Original Article

Combining the systemic inflammation response index and prognostic nutritional index to predict the prognosis of locally advanced elderly esophageal squamous cell carcinoma patients undergoing definitive radiotherapy

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Background: The systemic inflammation response index (SIRI) and prognostic nutritional index (PNI) have been shown to be correlated with the prognosis of various solid tumors. This study sought to investigate the prognostic value of the SIRI and the PNI individually and in combination in locally advanced elderly esophageal squamous cell carcinoma (ESCC) patients treated with radical radiotherapy.

Methods: The data of 192 ESCC patients aged ≥65 years, who had been treated with definitive radiotherapy between 2013 and 2016, were retrospectively analyzed. The optimal cutoff values of SIRI and PNI were determined by receiver operating characteristic curves. Kaplan-Meier curves and Cox proportional hazards models were used to analyze the effect of the SIRI and PNI on overall survival (OS) and progression-free survival (PFS). The areas under the curve were measured to evaluate the predictive ability of the SIRI, PNI, and SIRI combined with PNI for OS.

Results: The optimal cutoff values of the pretreatment SIRI and PNI were 1.03 and 49.60, respectively. The univariate and multivariate analyses demonstrated that T stage (P=0.021), TNM stage (P=0.022), synchronous chemotherapy (P=0.032), the SIRI (P=0.001), and the PNI (P=0.045) were independent prognostic factors for OS and N stage (P=0.004), synchronous chemotherapy (P=0.016) and the SIRI (P=0.004) were independent prognostic factors for PFS. The AUC of the combined SIRI and PNI (0.706; 0.612–0.801) was higher than those of the SIRI (0.648; 0.540–0.756) and the PNI (0.621; 0.523–0.720). Patients in the low-SIRI and high-PNI groups, especially those in clinical stage II or who received synchronous chemotherapy (P<0.001, P=0.002), had better OS and PFS than those in the other groups (P<0.001).

Conclusions: The SIRI and PNI are simple and reliable biomarkers for predicting long-term survival in elderly patients with locally advanced ESCC after radical radiotherapy. A high SIRI and a low PNI indicated poor prognosis, and the combination of the SIRI and PNI improved the accuracy of prognosis prediction and could be used to guide individualized treatment of patients.

Keywords: Esophageal squamous cell carcinoma (ESCC); elderly; radiotherapy; systemic inflammation response index (SIRI); prognostic nutritional index (PNI)

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Introduction

Esophageal cancer is a main cause of cancer-related deaths worldwide (1). In China, the newly diagnosed cases and deaths of esophageal cancer were 61,732 and 47,373, respectively, in 2015 (2). Esophageal squamous cell carcinoma (ESCC) is the most common pathological type of esophageal cancer in China, and accounts for about 90% of cases (3). Due to the aging Chinese population, the incidence of esophageal cancer among elderly patients continues to increase. Today, 70% of patients are aged >60 years (4). Due to diabetes, cardiovascular disease, chronic bronchitis, and other medical diseases, many elderly ESCC patients have poor surgical tolerance and experience postoperative complications. Definitive radiotherapy has become the primary treatment offered to elderly patients with locally advanced ESCC (5); however, patient prognosis remains poor due to local recurrence or distant metastasis (6). The traditional prognostic factor of tumor, node, metastasis (TNM) staging cannot be accurately determined in non-operative patients (7). Thus, more feasible and effective biomarkers need to be identified to improve the prognostic prediction of elderly ESCC patients undergoing definitive radiotherapy.

Inflammation plays an important role in the genesis, proliferation, and migration of tumors (8,9). In recent years, inflammatory biomarkers have become the focus of tumor research. The neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and monocyte to lymphocyte ratio have been found to be effective predictors of prognosis in many solid tumors (10-13). However, these inflammatory indexes only contain two types of immune-inflammation cells and their prognostic ability are limited. The systemic inflammation response index (SIRI), which is based on neutrophil, monocyte, and lymphocyte counts, is a novel composite inflammatory marker that can better predict the prognosis of solid neoplasms, such as pancreatic cancer, gastric cancer, and laryngeal carcinoma (14-16).

