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Retrospective Study

Nomogram based on tumor-associated neutrophil-to-lymphocyte ratio to predict survival of patients with gastric neuroendocrine neoplasms

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Author contributions: Cao LL, Lu J, Lin JX and Huang CM conceived the study, analyzed the data, and drafted the manuscript; Zheng CH helped critically revise the manuscript for important intellectual content; Li P, Xie JW, Wang JB, Chen QY, Lin M and Tu RH helped collect the data and designed the study; All authors read and approved the final manuscript.

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Abstract

AIM

To assess the predictive value of the tumor-associated neutrophil-to-lymphocyte ratio in terms of the clinical outcomes of patients with gastric neuroendocrine neoplasms after radical surgery.

METHODS

Data were retrospectively collected from 142 patients who were diagnosed with gastric neuroendocrine neoplasms and who underwent radical gastrectomy at our department from March 2006 to March 2015. These data were retrospectively analyzed, and a receiver operating characteristic curve analysis was used to identify the optimal value of the tumor-associated neutrophil-to-lymphocyte ratio. Univariate and multivariate survival analyses were used to identify prognostic factors. A nomogram was then applied to predict clinical outcomes after surgery.

RESULTS

The tumor-associated neutrophil-to-lymphocyte ratio was significantly associated with tumor recurrence, especially with liver metastasis and lymph node metastasis ($P < 0.05$ for both), but not with clinical characteristics ($P > 0.05$ for all). A multivariate Cox regression analysis identified the tumor-associated

neutrophil-to-lymphocyte ratio as an independent prognostic factor for recurrence-free survival and overall survival ($P < 0.05$ for both). The concordance index of the nomograms, which included the tumor-associated neutrophil-to-lymphocyte ratio, Ki-67 index, and lymph node ratio, was 0.788 (0.759) for recurrence-free survival (overall survival) and was higher than the concordance index of the traditional TNM staging system [0.672 (0.663)].

CONCLUSION

The tumor-associated neutrophil-to-lymphocyte ratio is an independent prognostic factor in patients with gastric neuroendocrine neoplasms. Nomograms that include the tumor-associated neutrophil-to-lymphocyte ratio, Ki-67 index, and lymph node ratio have a superior ability to predict clinical outcomes of postoperative patients.

Key words: Gastric neuroendocrine neoplasms; Tumor-associated neutrophil-to-lymphocyte ratio; Tumor recurrence; Prognosis

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Core tip: The study aimed to assess the predictive value of the tumor-associated neutrophil-to-lymphocyte ratio in terms of the clinical outcomes of 142 patients diagnosed with gastric neuroendocrine neoplasms. We demonstrated that the tumor-associated neutrophil-to-lymphocyte ratio was significantly correlated with tumor recurrence, especially with liver and lymph node metastasis. Moreover, the tumor-associated neutrophil-to-lymphocyte ratio was found to be an independent predictor of recurrence-free survival and overall survival, and combining it with the Ki-67 index and lymph node ratio could improve prognosis prediction in patients with gastric neuroendocrine neoplasms, as could applying the traditional TNM staging system.

Cao LL, Lu J, Lin JX, Zheng CH, Li P, Xie JW, Wang JB, Chen QY, Lin M, Tu RH, Huang CM. Nomogram based on tumor-associated neutrophil-to-lymphocyte ratio to predict survival of patients with gastric neuroendocrine neoplasms. *World J Gastroenterol* 2017; 23(47): 8376-8386 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i47/8376.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i47.8376>

INTRODUCTION

Gastric neuroendocrine neoplasms (g-NENs) are a highly heterogeneous and poorly understood group of relatively rare tumors that are derived primarily from enterochromaffin-like cells (ECL-cells) localized in the gastric mucosa^[1]. Due to an increased understanding of g-NENs and improved diagnostic techniques, the incidence of g-NENs, which account for 6% of all

neuroendocrine neoplasms, is increasing every year^[2]. However, due to significant differences in the clinical pathology and biological characteristics, our knowledge regarding g-NENs is still very limited^[3,4]. The World Health Organization (WHO, 2010) classifies g-NENs into the following subclasses: neuroendocrine tumors (g-NETs), neuroendocrine carcinoma (g-NEC), and mixed adenoneuroendocrine carcinoma (g-MANEC)^[5]. In addition to an early diagnosis, an important and effective component of proper management is the identification of the prognostic factors in patients with g-NENs. According to the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC), the TNM staging system, which accounts for invasion depth, lymph node status, and metastases, is one of the most important prognostic factors in patients with g-NENs^[6,7]. However, the prognostic factors of these tumors are complex and multifaceted and have not been clearly defined thus far^[8,9]. In the past decade, increasing evidence has suggested that both tumor-associated neutrophils (TANs) and tumor-associated lymphocytes (TALs) are significantly associated with patient prognosis. Elevated TANs and reduced TALs correlate with advanced stage and poor prognosis in a variety of human tumors, including cervical cancer^[10], hepatocellular carcinoma^[11], and pancreatic cancer^[12]. However, few studies have focused on the relationship between the tumor-associated neutrophil-to-lymphocyte ratio (TA-NLR) and the prognosis of patients with neuroendocrine neoplasms, particularly g-NENs.

