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Retrospective Study

Prognostic Value of Preoperative Immune-Nutritional Score Systems in Remnant Gastric Cancer Patients Undergoing Surgery

Immune-Nutritional Systems in RGC

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Abstract

BACKGROUND

Remnant gastric cancer (RGC) is defined as gastric cancer (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 RGC patients is crucial. A simple scoring system that combines multiple immune or nutritional indicators to identify nutritional or immune status before surgery is necessary.

AIM

This study aimed to evaluate the predictive effect of preoperative immune-nutritional score systems on 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 value, lymphocyte to monocyte ratio (LMR), neutrophil to lymphocyte ratio (NLR), serum albumin (ALB), and serum total cholesterol (TC) level. Patients with RGC were divided into groups according to the immune-nutritional risk. The relationship between 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 years to 87 years). No significant correlation was found between most pathological features and immune-nutritional status (p > 0.05). Patients with PNI score <45, CONUT score or NPS score ≥ 3

is considered to be at high immune-nutritional risk. The areas under the curve (AUC) of the receiver operating characteristic (ROC) curve of PNI, CONUT, and NPS systems for predicting postoperative survival were 0.611 (95%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), and NPS (p < 0.001). Survival analysis revealed a significant difference in OS between different immune-nutritional groups. PNI was 75 mo compared with 42 mo, P = 0.001; CONUT is 69 to 48 mo, P = 0.033; NPS is 77 to 40 mo; P < 0.001).

CONCLUSION
Preoperative immune-nutritional score systems is a reliable multidimensional prognostic scoring system for predicting the prognosis of patients with RGC, in which the NPS system has relatively effective predictive performance.

Key Words: Remnant gastric cancer (RGC); Immune-nutritional score; Prognostic nutritional index (PNI); Controlled nutritional status (CONUT); Naples prognostic score (NPS).

Core Tip: Three preoperative immune-nutritional score systems 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 score systems were significantly correlated with OS, PNI (P = 0.002), CONUT (P = 0.039), and NPS (p < 0.001). Survival analysis revealed a significant

difference in OS between different immune-nutritional groups, PNI (P = 0.001), CONUT (P = 0.033), and NPS (P < 0.001). Preoperative immune-nutritional score systems is a reliable multidimensional RGC prognostic scoring system.

INTRODUCTION

The incidence rate of gastric cancer (GC) ranks fifth, 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 factor is the remnant stomach after gastrectomy[2]. Remnant gastric cancer (RGC) is defined as GC that occurs five years or more after gastrectomy due to benign or malignant lesions. Reports shown that approximate 2%–3% of remnant stomach 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 the RGC carcinogenesis[5-7].

The treatment of RGC is a comprehensively based on surgery [8, 9]. However, the difference is that 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 is 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 affected the tumor growth, metastasis, angiogenesis, and the effect of antitumor therapy[17, 18]. Prognostic factors related to inflammation and nutrition, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), serum albumin (ALB), and total cholesterol (TC) levels, are associated with the prognosis of a variety of cancers, including GC, rectal cancer, and breast cancer[19-23].

However, the prediction of 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 Naples prognostic score system (NPS) established in recent years by combining preoperative TC content, serum ALB content, LMR, and NLR have also 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 aims to determine the prognostic value of three kinds of preoperative immune-nutritional score systems, namely PNI, CONUT, and NPS in patients with RGC, to examine their relationship with other clinicopathological features.

MATERIALS AND METHODS

Patients

The medical data of 43 patients with RGC in the First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital) and 11 patients in 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 are as follows. (I) The patient has a previous history of gastrectomy. (II) The interval from the occurrence of residual gastric cancer is five years or more. (III) After admission, the patient underwent radical resection of residual gastric cancer. (IV) The postoperative pathological diagnosis is gastric adenocarcinoma. (V) The patient did not receive any anticancer treatment from the diagnosis of RGC to surgery. (VI) The patient has detailed and extractable medical data and laboratory results. (VII) The patient has 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. (I) 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 CRP levels. (II) The patient has a history of malignant tumors other than gastric cancer. This study was approved by the medical ethics committee of Nanjing Medical University. These data are anonymous; therefore, relevant informed consent is not required.