Evidence suggests that ESCC patients, especially locally advanced elderly ESCC patients, are more likely to suffer from malnutrition than those with other tumors (17), and malnutrition can affect treatment tolerance and prognosis of esophageal cancer patients (18). Thus, it is important to pay attention to and evaluate the nutritional status of patients. Recently, the prognostic nutritional index (PNI), which is a novel index calculated using the serum albumin and lymphocyte count that is used to evaluate the nutritional immune status of cancer patients, has been found to have significant prognostic ability in lung cancer, renal cancer, and hepatocellular carcinoma (19-21).

There is increasing evidence that the SIRI and PNI reflects the level of inflammatory response and nutritional immunity and accurately predicts the prognosis of cancer patients; however, the relationship between SIRI, PNI, and the prognosis of elderly ESCC patients has not been confirmed. Thus, we conducted a retrospective study of locally advanced elderly ESCC patients (aged ≥65 years) undergoing radical radiotherapy to evaluate the value of the SIRI and PNI in predicting the prognosis of those patients, and creatively combined these two indicators (SIRI-PNI) for further prognostic analysis. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-784/rc).

Methods

All the procedures in this study involving human participants were conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was reviewed and approved by the Ethics Committee of The Fourth Hospital of Hebei Medical University (No.: 2021KY134). All the patients included in this study gave their informed consent for the treatment.

Patients

The data of 192 elderly ESCC patients treated with definitive radiotherapy from June 2013 to September 2016 at The Fourth Hospital of Hebei Medical University were retrospectively reviewed in this study. To be eligible to participate in the study, patients had to meet the following inclusion criteria: (I) be aged ≥65 years and have histologically confirmed ESCC; (II) with Eastern Cooperative Oncology Group (ECOG) performance status

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0–2; (III) have no distant metastasis and no history of other malignant tumors; (IV) have undergone a blood biochemical examination before treatment for which the results were available; (V) all patients had clinical stage II to III based on the American Joint Committee on Cancer (AJCC) 6th edition staging system.

Treatment

In this study, all patients received intensity-modulated radiation therapy. The total radiotherapy dose was 50.4–66 Gy, and the total radiotherapy frequency was 28–33 f. Using imaging data, including chest and abdomen computed tomography (CT), barium esophagram, endoscopy, ultrasound or positron emission tomography (PET)/CT, the gross tumor volume (GTV) was delineated in the treatment planning system. The GTV was then axially expanded to 0.5–0.8 cm, and 2–3 cm at the proximal and distal ends as the clinical target volume (CTV). The CTV was expanded to 0.5–1.0 cm as the planned target volume (PTV). Patients received synchronous chemotherapy, mainly platinum-based chemotherapy, for 1–2 cycles.

Blood sample collection and SIRI, PNI definition

The peripheral blood count and plasma albumin level of each patient within 2 weeks before radiotherapy were retrospectively collected. The following formula was used to calculate the SIRI: neutrophil count × monocyte count/lymphocyte count. The following formula was used to calculate the PNI: serum albumin level (g/L) + 5 × absolute lymphocyte count (10^9/L).

Follow-up evaluations

The patients in this study were followed up with regular outpatient examinations and telephone interviews every 3 months for the initial 2 years, and every 6 months thereafter. Each follow-up appointment included a physical examination, peripheral blood test, and barium esophagram and CT scans of the chest and abdomen. Overall survival (OS) was defined as the time from the first day of the pathological diagnosis to death or the last follow-up date. Progression-free survival (PFS) was defined as the time from the pathological diagnosis to disease progression, or as the last follow-up date for patients who were lost during the follow-up period.

Statistical analysis

SPSS (version 23.0, IBM, Armonk, NY, USA) and GraphPad Prism (version 8.0.2, San Diego, California, USA) software were used for the statistical analysis. The optimal cutoff values of the SIRI and PNI were determined by the receiver operating characteristic (ROC) curve with the highest Youden's index according to the OS of patients. The area under the curve (AUC) was measured to evaluate the predictive ability of the SIRI, the PNI, and the combined SIRI and PNI for OS. The Chi-square test was used to compare variables between groups, and the survival analysis was conducted using the Kaplan-Meier method. The Cox proportional hazards regression model was used for the univariate and multivariate analyses to identify prognostic factors associated with OS and PFS. 95% confidence intervals (CIs) were calculated to verify the accuracy of hazard ratio (HR). A P value <0.05 was considered statistically significant.

