

Combination of Haemoglobin and Prognostic Nutritional Index Predicts the Prognosis of Postoperative Radiotherapy for Esophageal Squamous Cell Carcinoma

This article was published in the following Dove Press journal:
Cancer Management and Research

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Purpose: To investigate the predictive effect of the combined markers of haemoglobin and prognostic nutritional index (PNI) on the long-term survival of patients undergoing post-operative radiotherapy for esophageal squamous cell carcinoma (ESCC).

Patients and Methods: A total of 238 patients were included in this retrospective analysis. PNI was calculated as the serum albumin level (g/L) + 5 × absolute lymphocyte count, and the cut-off values of PNI and haemoglobin were calculated by receiver operating characteristic (ROC) curve analysis. Then, we combined haemoglobin and PNI, named the H-PNI score, as a predictor of tumour prognosis. The patients were divided into three groups: H-PNI score of 2 (having both hyper-haemoglobin and high PNI), H-PNI score of 1 (having one of these haematological abnormalities), and H-PNI score of 0 (having neither hyper-haemoglobin nor high PNI). The overall survival (OS) rate was calculated using the Kaplan–Meier method, and survival differences between groups were evaluated using the Log rank test. Cox proportional hazards models were used for univariate and multivariate analyses. P values <0.05 indicated statistical significance.

Results: The cut-off values of haemoglobin and PNI were 132.5 (g/L) and 46.55, respectively. Kaplan–Meier analysis showed that patients with high haemoglobin and PNI levels had a significantly better prognosis than those with low haemoglobin and PNI levels (P = 0.015 and P = 0.002, respectively). Similarly, the survival rate was significantly lower in patients with an H-PNI score of 0 than in those with an H-PNI score of 1–2 (P=0.000). Univariate analysis indicated that differentiation, T and N classification, and H-PNI score were significantly associated with OS. Finally, differentiation (P=0.002), T and N classification (P=0.000), and H-PNI score (P=0.01) were independent prognostic factors for ESCC patients undergoing postoperative radiotherapy.

Conclusion: The H-PNI score was an independent prognostic factor for ESCC patients undergoing postoperative radiotherapy.

Keywords: retrospective analysis, haematological markers, nutritional status, overall survival

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Introduction

Esophageal cancer is one of the most common malignancies of the digestive tract, and its mortality ranks 4th among all malignant tumours. Especially in China, the morbidity and mortality rates are among the highest in the world.^{1,2} Because there are no obvious symptoms in the early stage, many patients are not diagnosed until

the middle or advanced stage, so the average five-year survival rate is only 17%.³ Current treatments include radical surgery, radiotherapy, chemotherapy and concurrent chemoradiotherapy. Although these treatments can be effective in relieving clinical symptoms, anorexia, vomiting and radiation oesophagitis may occur during chemoradiotherapy. At the same time, due to swallowing difficulties caused by the disease, many patients suffer from malnutrition, which affects their prognosis.^{4,5}

It has been reported that nutritional status is related to the clinical treatment outcomes of patients with Esophageal cancer,⁶ and nutritional intervention before chemoradiotherapy can improve the survival of patients with locally advanced esophageal cancer.⁷ Moreover, during chemoradiotherapy, the clinical efficacy of patients with good nutritional status was better than those with poor nutritional status.⁸ To date, several potential blood markers have been used to assess the nutritional status of cancer patients. The prognostic nutritional index (PNI) consists of serum albumin and absolute lymphocyte count,⁹ and it has been used to assess preoperative nutritional status, surgical risk, and postoperative complications in patients undergoing surgery. Researchers extended PNI to the field of tumours and found that PNI was associated with the prognosis of colorectal cancer, stomach cancer, lung cancer and breast cancer.^{10–13} Haemoglobin also has value in nutritional evaluation; however, the cumulative effect of haemoglobin and PNI on tumour patients has not been investigated. At the same time, there is no study on the correlation between the nutritional index and the survival of patients with postoperative radiotherapy for esophageal cancer. Therefore, this study investigated the effect of the combined markers of haemoglobin and PNI on the long-term survival of patients undergoing postoperative radiotherapy for esophageal cancer.

