World Journal of Gastrointestinal Surgery

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ORIGINAL ARTICLE

Retrospective Study

Prognostic value of preoperative immune-nutritional scoring systems in remnant gastric cancer patients undergoing surgery

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Abstract

BACKGROUND

Remnant gastric cancer (GC) is defined as GC that occurs five years or more after gastrectomy. Systematically evaluating the preoperative immune and nutritional status of patients and analyzing its prognostic impact on postoperative remnant gastric cancer (RGC) patients are crucial. A simple scoring system that combines multiple immune or nutritional indicators to identify nutritional or immune status before surgery is necessary.

AIM

To evaluate the value of preoperative immune-nutritional scoring systems in predicting the prognosis of patients with RGC.

METHODS

The clinical data of 54 patients with RGC were collected and analyzed retrospectively. Prognostic nutritional index (PNI), controlled nutritional status (CONUT), and Naples prognostic score (NPS) were calculated by preoperative blood indicators, including absolute lymphocyte count, lymphocyte to monocyte ratio, neutrophil to lymphocyte ratio, serum albumin, and serum total cholesterol. Patients with RGC were divided into groups according to the immune-nutritional risk. The relationship between the three preoperative immune-nutritional scores and clinical characteristics was analyzed. Cox regression and Kaplan–Meier analysis was performed to analyze the difference in overall survival (OS) rate between various immune-nutritional score groups.

RESULTS

The median age of this cohort was 70.5 years (ranging from 39 to 87 years). No significant correlation was found between most pathological features and immune-nutritional status ($P >$ 0.05). Patients with a PNI score < 45, CONUT score or NPS score ≥ 3 were considered to be at high immune-nutritional risk. The areas under the receiver operating characteristic curves of PNI, CONUT, and NPS systems for predicting postoperative survival were 0.611 [95% confidence interval (CI): 0.460–0.763; $P = 0.161$], 0.635 (95%CI: 0.485–0.784; $P = 0.090$), and 0.707 (95%CI: 0.566–0.848; $P = 0.009$), respectively. Cox regression analysis showed that the three immune-nutritional scoring systems were significantly correlated with OS (PNI: $P = 0.002$; CONUT: $P = 0.039$; NPS: $P < 0.001$). Survival analysis revealed a significant difference in OS between different immune-nutritional groups (PNI: 75 mo *vs* 42 mo, $P = 0.001$; CONUT: 69 mo *vs* 48 mo, $P = 0.033$; NPS: 77 mo *vs* 40 mo, $P < 0.001$).

CONCLUSION

These preoperative immune-nutritional scores are reliable multidimensional prognostic scoring systems for predicting the prognosis of patients with RGC, in which the NPS system has relatively effective predictive performance.

Key Words: Remnant gastric cancer; Immune-nutritional score; Prognostic nutritional index; Controlled nutritional status; Naples prognostic score

Core Tip: Three preoperative immune-nutritional scores of patients with remnant gastric cancer (RGC) were calculated, including prognostic nutritional index (PNI), controlled nutritional status (CONUT), and Naples prognostic score (NPS). Patients were divided into groups according to the immune-nutritional risk. The three immune-nutritional scoring systems were significantly correlated with overall survival (OS) (PNI: $P = 0.002$; CONUT: $P = 0.039$; NPS: $P < 0.001$). Survival analysis revealed a significant difference in OS between different immune-nutritional groups (PNI: 75 mo *vs* 42 mo, $P = 0.001$; CONUT: 69 mo *vs* 48 mo, $P = 0.033$; NPS: 77 mo *vs* 40 mo, $P < 0.001$). These preoperative immune-nutritional scores are reliable multidimensional RGC prognostic scoring systems.

INTRODUCTION

The incidence rate of gastric cancer (GC) ranks fifth among all malignancies, with an annual incidence of more than one million people. Thus far, GC is still one of the diseases that seriously affect the health system[1]. Many high-risk factors contribute to the occurrence of GC, one of which is the remnant stomach after gastrectomy[2]. Remnant GC (RGC) is defined as GC that occurs five years or more after gastrectomy due to benign or malignant lesions. Reports have shown that approximately 2%–3% of remnant stomachs will develop RGC[3,4]. The mechanism of the occurrence and development of RGC remains unclear. Bile reflux, the loss of vagus nerve, and the change in gastric mucosal microenvironment may play important roles in RGC carcinogenesis[5-7].

