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ORIGINAL ARTICLE

Retrospective Study

Significance of the preoperative neutrophil-to-lymphocyte ratio in the prognosis of patients with gastric cancer

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Abstract

AIM: To investigate the significance of the preoperative neutrophil-to-lymphocyte ratio (NLR) in the prognosis of patients with gastric cancer (GC).

METHODS: The clinical data of 291 GC patients were analysed retrospectively; these patients were divided into two groups according to their preoperative NLR: a high-NLR group (NLR $\geqslant$ 3.5, 131 cases) and a low-NLR group (NLR < 3.5, 160 cases). The clinicopathological characteristics and five-year survival rates of the two groups were compared. The NLR and other clinicopathological factors were subjected to univariate and multivariate survival analysis to evaluate the effects of the NLR on the prognosis of GC patients.

RESULTS: The lowest preoperative NLR among the 291 patients was 0.56, whereas the highest preoperative NLR was 74.5. The mean preoperative NLR was 5.99 ± 8.98. Age, tumour size, T staging, tumour-node-metastasis (TNM) staging and platelet count were significantly different between the high- and low-NLR groups (P < 0.05). The five-year survival rate of the high-NLR group was 17.0%, which was significantly lower than that of the low-NLR group (43.6%; 17.0% *vs* 43.6%, P < 0.05). The univariate analysis results showed that the five-year survival rate was related to age, tumour size, T staging, N staging, TNM staging, carcinoembryonic antigen value and NLR (P < 0.05). Multivariate analysis results showed that the NLR was an independent risk factor that likely affected the five-year survival rate of GC patients (P = 0.003, HR = 0.626, 95%CI: 0.460-0.852).

CONCLUSION: The preoperative NLR could be used as a prognostic factor for GC patients; in particular, a high NLR corresponded to poor prognosis of GC patients.

Key words: Gastric cancer; Neutrophil-to-lymphocyte ratio; Prognosis; Inflammation; Survival rate

Core tip: This research preliminarily investigated the relationship between the preoperative neutrophil-to-lymphocyte ratio (NLR) and gastric cancer. The results revealed that a high NLR corresponded to poor prognosis of gastric cancer patients. Furthermore, preoperative NLR could be used as a prognostic factor for these patients.

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INTRODUCTION

Gastric cancer (GC) is one of the most common types of gastrointestinal cancer; the mortality of GC ranks second among all malignancies[1]. Although the incidence of GC declined in recent years, prognosis has not greatly improved, and the five-year accumulative survival rate remains at approximately 25%[2]. GC is mainly treated by radical surgery; thus, factors associated with the prognosis of GC should be determined to effectively assist intervention therapy and to improve patient outcomes. The body's inflammatory response plays an important role in tumour occurrence and development[3]. Inflammatory responses can inhibit apoptosis, promote angiogenesis and damage DNA, thereby promoting tumour growth and proliferation[4,5]. In cancer patients who are in the aggressive phase, inflammatory response indicators, such as C-reactive protein levels and platelet count, are usually higher and are related to poor prognosis[6,7]. Similarly, the body's inflammatory response can cause changes in the peripheral white blood cell count, which is reflected as an increased neutrophil count and reduced lymphocyte count[8]. Therefore, NLR could be used as a good indicator of the systemic inflammatory state of cancer patients. NLR is closely related to the prognosis of various malignant tumours, such as liver cancer, colorectal cancer, breast cancer, bladder cancer and non-small cell lung cancer[9-14]. However, few studies have investigated the relationships of NLR and prognosis of GC patients[15-17]. This study aimed to investigate the effects of preoperative NLR in the prognosis of GC patients; our study also provided a reference for diagnostic and treatment strategies for GC.

MATERIALS AND METHODS

General information

A total of 291 GC cases treated and subjected to radical surgery in the Department of General Surgery, Nanjing First Hospital, China, from January 2005 to December 2009 were selected. These patients were not subjected to preoperative chemotherapy and were not affected by infectious diseases. The intraoperative situation confirmed that no distant metastasis was present. The patients' clinical and pathological data were collected (Table 1). Postoperative regular telephone or outpatient follow up was performed for six months to five years; the follow-up rate was 91.1%. The clinicopathological staging of this research was in accordance with the criteria of American Joint Committee on Cancer Staging (7th edition)[18].