Definition of immune-nutritional prognosis system

PNI score is defined as serum ALB (g/L) + 5 × Lymphocyte count (×109); a PNI score <45 indicates that the patient has 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 is considered to be at immune-nutritional risk. The grouping of serum ALB concentration was >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. The grouping of lymphocyte count was ≥1.6, 1.2–1.5, 0.8–1.1, and <0.8 (×109), respectively demonstrating scores of 0, 1, 2, and 3. 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 are considered to be non-immune-nutritional risks, those with NPS of 1 or 2 are regarded as mild immune-nutritional risks, and patients with NPS of 3 or 4 are considered to be 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) are regarded as one group.

Data   collection   and   follow-up

The clinical characteristics and pathological parameters of 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 are from routine blood tests, the levels of serum ALB and TC are respectively from liver and kidney function tests, and all blood samples are 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 six months. 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, USA) and GraphPad prism software (version 5.0) were used for statistical analysis 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 and scoring system. The Kaplan–Meier method was used for survival curve, 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 years 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 systems scoring groups among populations with different clinical characteristics. The results show that no significant correlation exists between most pathological features and immune-nutritional status in patients with RGC.

ROC curve of immune-nutritional systems for predicting postoperative survival Fasting blood indicators of patients are used to calculate the immune nutritional system. 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% confidence interval: 157– 179 mg/dL), and the average value of lymphocytes was 1.30 × 109/L(95% confidence interval [CI]: 1.16–1.44 × 109/L); the average value of monocytes is 0.40 × 109/L (95% confidence interval [CI]: 0.35–0.44 × 109/L), the average value of neutrophils is 3.61 × 109/L (95% confidence interval [CI]: 3.04–4.17 × 109/L), the calculated NLR is 3.22 (95% confidence interval: 2.45–4.00), and the LMR is 3.71 (95% confidence interval: 2.21–4.21). The curves of the three immune-nutritional scores for predicting postoperative survival were illustrated (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 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), cTNM 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, T stage, and OS (all p > 0.05) (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 low immune-nutritional risk was significantly higher than that of patients with high immune-nutritional risk. Among them, PNI is 75 to 42 mo, P = 0.001; CONUT is 69 to 48 mo, P = 0.033; NPS is 77 to 40 mo; p < 0.001 (Figure 2). This finding shows that the three

immune-nutritional systems can significantly predict the prognosis of patients. Considering effect, the NPS system demonstrates 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 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 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 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 their important significance in malignant tumors[37, 38]. Simultaneously, TC content is also one of the indicators of tumor prognosis. Hypocholesterolemia is associated with poor prognosis of many tumors, including prostate cancer and non-small cell lung cancer [22, 39]. Cholesterol integrates into 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 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 in 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 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 still has some limitations. First, the current study is retrospective. Although the data of two institutions are included, the sample size of patients is relatively small and the selection deviation is 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 segmentation points of laboratory indicators are obtained from previous literature reports. A new prediction system has not been developed. This system is established by creating new segmentation points based on the specificity of 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, immune-nutritional score systems PNI, CONUT, and NPS are the factors that affect the prognosis of patients with RGC. The results showed that poor immune-nutritional scores were associated with poor OS. Among the three immune-nutritional scoring systems, the NPS scoring system can accurately evaluate the prognosis of patients with RGC.

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 is 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 aims to determine the prognostic value of three kinds of preoperative immune-nutritional score systems, namely PNI, CONUT, and NPS in patients with RGC, to examine their relationship with other clinicopathological features.

Research methods

The curves of the three immune-nutritional scores for predicting postoperative survival were illustrated. 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%CI, 0.566–0.848; P = 0.009). The AUC 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. 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 low immune-nutritional risk was significantly higher than that of patients with high immune-nutritional risk. Among them, PNI is 75 to 42 mo, P = 0.001; CONUT is 69 to 48 mo, P = 0.033; NPS is 77 to 40 mo; p < 0.001.

Research conclusions

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

Research perspectives

This finding shows that the three immune-nutritional systems can significantly predict the prognosis of patients. Considering effect, the NPS system demonstrates the best prediction capability.

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