The treatment of RGC is often comprehensively based on surgery[8,9]. However, the prognosis of RGC is often worse than that of primary GC even after radical gastrectomy[10,11]. Notably, patients often have malnutrition and poor immune status[12,13] after gastrectomy, which may be one of the factors leading to the poor prognosis of RGC patients. Therefore, systematically evaluating the preoperative immune and nutritional status of patients and analyzing its prognostic impact on postoperative RGC patients are crucial.

An increasing number of studies have shown that the immune system plays a crucial role in the tumor microenvironment[14-16]. Meanwhile, the nutritional status of patients often affects tumor growth, metastasis, angiogenesis, and the efficacy of antitumor therapy[17,18]. Prognostic factors related to inflammation and nutrition, including neutrophil to lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, lymphocyte to monocyte ratio (LMR), serum albumin (ALB), and total cholesterol (TC), are

associated with the prognosis of a variety of cancers, including GC, rectal cancer, and breast cancer[19-23].

However, prognostic prediction based on a single marker is often inaccurate and may even be misleading. Therefore, a simple scoring system that combines multiple immune or nutritional indicators to identify nutritional or immune status before surgery is significantly better than single inflammatory or nutritional markers. The prognostic nutritional index (PNI), controlled nutritional status (CONUT), and a new inflammation related prognostic system named Naples prognostic score (NPS) established in recent years by combining preoperative TC content, serum ALB content, LMR, and NLR have been widely used to predict the prognosis of a variety of tumors[24-26]. However, studies on the prognosis of RGC patients predicted by preoperative immune-nutritional score systems are few.

Therefore, this retrospective cohort study aimed to determine the prognostic value of three preoperative immune-nutritional scoring systems, namely, PNI, CONUT, and NPS, in patients with RGC, and to examine their relationship with other clinicopathological features.

MATERIALS AND METHODS

Patients
The medical data of 43 patients with RGC at the First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital) and 11 patients at the Affiliated Suzhou Hospital of Nanjing Medical University (Suzhou Municipal Hospital) from January 2009 to July 2019 were collected. The inclusion criteria of this study were as follows: (1) The patient had a previous history of gastrectomy; (2) The interval from the occurrence of residual GC was five years or more; (3) After admission, the patient underwent radical resection of residual GC; (4) The postoperative pathological diagnosis was gastric adenocarcinoma; (5) The patient did not receive any anticancer treatment from the diagnosis of RGC to surgery; (6) The patient had detailed and extractable medical data and laboratory results; and (7) The patient had survival follow-up data of three years or more. By contrast, participants who met any of the following criteria were excluded from the final analysis: (1) The patient had any clinical evidence of infection or inflammatory disease. Infection was defined in this study as preoperative body temperature ≥ 37.5 °C or increased preoperative C-reactive-protein levels; and (2) The patient had a history of malignant tumors other than GC. This study was approved by the medical ethics committee of Nanjing Medical University. The data were anonymous; therefore, relevant informed consent was not required.

Definition of immune-nutritional prognosis systems
PNI score is defined as serum ALB (g/L) + 5 × Lymphocyte count (× 10^9); a PNI score < 45 indicated that the patient had immune-nutritional risk.

The CONUT score is defined as the sum of the three scores based on serum ALB concentration, lymphocyte count, and TC concentration. A score ≥ 3 was considered to be at immune-nutritional risk. Serum ALB concentration was grouped as > 35, 30–34.9, 25–29.9, and < 25 (g/L), and the scores of the four groups were 0, 2, 4, and 6, respectively. Lymphocyte count was grouped as ≥ 1.6, 1.2–1.5, 0.8–1.1, and < 0.8 (× 10^9), respectively, which had scores of 0, 1, 2, and 3, respectively. TC concentration was divided into groups ≥ 180, 140–179, 100–139, and < 100 mg/dL, with scores of 0, 1, 2, and 3, respectively.

