation-based indices alone.

Previous studies have also investigated the cutoff values of IBs, including NLR, PLR, and SII. In the study by Tong et al,[24] the association between the systemic immune-inflammation index and treatment response and overall survival in patients with stage III non-small cell lung cancer was explored. They suggested that cutoff values of ≥660 (SII), ≥3.57 (NLR), ≥147 (PLR), and ≤52.95 (PNI) were significantly associated with poorer overall survival. Similarly, Chen et al[26] analyzed liver cancer patients with bone metastasis undergoing radiotherapy and found optimal cutoff values of SII = 395.05, NLR = 5.43, and PLR = 108.23. In our study, the optimal cutoff values were 2.95 for NLRpre, 0.89 for SIRIpre, 365.30 for SIIpre, 388.20 for PLRpost, and 7.92 for NLRpost. These values were relatively lower than those reported in previous studies, which may be attributed to differences in patient populations. Given that elderly cancer patients often exhibit immune senescence, chronic low-grade inflammation, and multiple comorbidities, their IBs may present at lower baseline levels compared to younger patients.[27]

Although NLR, SII and SIRI showed prognostic value in univariate analysis, their intercorrelations necessitated special analytical approaches. Our PCA and stepwise regression analyses confirmed that systemic inflammation (represented by PC1) and post-treatment immune response (PC2) provide complementary information, while reducing redundancy among correlated markers. This aligns with recent findings by[28] demonstrating the need for dimensionality reduction when using composite inflammatory indices.

Despite the valuable insights provided by our study, there are some limitations. First, the study's retrospective and single-center design may introduce selection bias, which could limit the generalizability of our findings. Second, while our augmented sample size of 120 patients with 34 octogenarians provides improved statistical power compared to preliminary analyses, larger multicenter studies would further validate these findings. Third, while IBs provide a convenient means of assessing systemic inflammation, they do not account for tumor microenvironment-specific immune responses, such as immune cell infiltration. Future studies should incorporate tumor tissue analyses to further elucidate the relationship between systemic and local immune responses in elderly ESCC patients.

Future research should focus on validating our findings through multicenter, prospective studies with larger sample sizes. Additionally, combining IBs with other biomarkers, such as circulating tumor DNA (ctDNA) or immune checkpoint markers, may improve the accuracy of prognosis prediction. Further investigations should also explore the potential of IBs in guiding individualized treatment strategies, particularly in determining whether patients with higher inflammatory states may benefit from anti-inflammatory or immune-modulating therapies as adjuncts to standard RT/CRT.

Conclusions

In conclusion, this study compared the currently common IBs and demonstrated that a pre-treatment high NLR, SII, and SIRI, as well as a post-treatment high NLR and PLR, were significantly associated with poorer OS in elderly ESCC patients undergoing RT/CRT. However, in multivariate analysis, these IBs were not independent predictors of OS, suggesting that their prognostic value may be influenced by other clinical factors, such as age and treatment-related adverse events. These findings indicate that while IBs may serve as useful prognostic markers, their role in guiding regimen selection requires further validation. Future studies should explore their potential in combination with other biomarkers to improve prognosis prediction in elderly ESCC patients.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Peking University International Hospital (Approval No: [2024-KY-0044-01]), and informed consent was obtained from all participants.

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Author Contributions

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.

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Disclosure

All the authors report no conflicts of interest in this work.

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