This study investigated the utility of the TA-NLR as a prognostic indicator and evaluated its clinical value for the diagnosis and postoperative surveillance of patients undergoing radical surgery for g-NENs.

MATERIALS AND METHODS

General conditions

Overall, 173 patients who were diagnosed with g-NENs at Fujian Medical University Union Hospital between March 2006 and March 2015 were identified from a prospective database. The exclusion criteria for this study were as follows: metastatic disease confirmed preoperatively or during surgery ($n = 11$), perioperative death ($n = 1$), and incomplete/inaccurate medical records ($n = 19$). In all, 142 patients who underwent radical surgery were included in this study. The pathological data of these patients were reconfirmed by two pathologists according to the North American Neuroendocrine Tumor Society (NANETS) guidelines (2010)^[13]. In total, 27 (19.0%) patients were diagnosed with g-NETs, 45 (31.7%) with g-NEC, and 70 (49.3%) with g-MANEC. The ethics committee of Fujian Union Hospital approved this retrospective study. Written consent was obtained from the patients, and their information was stored in the hospital database and used for research.

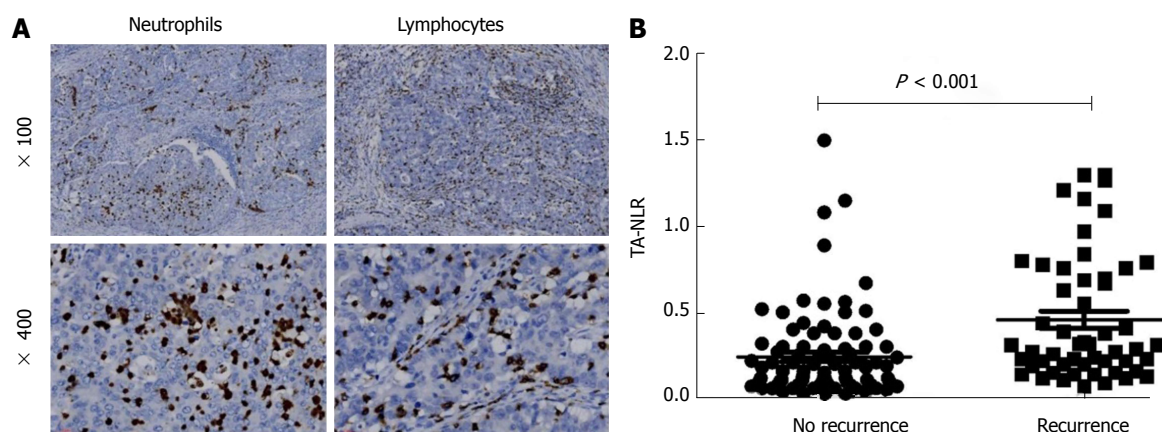


Figure 1 Relationship between the tumor-associated neutrophil-to-lymphocyte ratio and tumor recurrence. A: Representative immunohistochemical staining for CD15 (left) and CD8 (right); B: Significant differences in the TA-NLR were observed between the recurrence group ($0.46\% \pm 0.05\%$, mean \pm SE) and the non-recurrence group ($0.24\% \pm 0.03\%$, $P < 0.001$). TA-NLR: Tumor-associated neutrophil-to-lymphocyte ratio.

Immunohistochemistry analysis

Immunohistochemical staining for CD8 or CD15 was performed using formalin-fixed, paraffin-embedded tumor tissue sections (4- μ m-thick) from 142 g-NENs (Figure 1A). Briefly, the slides were baked at 65 °C for 2 h, deparaffinized with xylene, and rehydrated in graded alcohol. The slides were subjected to antigen retrieval *via* the high-pressure method in antigen retrieval solution. Endogenous peroxidase was inactivated using 3% H₂O₂ in methanol. Non-specific binding was blocked *via* incubation in 1% bovine serum albumin (BSA; Sigma-Aldrich; St. Louis, MO, United States) in phosphate buffered saline (PBS). Subsequently, the slides were incubated overnight at 4 °C with a primary monoclonal mouse antibody against CD8 or CD15 (1:100 dilution; Zhongshan Golden Bridge Biotech, Beijing, China). Normal goat serum was used as a negative control. After being washed with PBS, tissue sections were incubated with the secondary antibody (Zhongshan Golden Bridge Biotech, Beijing, China) for 20 min at room temperature and then stained with diaminobenzidine (DAB). Finally, the slides were counterstained in hematoxylin, dehydrated, and mounted with a coverslip.