Materials and Methods

Patients

In this retrospective study, we enrolled postoperative radiotherapy patients with esophageal cancer who were admitted to the Affiliated Yancheng First Hospital of Nanjing University Medical School from January 2010 to December 2018. All patients were treated with oesophagectomy and postoperative radiotherapy. The inclusion criteria for this study were as follows: (1) patients with histologically confirmed esophageal squamous cell carcinoma (ESCC); (2) patients who underwent postoperative radiotherapy (RT)

only or concurrent chemoradiotherapy (CCRT); and (3) patients with no distant metastasis. The exclusion criteria for this study were as follows: (1) patients who underwent neoadjuvant chemotherapy (n=1); (2) patients with incomplete histopathological data or preoperative haematologic examination (n=28); (3) patients who had interrupted radiation therapy (n=3); and (4) patients who could not be contacted (n=21). Finally, 238 patients were included in this study. Due to the retrospective nature of the study, the requirement for informed consent was waived, and the study was approved by the ethics committee of the Affiliated Yancheng First Hospital of Nanjing University Medical School. This study was conducted in accordance with the Declaration of Helsinki, and all information was anonymized prior to analysis.

Treatment

Radiotherapy was performed by 6 MV X-ray irradiation. First, the neck and chest were fixed with a piece of thermoplastic sheet. Imaging data from previous computed tomography (CT) simulation scans were transmitted to the RT treatment planning system to delineate tumour areas and organs at risk. The target volume included the postoperative tumour bed and high-risk lymphatic drainage area, and the total dose was 50 to 66 Gy, 1.8 to 2.0 Gy/fraction, 5 times/week. A high dose of 60–66 Gy was administered in some patients due to suspicious metastatic lymph nodes found on the medical image before radiotherapy. The restricted dose of normal tissues included a bi-lung V20 \leq 20%, an average bi-lung dose of \leq 20 Gy, a bi-lung V5 of $<$ 50%, a heart V30 of \leq 30%, and a maximum dose to the spinal cord of $<$ 45 Gy. We used 3-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT). Patients with severe postoperative complications were excluded. Among them, 65 patients received CCRT, and 173 patients received postoperative RT only. The chemotherapy regimens consisted mainly of 5-fluorouracil (1000 mg/m², days 1–3 and 29–31), single-agent S-1 (tegafur, gimeracil, and oteracil) (40–60 mg bid orally), or capecitabine tablets (1.5 g qd orally).

Definition of PNI

PNI was calculated as the serum albumin level (g/L) + 5 \times the absolute lymphocyte count.^{14–16}

Grading System for H-PNI

The cut-off values of haemoglobin and PNI were calculated by receiver operating characteristic (ROC) curve

analysis. The haemoglobin and prognostic nutritional index (H-PNI) score was classified into three groups according to each cut-off value of haemoglobin and PNI as follows: H-PNI score of 2 (both hyper-haemoglobin and high PNI), H-PNI score of 1 (one of these haematological abnormalities), and H-PNI score of 0 (neither hyper- nor high PNI).

Follow-Up

All patients were examined every 3 months for the first 2 years, every 6 months from the third year, and then once a year. We contacted the patients by telephone or letter, and the last follow-up time was May 31, 2020. Overall survival (OS) was defined as the time between surgery and patient death or the last follow-up. The median follow-up time for all patients was 35 months (range 3.3–132.1 months). The median follow-up time of the surviving patients was 58.5 months (range 19.3–132.1 months).

Statistical Analysis

Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The cut-off values were calculated by ROC curve analysis. Pearson's chi-square test was used to estimate the correlation between different categorical variables. The OS rate was calculated using the Kaplan–Meier method, and survival differences between groups were evaluated using the Log rank test. Cox proportional hazards models were used for univariate and multivariate analyses. P values <0.05 indicated statistical significance.

Results

Patient Characteristics

A total of 238 patients were included in this study, and their characteristics are shown in Table 1. Among the 238 patients, 162 were male and 76 were female, with a male:female ratio of 2.13:1. The median age was 64 years (range from 44 to 80). Well, moderate and poor tumour differentiation was found in 81, 90 and 67 patients, respectively. There were 46, 116 and 76 patients with stage I, II and III disease, respectively.

Up to the follow-up, a total of 113 patients died, 45 of whom died of uncertain reasons. Sixty-eight patients died from the following causes: tumour progression (n=21), malnutrition (n=13), and tumour progression and malnutrition (n=34). A total of 18 of the 68 patients had complications, including 6 patients with

gastrointestinal bleeding, 9 patients with pulmonary infection, 1 patient with heart failure, 1 patient with pulmonary infection complicated with heart failure and 1 patient with kidney failure. These data were obtained from the patients' last hospitalization and follow-up records. The incidence of malnutrition was as high as 69% among patients with known causes of death.