NPS is defined on the basis of the following four parameters: Serum ALB, TC, LMR, and NLR. NLR and LMR are calculated by dividing the neutrophil count by lymphocyte and monocyte counts in routine blood tests, respectively. Patients with serum ALB lower than 40 g/L, TC lower than 180 mg/dL, LMR lower than 4.44, or NLR higher than 2.96 will obtain 1 point; otherwise, it will be regarded as 0. The sum of the scores of the four parameters is an NPS score. Patients with an NPS score of 0 were considered to have non-immune-nutritional risks, those with an NPS of 1 or 2 were regarded have mild immune-nutritional risks, and patients with an NPS of 3 or 4 were considered to have severe immune-nutritional risks. In the actual grouping, patients with an NPS score of 0 (6/54) are few due to the generally poor nutritional status of patients with RGC; however, this score cannot be analyzed alone. Therefore, patients with an NPS score of 0–2 (no or mild immune nutritional risk) were regarded as one group.

Data collection and follow-up
The clinical characteristics and pathological parameters of the patients, including gender, age, histological type, pathological stage, and laboratory data, were retrospectively collected from the hospital information system. Among them, the data of neutrophils, lymphocytes, and monocytes were from routine blood tests, the levels of serum ALB and TC were respectively from liver and kidney function tests, and all blood samples were fasting blood samples. All patients were followed up regularly after radical gastrectomy. This study mainly obtained the survival information of patients through postoperative medical examination or telephone contact. The follow-up interval was once every 6 mo. The patient was followed up to death (event) or the last follow-up (censored).

Statistical analysis

IBM SPSS statistics 23.0 (SPSS, Inc., Chicago, Illinois, United States) and GraphPad prism software (version 5.0) were used for statistical analyses and mapping, respectively. *T*-test or chi-square test was used to analyze the differences in statistical data between various groups. The receiver operating characteristic (ROC) curve was generated to evaluate the difference in survival prediction capability between different scoring systems. The Kaplan–Meier method was used for survival analysis, and log-rank test was employed to compare the difference in prognosis between various immune-nutritional system groups. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of patients

According to the inclusion and exclusion criteria, a total of 54 patients with RGC were included in this study. Among these patients, 42 were male (77.8%) and 12 were female (22.2%), and the median age was 70.5 years (ranging from 39 to 87 years). A total of 28 patients (51.9%) and 26 patients (48.1%) had better or worse histological differentiation types, respectively. In addition, 26 patients had lymph node metastasis, accounting for 48.1% of all patients. Table 1 describes the potential different immune-nutritional system scoring groups among populations with different clinical characteristics. The results show that no significant correlation existed between most pathological features and immune-nutritional status in patients with RGC.

ROC curve analysis of immune-nutritional systems for predicting postoperative survival

Fasting blood indicators of the patients were used to calculate the immune-nutritional scores. Among these indicators, the average level of serum ALB was 38.75 g/L [95% confidence interval (CI): 35.98–38.93 g/L], TC was 168 mg/dL (95%CI: 157–179 mg/dL), and the average lymphocyte count was 1.30×10^9/L (95%CI: $1.16–1.44 \times 10^9$/L); the average monocyte count was 0.40×10^9/L (95%CI: $0.35–0.44 \times 10^9$/L), the average neutrophil count was 3.61×10^9/L (95%CI: $3.04–4.17 \times 10^9$/L), the calculated NLR was 3.22 (95%CI: 2.45–4.00), and the LMR was 3.71 (95%CI: 2.21–4.21).

The curves of the three immune-nutritional scores for predicting postoperative survival were plotted (Figure 1). NPS was found to have the largest area under the curve (AUC = 0.707; 95%CI: 0.566–0.848; P = 0.009). The AUC values of PNI and CONUT were 0.611 (95%CI: 0.460–0.763; P = 0.161) and 0.635 (95%CI: 0.485–0.784; P = 0.090), respectively.

Analysis of OS

Cox regression analysis showed that tumor gross classification (P = 0.014), pathological differentiation type (P = 0.032), lymph node metastasis ($P < 0.001$), clinical Tumor-Node-Metastasis status (P = 0.001), and three immune-nutritional scoring systems, namely, PNI (P = 0.002), CONUT (P = 0.039), and NPS ($P < 0.001$), were significantly correlated with OS. In addition, no significant correlation was found between age, sex, primary tumor size, and T stage and OS ($P > 0.05$ for all) (Table 2).