Two pathologists who were blinded to the clinical data reviewed the immunoreactivity under a light microscope. Inflammatory cells that had infiltrated the tumor nest and tumor stroma were analyzed, and inflammatory cells that were confined to lymph vascular spaces or within the vicinity of tumor necrosis or secretions were excluded from the analysis. Cases with tumor-infiltrating inflammatory cells present in 10 non-overlapping high-power fields ($\times 40$) were examined in representative areas on two slides of a given tumor (*i.e.*, a total of 20 fields per neoplasm). The number of tumor-related inflammatory cells was assessed in a semiquantitative manner using the mean value of high-power fields based on a $\times 40$ objective (magnification $\times 400$)^[14,15]. The TA-NLR was calculated

as the average number of neutrophils (CD15-positive cells) divided by the average number of T lymphocytes (CD8-positive cells). A receiver operating characteristic (ROC) curve analysis was performed in relation to the occurrence of recurrence and death from any cause. For all 142 patients, a TA-NLR of 0.21 had the highest sensitivity and specificity for both outcomes. Therefore, patients were categorized into the following two groups: low TA-NLR group (≤ 0.21 , 71 patients) and high TA-NLR group (> 0.21 , 71 patients).

Postoperative follow-up

The patients were monitored after surgery *via* telephone interviews, outpatient visits, and letters. Our department follows a standardized surveillance protocol and follows patients at three-month intervals for the first two years, six-month intervals for years two to five, and at least once per year five years after surgery. The postoperative follow-up data included clinical symptoms and signs, laboratory tests, imaging examinations, and endoscopy and biopsy results. In this study, the median follow-up time was 40 mo (range, 2-106 mo). The overall survival (OS) time was calculated as the number of months from the date of surgery to the date of last contact, date of death from any cause, or the date the end point was realized. The recurrence-free survival (RFS) time was calculated as the number of months from the date of surgery to the date of identification of disease recurrence (either radiological or histological), the date of death or last contact, or the date the end point was realized.

Statistical analysis

All enumeration and measurement data were analyzed using SPSS 17.0 for Windows (SPSS, Chicago, IL, United States). χ^2 test, Fisher's exact test, or unpaired Student's *t* test was utilized to compare the differences between the TA-NLR groups and the clinicopathological factors, as appropriate. A univariate survival analysis was performed using the Kaplan-Meier method. A

Table 1 Characteristics of the 142 patients with gastric neuroendocrine neoplasms with different tumor-associated neutrophil-to-lymphocyte ratios

Clinicopathological feature	TA-NLR		Univariate analysis	Multivariate analysis
	≤ 0.21 (n = 71)	> 0.21 (n = 71)	P value	P value
Age (yr)			0.322	
≤ 70	57	52		
> 70	14	19		
Gender			0.851	
Male	52	51		
Female	19	20		
Tumor site			0.099	
Upper	39	26		
Middle	10	15		
Lower	17	18		
Mixed	5	12		
Tumor size (cm)			0.593	
≤ 3.5	25	22		
> 3.5	46	49		
Ki-67 index (%)			0.081	
≤ 2	13	6		
≥ 3, ≤ 20	8	16		
>20	50	49		
Depth of invasion			0.044	0.406
T1	14	8		
T2	7	3		
T3	34	29		
T4	16	31		
Lymph node ratio			0.043	0.355
0	25	13		
> 0, ≤ 0.2	25	24		
> 0.2, ≤ 0.4	15	18		
> 0.4	6	16		
Lymphovascular invasion			0.610	
No	43	40		
Yes	28	31		
ASA status			0.805	
1 + 2	61	62		
3 + 4	10	9		
Postoperative complication			0.041	0.071
No	57	46		
Yes	14	25		
Surgical approach			0.855	
Endo/laparoscopic	49	50		
Open	22	21		

TA-NLR: Tumor-associated neutrophil-to-lymphocyte ratio.

multivariate survival analysis was performed using a Cox proportional hazards model, and the significant variables from the univariate analysis were included in the model. R software (version 3.2.0) was utilized to develop the nomograms and the forest plot. $P < 0.05$ was considered significant.

RESULTS

TA-NLR is not associated with clinicopathological factors

The univariate analysis revealed that the TA-NLR was associated with the invasion depth, LNR (lymph node ratio), and postoperative complications ($P < 0.05$ for all; [Table 1](#)). However, the multivariate analysis revealed no significant differences in the

clinicopathological factors between the two groups ($P > 0.05$ for all; [Table 1](#)). In addition, no significant differences were observed in the clinical symptoms, medical history, family history, active and past smoking histories, or history of heavy alcohol use between the two groups ($P > 0.05$ for all; [Table 2](#)).

Elevated TA-NLR is associated with a poor prognosis

As shown in [Figure 2](#), the RFS and OS were analyzed according to age, gender, tumor site and size, lymphovascular invasion, ASA status, postoperative complications, surgical approach, invasion depth, LNR, and Ki-67 index. The hazard ratios and 95% confidence interval (CI) for the RFS and OS were compared between the subgroups. The long-term survival time, including RFS and OS, was shorter in