Results

Patient demographics

A total of 192 elderly patients, who met the enrollment criteria, were included in this study, and a summary of their demographic characteristics are shown in *Table 1*. Among the 192 patients, 111 (57.8%) were male, and 81 (42.2%) were female. The patients had a median age of 73 years (range, 65–88 years). And, 104 (54.2%) patients had stage II disease, and 88 (45.8%) patients had stage III disease; 98 (51.0%) patients received ≥60 Gy, and 94 (49.0%) received <60 Gy; 93 patients (48.4%) received 1–2 cycles of synchronous chemotherapy, and 99 patients (51.6%) received radiotherapy alone.

The optimal cutoff values of the SIRI and the PNI

According to the blood count and plasma albumin value before treatment, the mean values of the SIRI and PNI were 1.52 and 48.71, respectively. The optimal pretreatment SIRI and PNI cutoff values were 1.03 and 49.60 according to the ROC curve and Youden's index. The AUCs of the SIRI and PNI were 0.648 (0.540–0.756) and 0.621 (0.523–0.720), respectively (see *Figure 1*). The patients were then divided into the following 2 groups according to the cutoff values: a low-SIRI group (SIRI <1.03, n=70), and a high-SIRI group (SIRI ≥1.03, n=122), and a low-PNI group (PNI

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Table 1 Characteristics of 192 locally advanced elderly ESCC patients grouped by pretreatment SIRI and PNI

Characteristics	Patients, n	SIRI			PNI		
		Low-SIRI (n=70)	High-SIRI (n=122)	P	Low-PNI (n=103)	High-PNI (n=89)	P
Age (years)				0.263			0.063
<73	94	38	56		44	50	
≥73	98	32	66		59	39	
Gender				0.454			0.873
Male	111	38	73		59	52	
Female	81	32	49		44	37	
Tumor location				0.592			0.159
Cervical	16	7	9		5	11	
Upper thoracic	48	20	28		23	25	
Middle thoracic	83	26	57		48	35	
Lower thoracic	45	17	28		27	18	
Tumor length (cm)				0.076			0.040
<6	99	42	57		46	53	
≥6	93	28	65		57	36	
T stage				0.079			0.249
T2	55	24	31		26	29	
T3	74	30	44		38	36	
T4	63	16	47		39	24	
N stage				0.849			0.962
N0	73	26	47		39	34	
N1	119	44	75		64	55	
TNM stage				0.033			0.024
II	104	45	59		48	56	
III	88	25	63		55	33	
Radiotherapy dose (Gy)				0.001			0.301
<60	94	45	49		54	40	
≥60	98	25	73		49	49	
Chemotherapy				0.015			0.584
Yes	93	42	51		48	45	
No	99	28	71		55	44	

ESCC, esophageal squamous cell carcinoma; SIRI, systemic inflammation response index; PNI, prognostic nutritional index.

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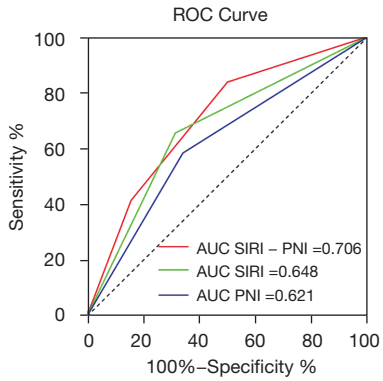

Figure 1 ROC curve analysis of the optimal cutoff values of the SIRI, PNI, and SIRI-PNI. ROC, receiver operating characteristic; SIRI, systemic inflammation response index; PNI, prognostic nutritional index.

<49.60, n=103), and a high-PNI group (PNI ≥49.60, n=89).

The relationship between the SIRI, PNI, and clinicopathological characteristics of ESCC

As *Table 1* shows, age, gender, tumor location, tumor length, T stage, N stage, TNM stage, radiotherapy dose, and synchronous chemotherapy were selected as important clinical factors, and their correlations with the SIRI and PNI were analyzed. The pretreatment SIRI was significantly correlated with TNM stage (P=0.033), radiotherapy dose (P=0.001), and synchronous chemotherapy (P=0.015). The two groups were similar in terms of age, gender, tumor location, tumor length, T stage, and N stage (P>0.05). The pretreatment PNI was significantly correlated with tumor length (P=0.040) and TNM stage (P=0.024). Other factors, such as age, gender, tumor location, T stage, N stage, radiotherapy dose, and synchronous chemotherapy, were not significantly correlated with the PNI (P>0.05).