Kaplan–Meier analysis was used to analyze the relationship between PNI, CONUT, and NPS scores and prognosis. The analysis showed that the median OS of patients with a low immune-nutritional risk was significantly higher than that of patients with a high immune-nutritional risk (PNI: 75 mo *vs* 42 mo, P = 0.001; CONUT: 69 mo *vs* 48 mo, P = 0.033; NPS: 77 mo *vs* 40 mo; $P < 0.001$) (Figure 2). This finding suggests that the three immune-nutritional systems can significantly predict the prognosis of patients. Of note, the NPS system demonstrated the best prediction capability.

DISCUSSION

An increasing number of studies have shown that immunity and nutrition are closely related to the occurrence and development of cancer, which has led to the research and development of biomarkers or prognostic scoring systems based on immunity and nutrition[14-16]. The nutritional status of patients is often worse after partial gastrectomy and frequently combined with poor immune status, leading to the crucial evaluation of immune-nutritional indicators in patients with RGC[12,13]. Appropriate treatment strategies can be formulated by evaluating the relationship between immune-nutritional systems and the postoperative prognosis of patients with RGC. Three immune-nutritional systems are analyzed in the current study based on the calculation of inflammatory cells in routine blood tests and nutritional indicators, such as ALB and TC. The results showed that PNI, CONUT, and NPS can accurately predict the postoperative OS of patients with RGC. Among the three scoring systems, NPS has a superior accuracy.

Inflammatory cells participate in the destruction of tumor cells and angiogenesis in the tumor microenvironment and regulate the sensitivity of tumors to radiotherapy and chemotherapy drugs. Lymphocytes are the main antitumor cells and play an important role in cell-mediated immune

Table 1 Clinical characteristics of patients and three immune-nutritional score systems

Characteristics	Immune–nutritional score systems						
	Values (*n* = 54)	PNI (*n* = 27/27)	*P* value	CONUT (*n* = 34/20)	*P* value	NPS (*n* = 32/22)	*P* value
Age (years)			1.000		0.368		0.047
< 70	26	13/13		18/8		19/7	
≥ 70	28	14/14		16/12		13/15	
Gender			1.000		0.713		0.216
Male	42	21/21		27/15		23/19	
Female	12	6/6		7/5		9/3	
Primary tumor size			0.790		0.581		1.000
≤ 3 cm	27	13/14		18/9		16/11	
> 3 cm	27	14/13		16/11		16/11	
Gross type			0.412		0.313		0.386
Non-ulcerative type	21	12/9		15/6		14/7	
Ulcerative type	33	15/18		19/14		18/15	
Differentiation			0.285		0.449		0.189
Well/Moderate	28	16/12		19/9		19/9	
Poor	26	11/15		15/11		13/13	
T stage			0.588		0.519		0.984
T1/T2	22	12/10		15/7		13/9	
T3/T4	32	15/17		19/13		19/13	
Lymph node metastasis			0.106		0.449		0.445
No	28	17/11		19/9		18/10	
Yes	26	10/16		15/11		14/12	
cTNM status			0.282		0.538		0.075
I/II	30	17/13		20/10		21/9	
III	24	10/14		14/10		11/13	

The number of cases, low risk cases/high risk cases were shown, p-value indicated the significance of different immune-nutritional risk between the patients with different clinical characteristics. PNI: Prognostic nutritional index; CONUT: Controlled nutritional status; NPS: Naples prognostic score; cTNM: Clinical Tumor-Node-Metastasis.

response by recognizing and killing cancer cells[27]. Lymphopenia is related to the adverse reactions and prognosis of a variety of malignant tumors, including GC[28,29]. However, patients with malignant tumor with increased neutrophil infiltration often have poor clinical outcomes. Neutrophils can promote tumor formation by releasing cytokines and stimulate tumor cell proliferation and metastasis [30,31]. Tumor-associated macrophages and blood monocytes are also involved in tumor progression and metastasis and the improvement of tumor microenvironment through a variety of mechanisms[32, 33]. Thus far, an increasing number of immune cell-based prognostic parameters, including NLR and LMR, have been studied and reported[19,20,34]. NLR and LMR are objective markers that reflect the inflammatory and immune status of the host. The increase in NLR and the decrease in LMR in patients are usually associated with a poor prognosis[21,35].