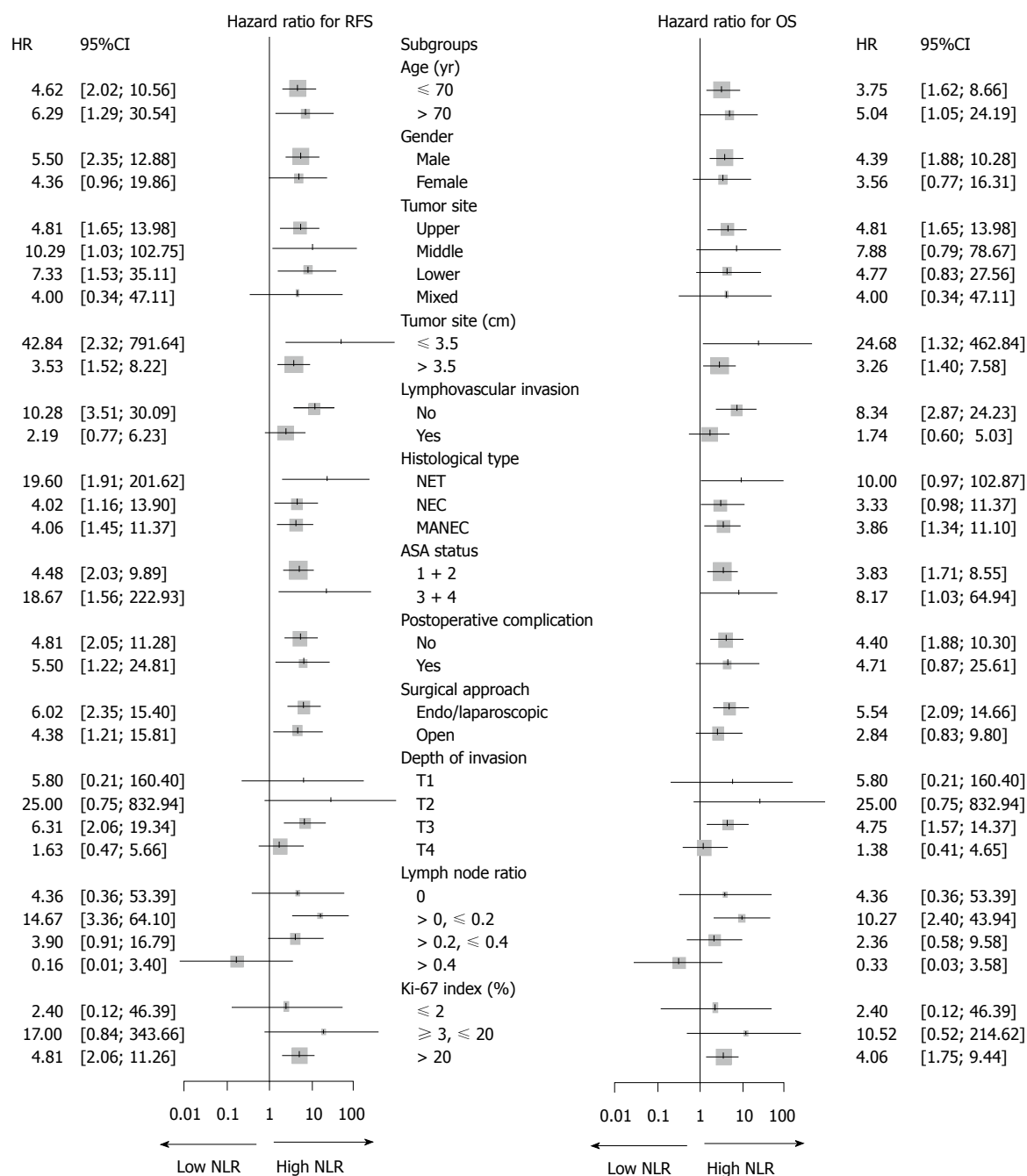


Figure 2 Forest plot showing the hazard ratios (oblongs) and 95% CIs (bars) for RFS (left) and OS (right) (according to subgroups) among 142 patients with gastric neuroendocrine neoplasms undergoing radical surgery. Long-term survival, including RFS and OS, was better among patients with a low TA-NLR than in patients with a high TA-NLR. g-NENs: Gastric neuroendocrine neoplasms. RFS: Recurrence-free survival; OS: Overall survival; TA-NLR: Tumor-associated neutrophil-to-lymphocyte ratio.

the high TA-NLR group compared with the low TA-NLR group.

TA-NLR is an independent prognostic factor for RFS and OS

The univariate analysis found that larger tumor size, occurrence of postoperative complications, greater invasion depth, higher LNR, higher Ki-67 index, and higher TA-NLR were prognostic indicators of poorer RFS ($P < 0.05$ for all; Table 3). The tumor size, invasion depth, LNR, Ki-67 index, and TA-NLR were

identified as prognostic indicators of OS ($P < 0.05$ for all; Table 4). According to the multivariate analysis, the Ki-67 index, LNR, and TA-NLR were independent prognostic factors of RFS and OS ($P < 0.05$ for all; Tables 3 and 4).