The effect of the SIRI and PNI on survival

All patients were followed up with until July 2021. One patient was lost during the follow-up period. The median follow-up time was 21.3 months (range, 3.8–95.1 months). Among the 192 elderly ESCC patients, the 1-, 3-, 5-year OS and PFS rates were 75.0%, 33.3%, and 24.9%, and 58.3%, 31.8%, and 21.4%, respectively. For patients in the low-SIRI group, the 1-, 3-, 5-year OS and PFS rates were 82.3%, 48.1%, and 40.4%, and 73.2%, 46.5%, and 38.5%, respectively. The corresponding rates for patients in the high-SIRI group were 69.9%, 23.0%, and 14.2%, and 46.4%, 19.4%, and 12.1%, respectively. The Kaplan-Meier analysis revealed that OS and PFS in the low-SIRI group were superior to those in the high-SIRI group (both P<0.001). The low-PNI patients' 1-, 3-, 5-year OS and PFS rates were 68.0%, 26.2%, and 18.4% and 52.5%, 24.8%, and 17.4%, respectively. The corresponding rates for the high-PNI patients were 83.1%, 40.4%, and 32.5%, and 62.4%, 35.2%, and 30.7%, respectively. The low-PNI group had significantly worse OS and PFS than the high-PNI group (P=0.005, P=0.040; see *Figure 2*).

Univariate and multivariate survival analysis

The univariate analysis revealed that tumor length (P=0.008), T stage (P=0.002), TNM stage (P=0.003), radiotherapy dose (P=0.017), synchronous chemotherapy (P=0.007), the pretreatment SIRI (P<0.001) and PNI (P=0.005) were significant prognostic factors associated with OS. Conversely, tumor length (P=0.045), T stage (P=0.026), N stage (P=0.004), TNM stage (P=0.011), radiotherapy dose (P=0.001), synchronous chemotherapy (P=0.009), the pretreatment SIRI (P<0.001) and PNI (P=0.040) were significant prognostic factors associated with PFS in elderly ESCC patients. The multivariate analysis demonstrated that T stage (P=0.021), TNM stage (P=0.022), synchronous chemotherapy (P=0.032), the SIRI (P=0.001), and PNI (P=0.045) were independent prognostic factors for OS and N stage (P=0.004), synchronous chemotherapy (P=0.016) and the SIRI (P=0.004) were independent prognostic factors for PFS (see *Table 2*).

Predictive value of the SIRI-PNI in the prognosis of elderly ESCC patients

Finally, to improve the accuracy and stability of prognosis prediction for elderly ESCC, we analyzed the SIRI and PNI in combination (i.e., the SIRI-PNI). A total of 192 patients were classified into three groups according to the following criteria: (I) the high-risk group (patients with a high SIRI and a low PNI); (II) the medium-risk group (patients with a high SIRI and a high PNI, or a low SIRI and a low PNI; and (III) the low-risk group (patients with a low SIRI and a high PNI). According to the ROC curve, the AUC for the SIRI-PNI was 0.706 (0.612–0.801) (see *Figure 1*). The Kaplan-Meier analysis showed that the 1-, 3-, 5-year OS rates of the low-risk group (n=41) were 86.4%, 59.1%, and 49.9%, respectively, which were significantly better than

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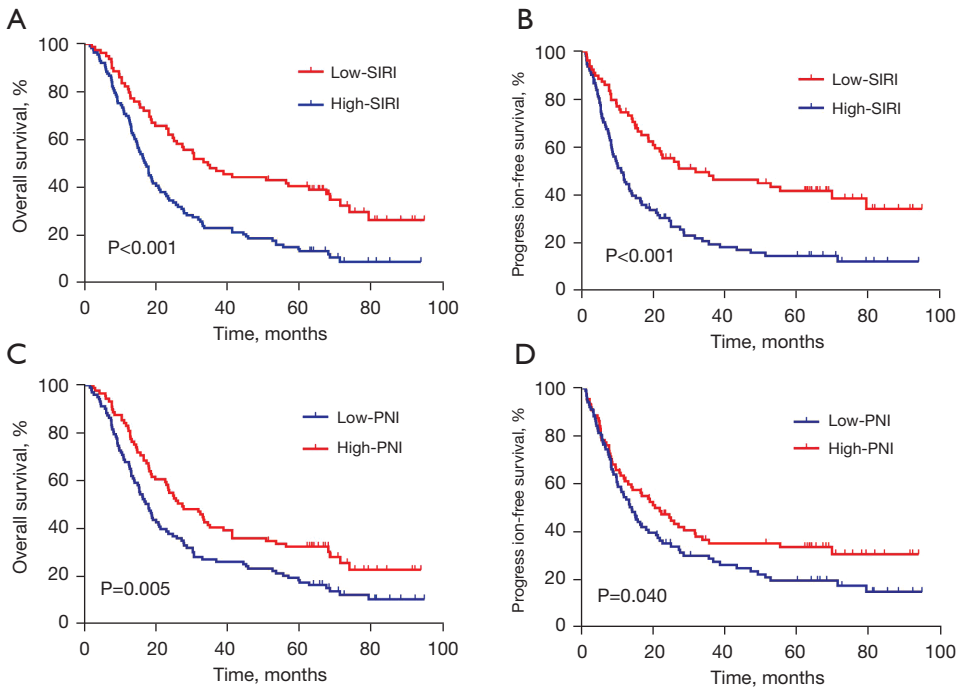