Malnutrition is closely related to tumor growth, angiogenesis, and progression. Serum ALB concentration is an important marker of nutrition. In a variety of tumors, patients with hypoalbuminemia usually represent a high degree of malignancy, which often indicates a poor prognosis[23,36]. Almost all nutritional prognosis scoring systems cover serum ALB levels, such as C-reactive protein to ALB ratio, Glasgow diagnostic score, as well as PNI, CONUT, and NPS discussed in this study, due to its important significance in malignant tumors[37,38]. Simultaneously, TC content is also one of the indicators of tumor prognosis. Hypocholesterolemia is associated with a poor prognosis in many tumors, including prostate cancer and non-small cell lung cancer[22,39]. Cholesterol integrates into

Table 2 Cox regression analysis of overall survival

Characteristic	OS		
	HR	95%CI	*P* value
Age (years)			0.500
< 70	1.000	0.605-2.796	
≥ 70	1.301		
Gender			0.451
Male	1.000	0.261-1.1.816	
Female	0.689		
Primary tumor size			0.926
≤ 3 cm	1.000	0.479-2.242	
> 3 cm	1.037		
Gross type			0.014
Non-ulcerative type	1.000	1.285-8.932	
Ulcerative type	3.388		
Differentiation			0.032
Well/Moderate	1.000	1.083-5.629	
Poor	2.469		
T stage			0.289
T1/T2	1.000	0.671-3.823	
T3/T4	1.601		
Lymph node metastasis			<0.001
No	1.000	1.963-10.472	
Yes	4.534		
cTNM stage			0.001
I/II	1.000	1.734-9.117	
III	3.976		
PNI group			0.002
Low risk	1.000	1.724-10.030	
High risk	4.158		
CONUT group			0.039
Low risk	1.000	1.041-4.666	
High risk	2.204		
NPS group			< 0.001
Low risk	1.000	1.879-9.425	
High risk	4.208		

PNI: Prognostic nutritional index; CONUT: Controlled nutritional status; NPS: Naples prognostic score; cTNM: Clinical Tumor-Node-Metastasis; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval.

specialized lipoprotein membrane domains, forms signal transduction mechanisms, and participates in a variety of key cellular signaling pathways[40].

The scoring system formed by combining immune and nutritional indicators can effectively reflect the physical condition of patients and improve the efficacy of predicting prognosis. This study calculated the PNI, CONUT, and NPS scores of patients according to their blood indicators. Survival analysis revealed that the three scoring systems can show good prediction efficiency. PNI, an index
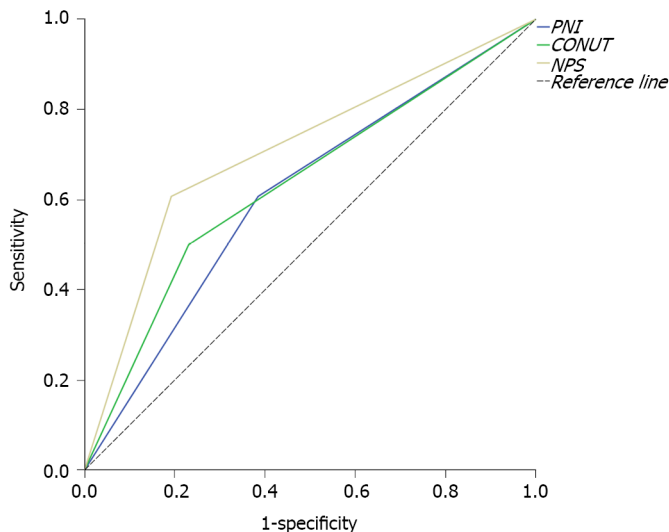
Figure 1 Receiver operating characteristic curve analyses for prognostic nutritional index, controlled nutritional status, and Naples prognostic score systems. ROC: Receiver operating characteristic; PNI: Prognostic nutritional index; CONUT: Controlled nutritional status; NPS: Naples prognostic score.