TA-NLR is significantly correlated with recurrence site

The TA-NLR was significantly higher in the recurrence group than in the non-recurrence group ($P < 0.05$ for both; Figure 1B). Details regarding the recurrence site following surgery are listed in Table 5. The recurrence

Table 2 Characteristics of 142 patients with gastric neuroendocrine neoplasms with different levels of tumor-associated neutrophil-to-lymphocyte ratios

Patient feature	TA-NLR		Univariate analysis <i>P</i> value
	≤ 0.21 (<i>n</i> = 71)	> 0.21 (<i>n</i> = 71)	
Symptom			
Abdominal pain	46	41	0.390
Dysphagia	14	12	0.665
Nausea	12	9	0.480
Vomiting	5	5	1.000
Acid-reflux	9	4	0.156
Anemia	10	13	0.495
Abdominal distention	6	8	0.575
Gastrointestinal blood loss	12	14	0.665
Weight loss	24	29	0.386
No symptoms	2	7	0.105
Medical history			
Hypertension	19	15	0.432
Diabetes	7	3	0.202
Coronary heart disease	4	4	1.000
Chronic gastritis	44	38	0.796
Family history	5	6	0.754
Smoking	26	27	0.862
Drinking	6	4	0.515

TA-NLR: Tumor-associated neutrophil-to-lymphocyte ratio.

rate was significantly higher in the high TA-NLR group compared with the low TA-NLR group ($P < 0.001$). Additionally, an elevated TA-NLR was significantly associated with both liver metastasis and lymph node metastasis ($P < 0.05$ for both).

TA-NLR, combined with the Ki-67 index and LNR, is a superior prognostic prediction system

Prognostic nomograms were established using R software (Figure 3). The C-index of the nomograms for RFS (OS), which included the TA-NLR, LNR, and Ki-67 index, was 0.788 (0.759). However, the C-index of the TNM staging system for RFS (OS) was 0.673 (0.662) (Figure 4). Thus, both the TNM staging system and the nomograms had superior abilities to predict clinical outcomes for patients with g-NENs.

DISCUSSION

Neuroendocrine neoplasms, particularly g-NENs in the digestive system, are a unique subgroup of tumors with great clinical heterogeneity and varied biology. In recent years, with the growing popularity of upper gastrointestinal endoscopy and increasing improvements in diagnostic techniques, the reported incidence of g-NENs has increased each year, and currently, the incidence is approximately 0.3 per 100 thousand^[16,17]. According to previous studies, a patient's prognosis is significantly associated with the clinical and pathological parameters as well as the biological characteristics of g-NENs^[18-20]. However, the independent prognostic factors for g-NEN patients are still controversial. To our knowledge, studies have

reported individual prediction models for the prognosis of g-NENs. We evaluated the prognostic value of TA-NLR in patients with g-NENs and further established a tumor prognosis prediction model to provide a basis for individual clinical therapy.

In most cases, the clinical symptoms of g-NENs are not typical because they depend on the location and invasiveness of the primary tumor or metastases. The symptoms mainly include abdominal pain, abdominal distension, difficulty swallowing, nausea, and vomiting. In this study, abdominal pain was the most common symptom, followed by weight loss, difficulty swallowing, and gastrointestinal bleeding; this finding is consistent with previous reports^[21]. In addition, approximately 6% of the patients without any clinical symptoms were diagnosed *via* physical examinations. Among asymptomatic patients, approximately 40% were diagnosed with g-NEC or g-MANEC, although most of them were diagnosed with g-NETs. Therefore, postoperative follow-up is still essential for patients who have no clinical symptoms.

In recent years, substantial evidence has revealed that pathological stage is closely related to the prognosis of patients with g-NENs. Deep tumor invasion, lymph node metastasis, and distant metastasis were associated with decreased long-term survival^[8,9,22]. The Ki-67 index, as a marker of cell proliferation, is widely used to evaluate the malignant potential of neuroendocrine tumors. The European Neuroendocrine Tumor Society (ENETS) and the WHO adopted a three-tier classification system based on the Ki-67 index for gastrointestinal pancreatic neuroendocrine tumors (G1: ≤ 2%; G2: 3%-20%; G3: > 20%). The Ki-67 index combined with a pathological staging system improves the diagnosis and prognosis prediction of patients with neuroendocrine tumors, and it is thus widely used in clinical practice. In this study, the rate of lymph node metastasis and the Ki-67 index were independent risk factors for OS and RFS in patients with g-NENs. In addition, increasing evidence has confirmed that the tumor-associated inflammatory response is closely related to the prognosis of patients with malignant tumors^[12,23,24]. However, the relationship between the tumor-associated inflammatory response and g-NENs is unclear. Our study is the first to confirm that the TA-NLR is significantly associated with the prognosis of patients with g-NENs. We observed, through a univariate analysis, that the RFS and OS rates in patients with a TA-NLR > 0.21 were significantly lower than the rates in patients with a TA-NLR < 0.21. The multivariate analysis further revealed that the TA-NLR was an independent risk factor for patients with g-NENs.