Cut-off Value of Haemoglobin and PNI

According to ROC curve analysis, haemoglobin =132.5 (g/L) was selected as the evaluation cut-off point. There were 115 patients in the high haemoglobin group (haemoglobin greater than or equal to 132.5) and 123 patients in the low haemoglobin group (haemoglobin less than 132.5). Taking PNI=46.55 as the optimal cut-off point, 161 patients were included in the high PNI group (PNI greater than or equal to 46.55), and 77 patients were included in the low PNI group (PNI less than 46.55). The area under the curve of haemoglobin was 0.653 (P=0.001), while the area under the curve of PNI was 0.604 (P=0.018) (Figure 1).

Correlations Between the H-PNI Score and Clinicopathological Parameters

The associations of the H-PNI score and clinicopathological characteristics are presented in Table 2. According to the grading system of the H-PNI score, 59 (24.8%), 82 (34.5%), and 97 (40.7%) patients had H-PNI scores of 0, 1, and 2, respectively. The results showed that the H-PNI score was highly associated with sex (P=0.000) and age (P=0.000). No significant correlations were identified between H-PNI and tumour location, tumour length or other parameters.

Survival Analysis Based on Haemoglobin, PNI Levels or H-PNI Score

Based on the cut-off value of the haemoglobin level, 115 and 123 patients were classified into groups with high (≥ 132.5 g/L) or low (< 132.5 g/L) haemoglobin levels, respectively. Furthermore, 161 and 77 patients had high (≥ 46.55) and low (< 46.55) PNI levels, respectively, according to the determined cut-off value for PNI. Patients with high haemoglobin and PNI levels had a significantly better prognosis than those with low haemoglobin and PNI levels (P = 0.015 and P = 0.002, respectively; Figure 2A and B). Similarly, 59 and 179 patients had H-PNI scores of 0 and 1–2, respectively.

Table 1 Baseline Characteristics of the Patients with ESCC (n=238)

Characteristics	No. of Patients	Proportion (%)
Gender		
Male	162	68.1
Female	76	31.9
Age		
<65	125	52.5
≥65	113	47.5
Tumour location		
Upper	80	33.6
Middle	146	61.3
Lower	12	5.0
Tumour length		
<5cm	115	48.3
≥5cm	123	51.7
Differentiation		
Well	81	34.0
Moderate	90	37.8
Poor	67	28.2
T classification		
T1	19	8.0
T2	87	36.6
T3	131	55.0
T4	1	0.4
N classification		
N0	127	53.4
N1	79	33.2
N2	29	12.2
N3	3	1.3
TNM stage		
I	46	19.3
II	116	48.7
III	76	31.9
Treatment modalities		
RT	173	72.7
CCRT	65	27.3

Abbreviations: ESCC, esophageal squamous cell carcinoma; T, tumour; N, lymph node; TNM, tumour-node-metastasis; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

The survival rate was significantly lower in patients with an H-PNI score of 0 than in those with an H-PNI score of 1–2 (P=0.000, Figure 2C).

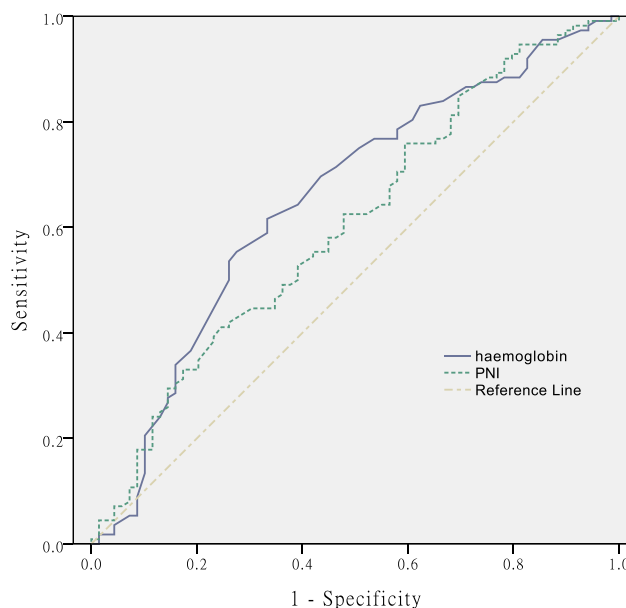


Figure 1 The ROC curve grouped by haemoglobin and PNI. **Abbreviations:** PNI, prognostic nutritional index; ROC, receiver operating characteristic.