related to ALB concentration and lymphocyte count, has been used to predict the risk of postoperative complications and the OS of patients with GC and other cancers[24,41,42]. The CONUT score is an index related to ALB concentration, lymphocyte count, and TC concentration. Studies have shown that the CONUT score is strongly correlated with the survival rate of patients with thyroid cancer; it is also an independent risk factor for lung cancer prognosis[25,43]. NPS is an index related to serum ALB concentration, TC concentration, LMR, and NLR and has been proven to be a predictor of OS in a variety of tumors. NPS has better predictive value than clinical prognostic parameters alone in patients with resected pancreatic cancer[26]. In esophageal cancer, high NPS is associated with a poor prognosis in locally advanced patients[44]. NPS can also predict the prognosis of endometrial cancer patients and may play an important role in clinical guidance[45].

In RGC, the clinical data of immune-nutritional scoring systems are still lacking; particularly, no relevant literature is available for the prediction of postoperative OS. PNI, CONUT, and NPS are comprehensive predictive evaluation methods that are easy to obtain. They represent the entire systemic inflammation and nutritional status of patients with RGC from many aspects. Meanwhile, the results show that NPS has the strongest prediction efficiency among the three prediction systems according to survival analysis.

This study has some limitations. First, the current study is retrospective. Although the data of two institutions were included, the sample size of patients was relatively small and the selection deviation was inevitable due to the low incidence and radical resection rate of RGC, respectively. For example, this study found significant differences in gender between different NPS groups, which may represent a selection bias. This bias may reduce the universality of the research results. Second, the cutoff points of laboratory indicators were obtained from previous literature reports. A new prediction system has not been developed. This system should be established by creating new cutoff points based on RGC, possibly leading to the weakening of the prediction capability of immune-nutritional indicators. However, the predictive significance of the three immune-nutritional systems in the prognosis of patients with RGC still shows considerable value.

CONCLUSION

In this study, the immune-nutritional score systems PNI, CONUT, and NPS were the factors that affected the prognosis of patients with RGC. The results showed that poor immune-nutritional scores were associated with a poor OS. Among the three immune-nutritional scoring systems, the NPS scoring system can more accurately evaluate the prognosis of patients with RGC.
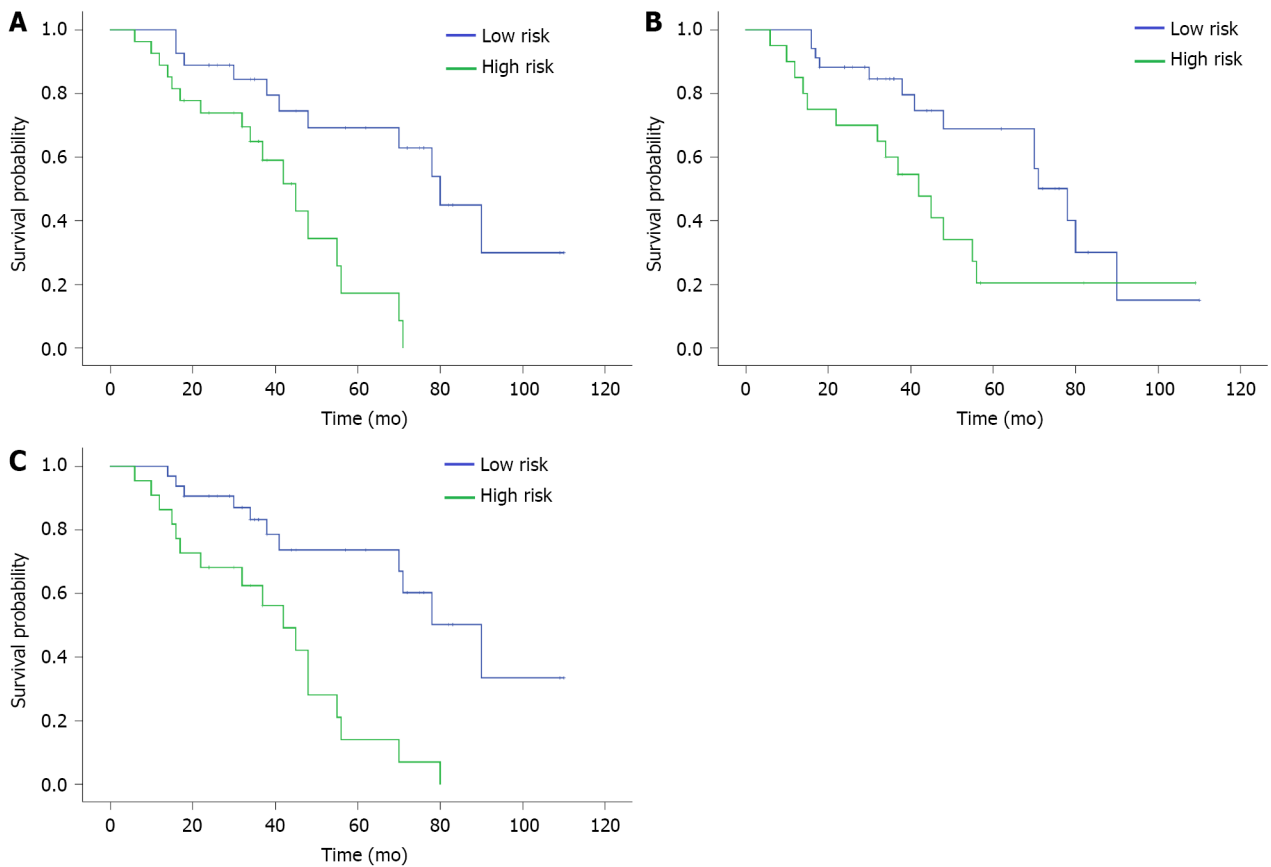
Figure 2 Kaplan-Meier survival curves for overall survival based on prognostic nutritional index, controlled nutritional status, and Naples prognostic score stratification. A: Prognostic nutritional index; B: Controlled nutritional status; C: Naples prognostic score. PNI: Prognostic nutritional index; CONUT: Controlled nutritional status; NPS: Naples prognostic score.