Postoperative local recurrence and distant metastasis are the leading causes of death for patients with malignant tumors. Liver metastasis, peritoneal metastasis, and lymph node metastasis were the

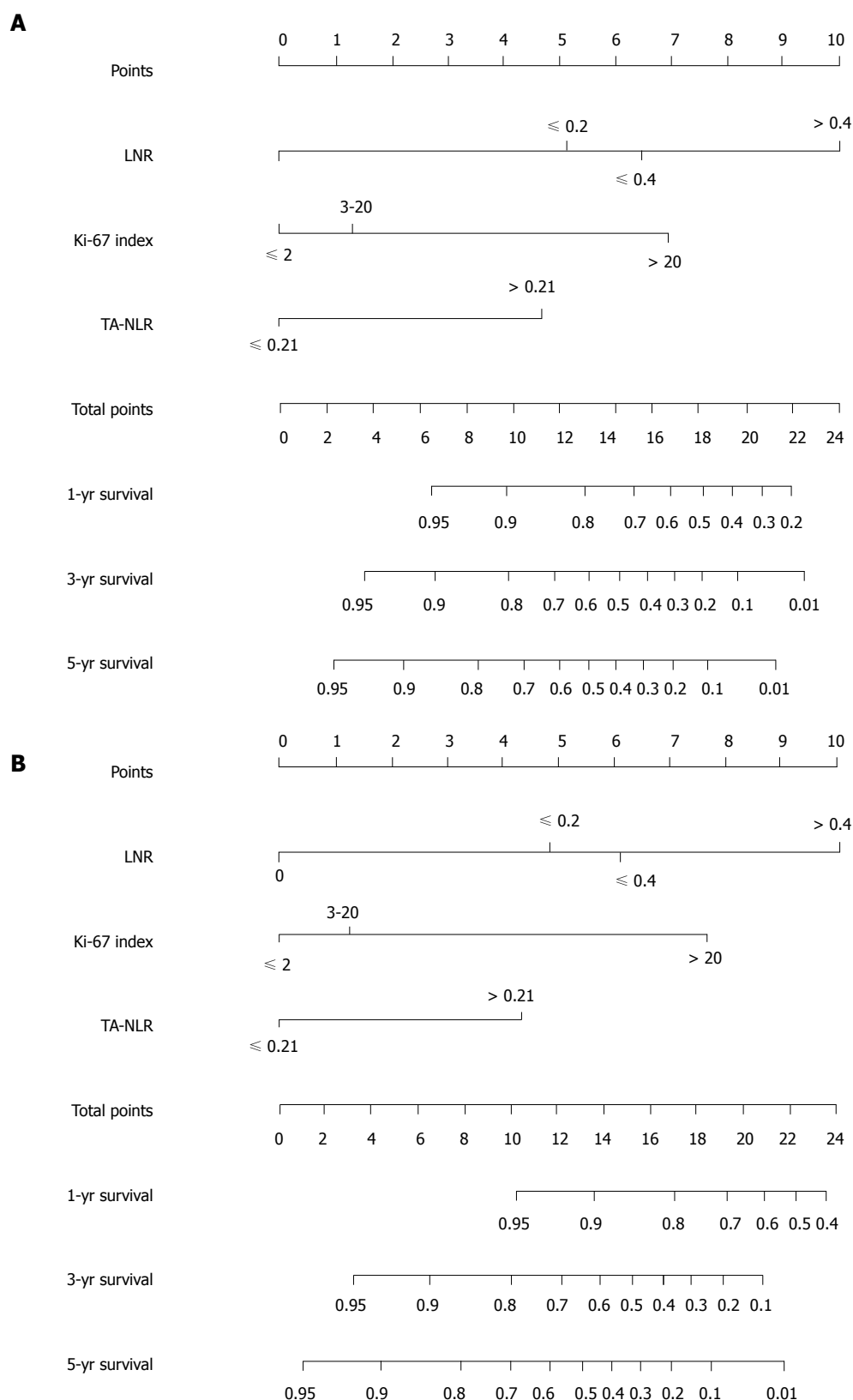


Figure 3 Nomograms for the prediction of recurrence-free survival (A) and overall survival (B) in patients following gastric neuroendocrine neoplasm resection; the C-index was 0.788 and 0.759 for RFS and OS, respectively. LNR: Lymph node ratio; TA-NLR: Tumor-associated neutrophil-to-lymphocyte ratio.

main types of tumor recurrence. The proportions of patients with these types of recurrence were 72%, 28%, and 25%, respectively. The spleen, kidney, and

brain were relatively rare sites of recurrence. Our results are similar to those of previous reports^[9]. In the present study, the TA-NLR was closely related to tumor

Table 3 Variables associated with recurrence-free survival according to the Cox proportional hazards regression model

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	P value	Hazard ratio	95%CI	P value
Age (yr)			0.790			
≤ 70	Reference					
> 70	1.083	0.602-1.950				
Gender			0.126			
Male	Reference					
Female	0.608	0.322-1.149				
Tumor site			0.770			
Upper	Reference					
Middle	0.825	0.389-1.751				
Lower	0.885	0.465-1.682				
Mixed	1.348	0.588-3.091				
Tumor size (cm)			0.004			0.671
≤ 3.5	Reference			Reference		
> 3.5	2.740	1.385-5.421		NA	NA	
Lymphovascular invasion			0.144			
No	Reference					
Yes	1.471	0.876-2.468				
ASA status			0.190			
1 + 2	Reference					
3 + 4	1.551	0.804-2.993				
Postoperative complication			0.029			
No	Reference			Reference		0.305
Yes	1.869	1.065-3.278		NA	NA	
Surgical approach			0.249			
Endo/laparoscopic	Reference					
Open	0.733	0.432-1.243				
Depth of invasion			0.005			0.557
T1	Reference			Reference		
T2	5.328	0.483-58.789		NA	NA	
T3	11.722	1.587-86.603		NA	NA	
T4	19.301	2.629-141.682		NA	NA	
Lymph node ratio			< 0.001			< 0.001
0	Reference			Reference		
> 0, ≤ 0.2	5.490	1.623-18.568		3.338	0.962-11.581	
> 0.2, ≤ 0.4	8.091	2.393-27.351		4.6	1.317-16.066	
> 0.4	17.946	5.239-61.480		10.266	2.906-36.266	
Ki-67 index (%)			0.004			< 0.001
≤ 2	Reference			Reference		
≥ 3, ≤ 20	3.013	0.639-14.203		1.501	0.305-7.393	
> 20	7.047	1.709-29.053		4.999	1.140-21.927	
TA-NLR			< 0.001			< 0.001
≤ 0.21	Reference			Reference		
> 0.21	3.366	1.890-5.992		2.974	1.630-5.426	