Univariate and Multivariate Prognostic Analyses

Our results showed that differentiation, T and N classification, and H-PNI score were significantly associated with OS using univariate analysis. The results of multivariate analysis indicated that these factors were all independent prognostic factors (Table 3).

Discussion

Malnutrition is very common in ESCC patients. Early nutritional risk screening and timely nutritional intervention are of great significance to improve the quality of life and prolong the survival time of patients. At present, the commonly used nutrition screening tools are the Patient Generated-Subjective Global Assessment (PG-SGA), Nutritional Risk Screening 2002 (NRS-2002), Controlling Nutritional Status (CONUT) score, etc.¹⁷ The PG-SGA is a nutritional assessment tool recommended by the American Society of Parenteral Enteral Nutrition (ASPEN) and has been used to evaluate other nutritional assessment tools. It includes patient self-assessment and medical staff assessment, consisting of body mass, food intake, symptoms, activity, physical function, disease, stress status and physical examination, with a high degree of professionalism, sensitivity and specificity.^{18,19} The PG-SGA has the unique advantage of

Table 2 Relationship Between H-PNI Score and Clinicopathological Characteristics (n = 238)

Factors	H-PNI Score			X ²	P-value
	0 (n=59)	1 (n=82)	2 (n=97)		
Gender				16.604	0.000
Male	37	45	80		
Female	22	37	17		
Age(years)				24.298	0.000
<65	18	39	68		
≥65	41	43	29		
Tumour location				2.648	0.266
Upper	19	33	28		
Middle +Lower	40	49	69		
Tumour length(cm)				0.280	0.869
<5	30	38	47		
≥5	29	44	50		
Differentiation				3.616	0.460
Well	22	25	34		
Moderate Poor	17 20	33 24	40 23		
T classification				2.883	0.237
T1-T2	21	37	48		
T3-T4	38	45	49		
N classification				0.823	0.663
N0	31	41	55		
N1-N3	28	41	42		
TNM stage				4.999	0.082
I	6	16	24		
II-III	53	66	73		
Treatment modalities				0.552	0.759
RT	44	61	68		
CCRT	15	21	29		

Abbreviations: H-PNI score, haemoglobin and prognostic nutritional index score; T, tumour; N, lymph node; TNM, tumour-node-metastasis; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

the unification of qualitative evaluation and quantitative evaluation, which differs from other nutrition evaluation tools. The NRS-2002 focuses on patients' nutritional status and disease severity to assess the impact of nutritional interventions on clinical outcomes. The Chinese Society of Clinical Oncology (CSCO) recommended the NRS-2002 as the preferred tool for nutritional screening in hospitals. Its

evaluation mainly includes three aspects: the degree of malnutrition, the severity of the disease, and whether the age of the patient is greater than 70 years. The NRS-2002 has a high positive detection rate for patients at nutritional risk and can be used as a reliable nutritional screening tool.²⁰⁻²² The CONUT score is a screening tool for the early detection of malnutrition in hospitalized patients. It is mainly an indicator based on serum albumin, total cholesterol concentration and peripheral blood lymphocyte count. It is a simple and economical method to objectively and comprehensively predict prognosis.²³ In addition, weight is the easiest and most intuitive indicator for nutritional assessment. Weight loss is common in patients with esophageal cancer and reflects changes in the balance of energy and protein. Therefore, body mass index (BMI) is often calculated to assess patients' nutritional status.