Figure 2 Kaplan-Meier curves for OS and PFS according to the SIRI (A,B) and the PNI (C,D) for 192 locally advanced elderly ESCC patients. OS, overall survival; PFS, progression-free survival; SIRI, systemic inflammation response index; PNI, prognostic nutritional index; ESCC, esophageal squamous cell carcinoma.

those for the medium-risk group (n=69) 75.6%, 26.9%, and 20.5% and the high-risk group (n=82) 65.7%, 22.9%, and 11.4% (P<0.001). Additionally, the 1-, 3-, 5-year PFS rates of the low-risk group were 76.8%, 53.7%, and 44.5%, which were also superior to those of the medium-risk group of 53.3%, 25.3%, and 18.3%, and the high-risk group of 48.5%, 22.3%, and 10.7% (P<0.001) (see *Figure 3*).

The predictive value of the SIRI-PNI for OS was further stratified according to TNM stage and synchronous chemotherapy. As *Figure 4* shows, among the 104 patients with stage II ESCC, the low-risk group had better OS than the medium- and high-risk groups (P<0.001). Similarly, among the 93 patients who received synchronous chemotherapy, the low-risk group also had a superior prognosis compared to the other two groups (P=0.002). There were no statistical differences among the three groups in relation to stage III or radiotherapy alone (P=0.595, P=0.311, respectively).

Discussion

Inflammation is considered a vital factor in the process of tumorigenesis and metastasis, and the nutritional immune status of the system is an important part of the inflammatory response (8,9). For elderly patients, immune function gradually declines with age, which leads to a weakened ability to fight inflammation, tumor, autoimmune diseases, etc. Recently, many studies have shown that the SIRI and PNI, which reflect patients' inflammation and nutritional immune status, have great value in evaluating the prognosis of many solid tumors (22-24). To our knowledge, this is the first study to examine the SIRI and PNI in non-surgical elderly ESCC patients. We found that the SIRI and PNI can effectively predict the prognosis of elderly patients with locally advanced ESCC who have undergone definitive radiotherapy, a high SIRI and a low PNI indicate poor prognosis and these two indicators are independent prognostic factors for the OS of ESCC patients. In addition, the combination of the SIRI and PNI could significantly improve the accuracy of prognosis prediction.

The mechanism by which an elevated SIRI leads to poor outcomes for cancer patients remains unclear. There are a number of possible explanations for this phenomenon. The SIRI is a composite inflammatory marker formed by neutrophil, monocyte, and lymphocyte counts. One cause of an elevated SIRI is increased neutrophil and monocyte

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Table 2 Univariate and multivariate analyses of prognostic factors for OS and PFS in elderly ESCC patients