TA-NLR: Tumor-associated neutrophil-to-lymphocyte ratio.

recurrence, and a high incidence of liver metastasis and lymph node metastasis was observed in patients with a high TA-NLR. Thus, during the postoperative follow-up period, clinicians should utilize the prognostic value of the TA-NLR, as well as clinical characteristics, to discover potential hepatic or lymph node metastases at an earlier time point.

Nomograms, as a new type of statistical prediction model, are currently widely used in clinical practice for the majority of cancer types^[25,26]. Prognostic nomograms enable the use of a combination of multiple relevant clinical predictors and can be utilized to predict RFS and OS for individual patients. For many cancers, nomograms compare favorably to the traditional TNM staging system and have been

proposed as an important tool in clinical practice^[13,27]. In this study, we established prognostic nomograms for g-NENs by combining the TA-NLR, Ki-67 index, and LNR. This combination had a high predictive ability, as did the traditional TNM staging system. Therefore, the combination of the TA-NLR, Ki-67 index, and LNR, as a novel prognostic system, may provide simple, more accurate prognostic predictions.

This study had some limitations. The study was uncontrolled and performed in a single institution. The results should be confirmed by subsequent prospective studies. Some heterogeneity was also present in this study, as it included multiple histological types (including NET, NEC, and MANEC), which do not represent a specific progression of a unique

Table 4 Variables associated with overall survival according to the Cox proportional hazards regression model

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	P value	Hazard ratio	95%CI	P value
Age (yr)			0.566			
≤ 70	Reference					
> 70	1.197	0.648-2.211				
Gender			0.190			
Male	Reference					
Female	0.640	0.329-1.247				
Tumor site			0.190			
Upper	Reference					
Middle	0.687	0.313-1.509				
Lower	0.540	0.255-1.145				
Mixed	1.441	0.628-3.307				
Tumor size (cm)			0.002			0.214
≤ 3.5	Reference			Reference		
> 3.5	3.591	1.618-7.969		NA	NA	
Lymphovascular invasion			0.214			
No	Reference					
Yes	1.417	0.818-2.455				
ASA status			0.118			
1 + 2	Reference					
3 + 4	1.736	0.870-3.465				
Postoperative complication			0.320			
No	Reference					
Yes	1.380	0.732-2.603				
Surgical approach			0.276			
Endo/laparoscopic	Reference					
Open	0.736	0.425-1.276				
Depth of invasion			0.024			0.646
T1	Reference			Reference		
T2	5.524	0.501-60.954		NA	NA	
T3	10.793	1.455-80.038		NA	NA	
T4	15.632	2.116-115.464		NA	NA	
Lymph node ratio			< 0.001			0.002
0	Reference			Reference		
> 0, ≤ 0.2	4.791	1.402-16.370		2.854	0.813-10.027	
> 0.2, ≤ 0.4	6.676	1.956-22.790		3.724	1.054-13.162	
> 0.4	14.677	4.218-51.074		9.152	2.528-33.129	
Ki-67 index (%)			0.002			< 0.001
≤ 2%	Reference			Reference		
≥ 3%, ≤ 20%	2.168	0.437-10.751		1.584	0.313-8.008	
> 20%	6.582	1.589-27.269		5.535	1.238-24.752	
TA-NLR			< 0.001			0.003
≤ 0.21	Reference			Reference		
> 0.21	2.938	1.610-5.360		2.617	1.389-4.928	

TA-NLR: Tumor-associated neutrophil-to-lymphocyte ratio.

pathologic process. Due to the low incidence of g-NENs and the limited number of samples in the study, a statistical analysis could not be conducted for any one histological type. We will focus on each of the three histological types in the future, after more cases have been accumulated. However, to our knowledge, our study enrolled more patients with g-NENs than similar reports in the literature, and for the first time, we demonstrated that the TA-NLR was able to predict long-term survival relatively accurately in patients. Our study could be the basis for a subsequent prospective clinical study.

As a simple and inexpensive inflammatory biomarker, the TA-NLR is significantly correlated with tumor recurrence, especially with liver and lymph node

metastasis. The TA-NLR is an independent predictor of RFS and OS, and its combination with the Ki-67 index and LNR could improve prognosis prediction in g-NEN patients undergoing radical surgery, as could the traditional TNM staging system.