In this study, we evaluated the prognostic value of preoperative haemoglobin and PNI levels in ESCC patients undergoing postoperative radiotherapy. Previous studies have indicated that preoperative nutritional risk screening has predictive value for the prognosis of patients with esophageal cancer, and prognostic nutritional indicators can objectively reflect the nutritional status of patients through the calculation of haematological parameters, thus indicating the long-term survival of patients.²⁴⁻²⁷ PNI was calculated from the serum albumin level and lymphocyte count. Serum albumin reflects the total protein content of the body and is an appropriate biomarker for monitoring protein energy malnutrition in cancer patients. Thus, a lack of serum albumin indicates poor nutritional status and poor outcomes.²⁸⁻³¹ Lymphocytes inhibit tumour cell proliferation, migration, and angiogenesis, so a low lymphocyte count can lead to undesirable results and is a sign of impaired immune defence due to malnutrition.³²⁻³⁴ Numerous previous studies have linked inflammatory responses to cancer progression and lower survival rates. For example, the neutrophil-to-lymphocyte ratio (NLR) is an inflammatory response indicator. A higher preoperative NLR was found to increase the risk of recurrence in patients with esophageal cancer resection.³⁵ In another study, an increased platelet-to-lymphocyte ratio (PLR) indicated a poorer prognosis in ESCC patients.^{36,37} Low haemoglobin is common in a variety of tumours, such as lung,³⁸ breast,³⁹ and gastric cancers,⁴⁰ but the specific mechanism has not been thoroughly studied. It has been proposed that soluble molecules secreted by tumour cells, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha), can reduce haemoglobin levels by changing the haematopoietic environment.⁴¹ To our knowledge, this is the first study to examine the relationship