Characteristics	OS		PFS	
	HR (95% CI)	P	HR (95% CI)	P
Univariate analysis				
Age (years)		0.118		0.167
<73	1		1	
≥73	1.289 (0.938–1.170)		1.272 (0.904–1.789)	
Gender		0.425		0.443
Male	1		1	
Female	0.877 (0.635–1.211)		0.873 (0.617–1.236)	
Tumor location		0.108		0.084
Cervical	1		1	
Upper thoracic	1.187 (0.718–1.960)		1.314 (0.621–2.780)	
Middle thoracic	1.389 (0.853–2.215)		1.716 (0.846–3.840)	
Lower thoracic	1.286 (0.763–1.996)		1.307 (0.601–1.996)	
Tumor length (cm)		0.008		0.045
<6	1		1	
≥6	1.540 (1.121–2.116)		1.418 (1.007–1.996)	
T stage		0.002		0.026
T2	1		1	
T3	1.931 (1.281–2.910)		1.717 (1.112–2.652)	
T4	1.949 (1.276–2.977)		1.719 (1.104–2.677)	
N stage		0.066		0.004
N0	1		1	
N1	1.371 (0.979–1.921)		1.726 (1.185–2.513)	
TNM stage		0.003		0.011
II	1		1	
III	1.628 (1.186–2.236)		1.559 (1.108–2.193)	
Radiotherapy dose (Gy)		0.017		0.001
<60	1		1	
≥60	0.680 (0.495–0.933)		0.549 (0.389–0.775)	
Chemotherapy		0.007		0.009
Yes	1		1	
No	1.553 (1.128–2.140)		1.578 (1.119–2.225)	
SIRI		<0.001		<0.001
Low	1		1	
High	2.044 (1.460–2.862)		2.203 (1.531–3.171)	

Table 2 (*continued*)

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Table 2 (*continued*)

Characteristics	OS		PFS	
	HR (95% CI)	P	HR (95% CI)	P
PNI		0.005		0.040
Low	1		1	
High	0.632 (0.458–0.872)		0.711 (0.514–0.984)	
Multivariate analysis				
Tumor length (cm)		0.434		0.755
<6	1		1	
≥6	1.210 (0.750–1.951)		1.083 (0.656–1.790)	
T stage		0.021		0.058
T2	1		1	
T3	1.574 (0.991–2.500)		1.580 (0.970–2.572)	
T4	0.881 (0.424–1.830)		0.955 (0.435–2.096)	
N stage				0.004
N0			1	
N1			1.837 (1.214–2.780)	
TNM stage		0.022		0.478
II	1		1	
III	1.748 (1.085–2.816)		1.219 (0.705–2.109)	
Radiotherapy dose (Gy)		0.200		0.104
<60	1		1	
≥60	0.807 (0.580–1.121)		0.731 (0.500–1.067)	
Chemotherapy		0.032		0.016
Yes	1		1	
No	1.437 (1.031–2.002)		1.573 (1.090–2.271)	
SIRI		0.001		0.004
Low	1		1	
High	1.875 (1.279–2.749)		1.881 (1.231–2.876)	
PNI		0.045		0.538
Low	1		1	
High	0.710 (0.508–0.992)		0.892 (0.619–1.285)	

ESCC, esophageal squamous cell carcinoma; OS, overall survival; PFS, progression-free survival; SIRI, systemic inflammation response index; PNI, prognostic nutritional index; HR, hazard ratio; CI, confidence interval.

counts. Neutrophils enhance the oxidative stress reaction by releasing reactive oxygen species, arginine kinases, and other substances, leading to deoxyribonucleic acid damage, and mutation accumulation, and increasing the occurrence of tumors (25). Additionally, neutrophils also suppress the activity of natural killer cells and accelerate

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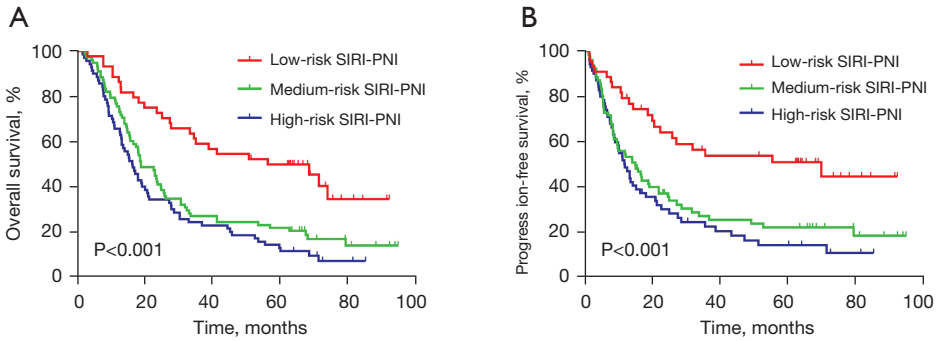

Figure 3 Overall survival and progression-free survival curves for 192 locally advanced elderly ESCC patients according to the combined SIRI and PNI. ESCC, esophageal squamous cell carcinoma; SIRI, systemic inflammation response index; PNI, prognostic nutritional index.