COMMENTS

Background

The incidence of gastric neuroendocrine neoplasms (g-NENs), which account for 6% of all neuroendocrine neoplasms, is increasing every year. In addition to an early diagnosis, an important and effective component of proper management is the identification of the prognostic factors in patients with g-NENs. However, the prognostic factors for these tumors are complex and multifaceted and have not been clearly defined thus far. Few studies to date have focused on the relationship between the tumor-associated neutrophil-to-

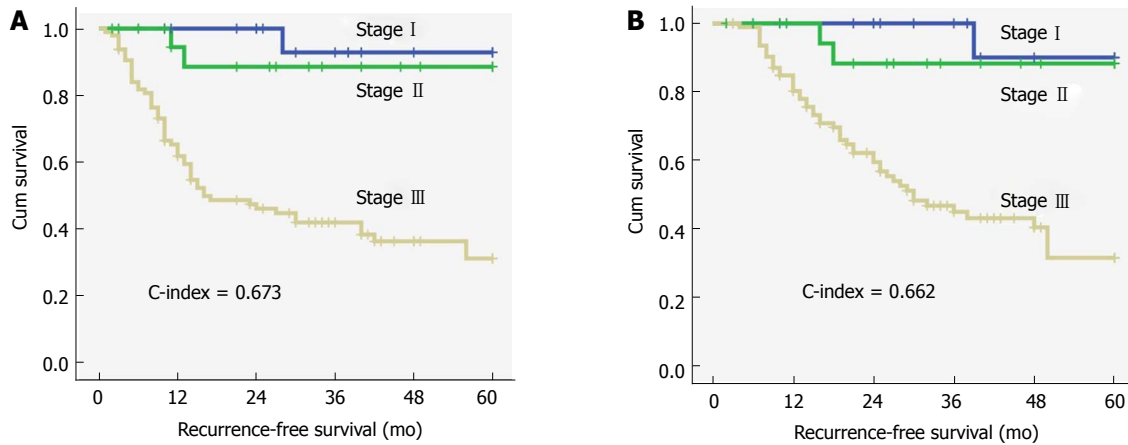


Figure 4 Survival curves for recurrence-free survival (A) and overall survival (B) according to the traditional TNM staging system (NCCN 2015); the C-index was 0.673 and 0.662 for RFS and OS, respectively.

Table 5 Site of recurrence after surgery

Site of recurrence	TA-NLR		P value
	≤ 0.21 (n = 71)	> 0.21 (n = 71)	
Liver	10	28	0.001
Peritoneal cavity	6	9	0.413
Lymph node	2	11	0.009
Lung	3	4	0.721
Bone	0	5	0.058
Adrenal gland	1	4	0.366
Pancreas	2	2	1.000
Locoregional recurrence	2	3	0.683
Spleen	0	2	0.496
Kidney	1	1	1.000
Brain	0	1	1.000
Number of patients with recurrence	15	38	< 0.001

TA-NLR: Tumor-associated neutrophil-to-lymphocyte ratio.

lymphocyte ratio (TA-NLR) and the prognosis of patients with g-NENs.

Research frontiers

In the past decade, increasing evidence has suggested that both tumor-associated neutrophils (TANs) and tumor-associated lymphocytes (TALs) are significantly associated with patient prognosis. Elevated TANs and reduced TALs correlate with advanced stage and poor prognosis in a variety of human tumors, including cervical cancer, hepatocellular carcinoma, and pancreatic cancer.

Innovations and breakthroughs

This study enrolled more patients with g-NENs than similar reports in the literature and, for the first time, demonstrated that the TA-NLR was able to predict long-term survival relatively accurately in patients.

Applications

This study established a novel prognostic system that included the TA-NLR, Ki-67 index, and lymph node ratio, which may provide simple, more accurate prognostic predictions. Moreover, as a simple and inexpensive inflammatory biomarker, the TA-NLR is significantly correlated with tumor recurrence, especially with liver and lymph node metastasis. Thus, during the postoperative follow-up period, clinicians should utilize the prognostic value of the TA-NLR, as well as clinical characteristics, to discover potential hepatic or lymph node metastases at an earlier time point.

Terminology

Gastric neuroendocrine neoplasms (g-NENs), a highly heterogeneous and poorly understood group of relatively rare tumors, are derived primarily from enterochromaffin-like cells (ECL-cells) localized in the gastric mucosa. The World Health Organization (WHO, 2010) classifies g-NENs into the following subclasses: neuroendocrine tumors (g-NETs), neuroendocrine carcinoma (g-NEC), and mixed adenoneuroendocrine carcinoma (g-MANEC).

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Previous studies have established that elevated TANs and reduced TALs correlate with advanced stage and poor prognosis in a variety of human tumors, including cervical cancer, hepatocellular carcinoma, and pancreatic cancer. In this study, the authors demonstrated that the TA-NLR is an independent predictor of RFS and OS and that it is also significantly correlated with tumor recurrence, especially with liver and lymph node metastasis. However, as the authors indicate, this study was uncontrolled and was performed within a single institution. The results should therefore be confirmed in subsequent prospective studies.

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