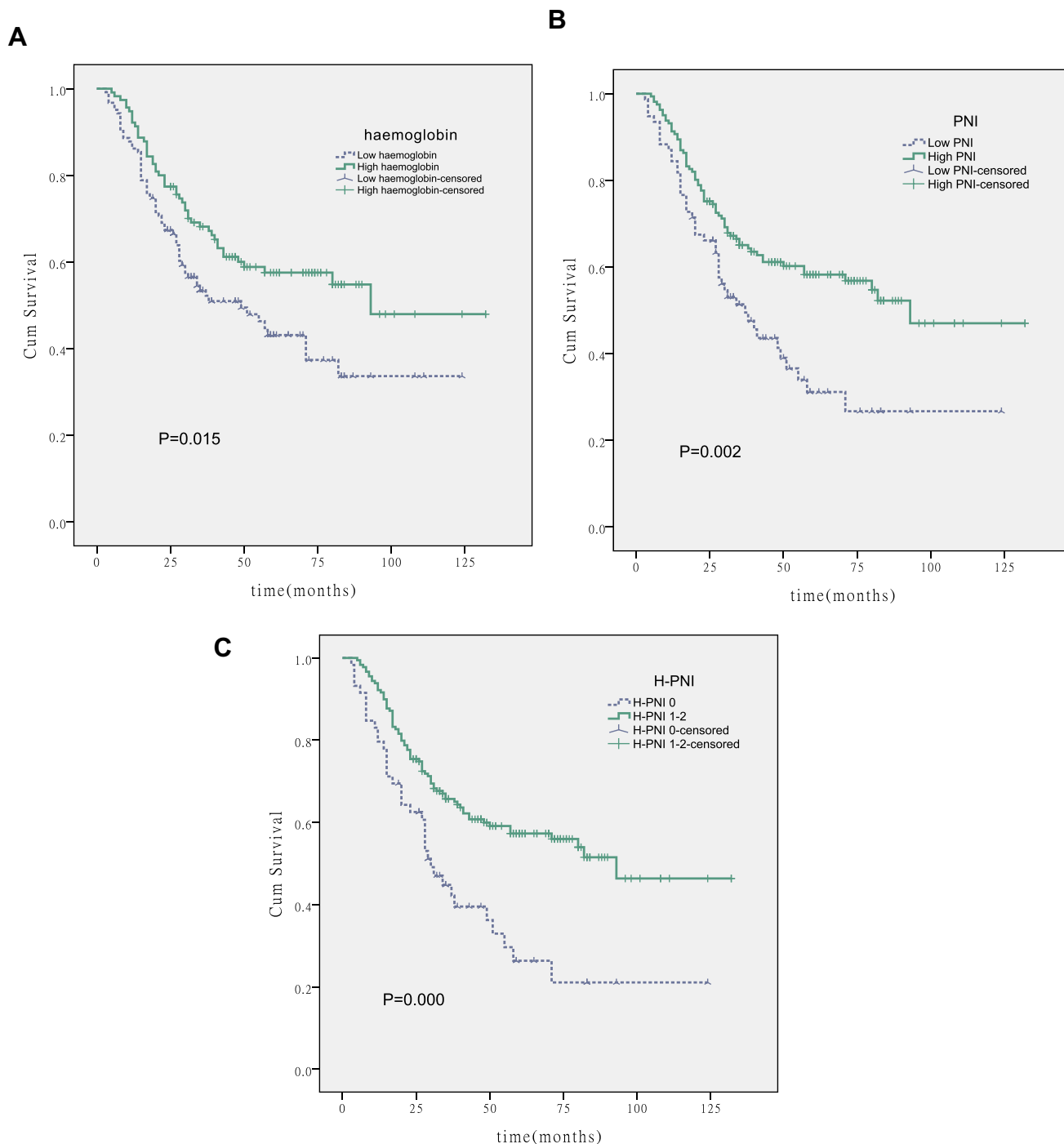


Figure 2 Kaplan–Meier curves for OS stratified according to haemoglobin, PNI, and H-PNI. **(A)** OS curves grouped by haemoglobin cut-off value ($P=0.015$). **(B)** OS curves stratified according to PNI cut-off value ($p=0.002$). **(C)** OS curves stratified by H-PNI score ($P=0.000$).

Abbreviations: OS, overall survival; PNI, prognostic nutritional index; H-PNI score, haemoglobin and prognostic nutritional index score.

between preoperative haemoglobin levels and prognosis in patients with ESCC. Furthermore, we simultaneously studied haemoglobin and PNI to explore the relationship between these indicators and the prognosis of ESCC patients undergoing postoperative radiotherapy.

The most unique aspect of this study is that we evaluated the clinical significance of the H-PNI score, which combines the haemoglobin level and PNI, in ESCC patients who underwent surgery and postoperative radiotherapy. The results of our study showed that the median survival times were 30 and 93

Table 3 Univariate and Multivariate Analyses for the Prediction of Overall Survival in Patients with ESCC (n=238)

Factors	Univariate Analysis			Multivariate Analysis		
	HR	95%CI	P-value	HR	95%CI	P-value
Gender (male/female)	1.200	0.800–1.800	0.379			
Age (<65/≥65)	1.390	0.959–2.012	0.082	1.234	0.825–1.845	0.306
Tumour location (upper/middle+lower)	1.241	0.830–1.855	0.293			
Tumour length (<5cm/≥5cm)	1.275	0.879–1.848	0.200			
Differentiation (well+moderate/poor)	2.068	1.408–3.038	0.000	1.853	1.244–2.758	0.002
T classification (T1-T2/T3-T4)	2.263	1.521–3.367	0.000	2.156	1.431–3.249	0.000
N classification (N0/N1-N3)	2.120	1.453–3.094	0.000	2.165	1.461–3.207	0.000
H-PNI (0/1-2)	2.070	1.398–3.066	0.000	1.741	1.144–2.651	0.010
Treatment modalities (RT/CCRT)	1.413	0.953–2.097	0.085	0.973	0.638–1.484	0.900

Abbreviations: ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; T, tumour; N, lymph node; H-PNI score, haemoglobin and prognostic nutritional index score; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

months in patients with H-PNI scores of 0 and 1–2, respectively ($P = 0.000$). This result suggested that patients with a high H-PNI score have a better prognosis. Moreover, univariate and multivariate prognostic analyses showed that the H-PNI score was an independent prognostic factor for patients ($P = 0.010$). In addition to the H-PNI score, differentiation and T and N classification were also independent prognostic factors.

This study had some limitations. First, the patients enrolled in this retrospective study were treated in a single institution. Second, the blood parameters related to the H-PNI score were collected only at a time point before the surgery, and they were not fully recorded and analysed during the treatment and follow-up. This is noteworthy because blood parameters can be affected by a variety of pathological conditions during or after treatment and change over time. Third, only 238 ESCC patients were enrolled in this study, and the sample size was insufficient. Finally, this study is a retrospective analysis. Due to the limited medical records and the lack of clinical expertise of patients' family members, it is impossible to make an accurate judgement on the cause of death of the patients, so there is insufficient evidence to support whether malnutrition was the main cause of death. Based on the above limitations, large-scale multi-centre clinical studies are needed to confirm the study's findings.

Conclusion

The H-PNI score is an independent prognostic factor for ESCC patients. Since it is determined by blood examinations, using the H-PNI score to predict the prognosis of patients is a simple and economical method. For patients

with low preoperative H-PNI scores, nutritional support can be provided as early as possible to improve the survival time and quality of life of patients.

Acknowledgment

This study was supported by the Medical Science and Technology Development Project of Yancheng (YK2019007).

Disclosure

The authors report no conflicts of interest in this work.

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