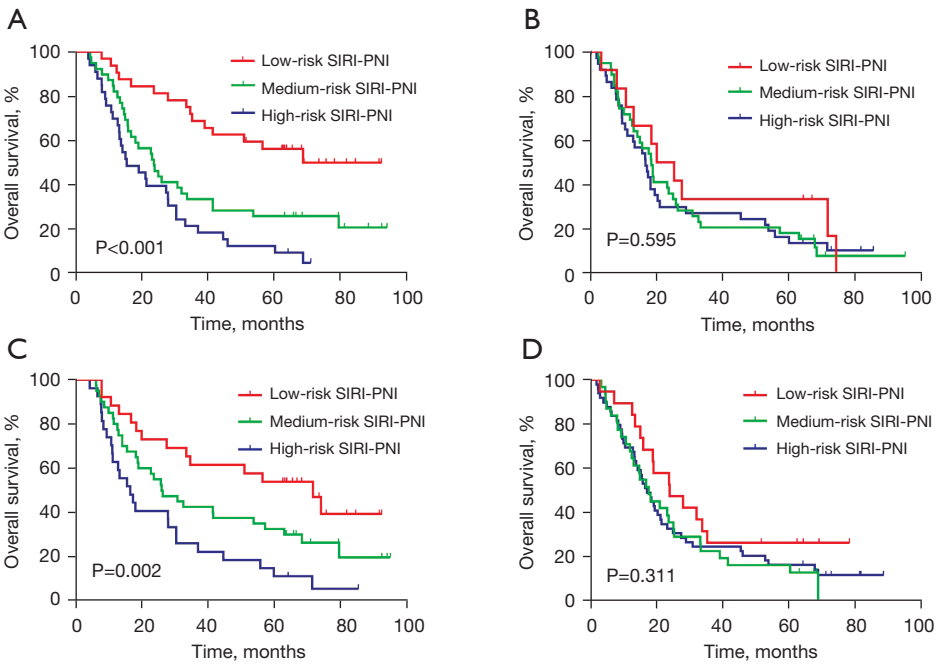

Figure 4 Overall survival curves for elderly ESCC patients with stage II (A), stage III (B), with synchronous chemotherapy (C), and radiotherapy alone (D) according to the combined SIRI-PNI. ESCC, esophageal squamous cell carcinoma; SIRI, systemic inflammation response index; PNI, prognostic nutritional index.

tumor angiogenesis by secreting vascular endothelial growth factor and matrix metalloproteinases, promoting tumor growth and metastasis (26). Monocytes are the main source of tumor-associated macrophages, which promote tumor cell infiltration and angiogenesis and inhibit immune surveillance. Thus, monocytes can reflect the tumor load status instead of tumor-associated macrophages in the peripheral blood (27). Another reason for an elevated SIRI is a decrease in the lymphocyte count. Lymphocytes are an important part of the anti-tumor immune response. However, the systemic inflammatory response induced by malignant tumor cells inhibits the cellular function of lymphocytes and enables tumor cells to evade immune surveillance. Further, lymphocytes not only inhibit the proliferation and migration of tumor cells, but also eliminate residual tumor cells (28). Thus, an elevated SIRI contributes to tumor angiogenesis and tumor cell invasion and metastasis, leading to a poor prognosis in elderly ESCC

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patients.

In recent years, several studies have confirmed the value of the PNI in predicting the prognosis of gastrointestinal tumors; however, previous studies on the relationship between the PNI and the prognosis of esophageal cancer have mainly used surgical patients. Zhang *et al.* (29) retrospectively analyzed 655 patients with resected ESCC who underwent esophagectomy, and divided the patients into a high-PNI group and a low-PNI group using an optimal cutoff value of 52.28. The results showed that the high-PNI group had a significantly better OS rate than the low-PNI group (P<0.001). Our results also showed that the PNI was an independent prognostic factor for the OS of ESCC patients. The cutoff value of the PNI in our study was 49.60, a figure lower than that of Zhang's study, which indicates that the immuno-nutritional status of elderly inoperable ESCC patients was worse than that of resected patients. The PNI is composed of the serum albumin level and lymphocyte count, which comprehensively reflect the nutritional status and immune function of ESCC patients. Serum albumin is a crucial nutritional marker. Tumor-related inflammation and malnutrition inhibit albumin synthesis, while hypoalbuminemia reflects the level of the inflammatory response and may have a negative effect on the prognosis of patients (30,31). Serum albumin also plays a vital role in the transport of cholesterol, fatty acids, and other substances; thus, a decrease in the level of serum albumin can lead to poor outcomes (32). Conversely, a reduced lymphocyte count may indicate impaired immune surveillance and contribute to tumor invasion and metastasis (33).