ARTICLE HIGHLIGHTS

Research background

The mechanism of the occurrence and development of remnant gastric cancer (RGC) remains unclear. Systematically evaluating the preoperative immune and nutritional status of patients and analyzing its prognostic impact on postoperative RGC patients are crucial.

Research motivation

In RGC, the clinical data of immune-nutritional scoring systems are still lacking; particularly, no relevant literature is available for the prediction of postoperative overall survival (OS). Prognostic nutritional index (PNI), controlled nutritional status (CONUT), and Naples prognostic score system (NPS) are comprehensive predictive evaluation methods that are easy to obtain. They represent the entire systemic inflammation and nutritional status of patients with RGC from many aspects.

Research objectives

This retrospective cohort study aimed to determine the prognostic value of three preoperative immune-nutritional score systems, namely, PNI, CONUT, and NPS, in patients with RGC, and to examine their relationship with other clinicopathological features.

Research methods

The curves of the three immune-nutritional scores for predicting postoperative survival were plotted. Kaplan–Meier analysis was used to analyze the relationship between PNI, CONUT, and NPS scores and prognosis.

Research results

NPS was found to have the largest area under the curve [AUC = 0.707; 95% confidence interval (CI): 0.566–0.848; $P = 0.009$]. The AUC values of PNI and CONUT were 0.611 (95%CI: 0.460–0.763; $P = 0.161$) and 0.635 (95%CI: 0.485–0.784; $P = 0.090$), respectively. The three immune-nutritional scoring systems,

PNI (P = 0.002), CONUT (P = 0.039), and NPS (P < 0.001), were significantly correlated with OS. Median OS of patients with a low immune-nutritional risk was significantly higher than that of patients with a high immune-nutritional risk (PNI: 75 mo *vs* 42 mo, P = 0.001; CONUT: 69 mo *vs* 48 mo, P = 0.033; NPS: 77 mo *vs* 40 mo, P < 0.001).

Research conclusions

Poor immune-nutritional scores are associated with a poor OS. Among the three immune-nutritional scoring systems, the NPS scoring system can more accurately evaluate the prognosis of patients with RGC.

Research perspectives

The finding shows that the three immune-nutritional systems can significantly predict the prognosis of patients. Of note, the NPS system demonstrates the best prediction capability.

FOOTNOTES

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