Both the SIRI and PNI are independent prognostic factors for ESCC, but their own predictive values were relatively low in this study; thus, we further explored the value of the SIRI combined with the PNI (the SIRI-PNI) in predicting long-term survival after radical radiotherapy in locally advanced elderly ESCC patients. We found that the combined SIRI-PNI had a larger AUC than either the SIRI or PNI alone, and the combined SIRI-PNI was significantly associated with OS and PFS in elderly ESCC patients. Thus, the SIRI-PNI was found to be the most accurate prognostic indicator of nutritional inflammation and effectively supplemented the lack of accurate TNM staging in non-surgical ESCC patients. We further stratified the survival of patients at different TNM stages and synchronous chemotherapy, and found that the combined SIRI-PNI was only significantly correlated with OS in patients with stage Ⅱ ESCC and those undergoing synchronous chemotherapy, and SIRI-PNI had better separation of survival curves in these subgroups than in the whole group. We also confirmed that the combined SIRI-PNI is suitable for the choice of initial treatment; however, only patients with better immuno-nutritional status and lower inflammation will benefit from synchronous chemotherapy.

Nowadays, concurrent chemoradiotherapy has been recommended as the standard treatment for inoperable locally advanced esophageal cancer, but there is still some controversy about whether concurrent chemoradiotherapy is superior to radiotherapy alone in elderly patients (34,35). Our study showed that concurrent chemoradiotherapy was an independent prognostic factor for OS and PFS in 192 elderly patients with locally advanced esophageal cancer. The differences in these results may be related to age division, chemotherapy regimens, radiation dose and ECOG performance status of patients. Therefore, a reasonable treatment for elderly ESCC patients needs to be further confirmed by multi-center prospective clinical trials.

In recent years, combining immunotherapy with chemoradiotherapy has shown promising prospects in the treatment of unresectable esophageal cancer (36,37). However, the optimal timing of immunotherapy and chemoradiotherapy is still unclear, which may be related to the two-sided effects of chemoradiotherapy on immune function of ESCC patients. Chemoradiotherapy can activate the cGAS-STING pathway, promote the priming and activation of cytotoxic T cells, and also play a positive regulatory role on the tumor microenvironment (38); On the other side, chemoradiotherapy may negatively impact T lymphocytes through the irradiation of lymph nodes and the extensive cytotoxic effects of chemotherapy drugs (39). In this study, both SIRI and PNI contained lymphocytes, which reflected the immune status of patients. Therefore, we can investigate the effect of chemoradiotherapy on immune function by observing the changes in SIRI and PNI during treatment, which provided evidence for clinical optimization of the selection of radiation dose, irradiated field, chemotherapy regimen and timing of combined immunotherapy for ESCC patients.

This study had several limitations. First, as a single-center retrospective study, the sample size was relatively small, and there may have been some bias in the selection of cases. Thus, a multi-center prospective study with a larger sample size should be conducted. Second, given that the SIRI and PNI values may be affected by various factors, such as radiotherapy, chemotherapy, and anti-inflammatory,

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or nutritional support during treatment, we only calculated and applied pre-radiotherapy indicators to evaluate and predict the survival of locally advanced elderly ESCC patients. Finally, in this study, as the AUC values of these indicators were relatively low, it is necessary to construct a more sensitive prognostic model for ESCC patients.

To conclude, we found that the pretreatment SIRI and PNI are simple, inexpensive, and reliable indicators for predicting the prognosis of elderly patients with locally advanced ESCC after radical radiotherapy. The combined SIRI-PNI was more accurate at predicting patient prognosis than either indicator alone. These new biomarkers can contribute to the individual selection of clinical treatment plans. A larger sample size prospective study at multi-centers needs to be conducted to validate these findings.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-784/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (No.: 2021KY134) and informed consent was taken from all the patients.

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