Blood sampling

Neutrophil, lymphocyte and platelet counts and carcinoembryonic antigen (CEA) values of the patients were collected one week before these patients underwent surgery. NLR was then calculated, and 3.5 was set as a critical value. The patients were then divided into two groups: high-NLR group (NLR $\geqslant$ 3.5) with 131 cases and low-NLR group (NLR < 3.5) with 160 cases.

Statistical analysis

Data were statistically analysed using SPSS 20.0 statistical software. Counted data were subjected to a χ^2 test. Variables likely to affect NLR were evaluated by logistic regression. The survival rate was calculated according to the Kaplan-Meier method. Survival rates were then compared by performing log-rank tests. Univariate and multivariate survival analyses were also conducted using a Cox proportional hazards model, in which $P < 0.05$ was considered statistically significant.

RESULTS

Relationships of preoperative NLR and other clinicopathological factors

The lowest preoperative NLR of the 291 patients was 0.56, whereas the highest NLR was 74.5. The mean NLR was 5.99 ± 8.98. The distributions of NLR were listed as follows: NLR < 1.5, 35 cases; 1.5 $\leqslant$ NLR < 2.5, 27 cases; 2.5 $\leqslant$ NLR < 3.5, 53 cases; 3.5 $\leqslant$ NLR < 4.5, 42 cases; 4.5 $\leqslant$ NLR < 5.5, 15 cases; and NLR $\geqslant$ 5.5, 74 cases. The compared *P* values among different survival-rate groups were as follows (Figure 1A): $P = 0.953$ (NLR < 1.5 and 1.5 $\leqslant$ NLR < 2.5); $P = 0.066$ (1.5 $\leqslant$ NLR < 2.5 and 2.5 $\leqslant$ NLR < 3.5); $P = 0.010$ (2.5 $\leqslant$ NLR < 3.5 and 3.5 $\leqslant$ NLR < 4.5); $P = 0.703$ (3.5 $\leqslant$ NLR < 4.5 and 4.5 $\leqslant$ NLR < 5.5); and $P = 0.852$ (4.5 $\leqslant$ NLR < 5.5 and NLR $\geqslant$ 5.5). On the basis of these results ($P = 0.010$; 2.5 $\leqslant$ NLR < 3.5 and 3.5 $\leqslant$ NLR < 4.5), we selected NLR = 3.5 as the threshold. The patients were then divided into a high-NLR group (NLR $\geqslant$ 3.5) and a low-NLR group (NLR < 3.5).

Age, tumour size, T staging, tumour-node-metastasis (TNM) staging and platelet count significantly differed between high- and low-NLR groups ($P < 0.05$).

Table 1 Comparison of clinicopathological characteristics between high- and low-neutrophil-to-lymphocyte groups *n* (%)

Clinicopathological feature	*n*	High-NLR group	Low-NLR group	χ^2	*P* value
Gender				0.163	0.686
Male	210	93 (44.3)	117 (55.7)		
Female	81	38 (46.9)	43 (53.1)		
Age				12.377	0.000
< 65 yr	142	49 (34.5)	93 (65.5)		
⩾ 65 yr	149	82 (55.0)	67 (45.0)		
Tumor size				20.852	0.000
< 5 cm	143	45 (31.5)	98 (68.5)		
⩾ 5 cm	148	86 (58.1)	62 (41.9)		
Differentiation degree					
Middle and high differentiation	130	59 (45.4)	71 (54.6)	0.013	0.910
Low differentiation	161	72 (44.7)	89 (55.3)		
T staging					
T1	20	2 (10.0)	18 (90.0)	20.731	0.000
T2	29	13 (41.4)	16 (58.6)		
T3	177	74 (41.8)	103 (58.2)		
T4	65	42 (64.6)	23 (35.4)		
N staging				4.185	0.242
N0	55	18 (32.7)	37 (67.3)		
N1	127	60 (47.2)	67 (52.8)		
N2	78	38 (48.7)	40 (51.3)		
N3	31	15 (48.4)	16 (51.6)		
TNM staging				11.363	0.003
Stage Ⅰ	32	8 (25.0)	24 (75.0)		
Stage Ⅱ	123	49 (39.8)	74 (60.2)		
Stage Ⅲ	136	74 (54.4)	62 (45.6)		
platelet counting				9.672	0.002
< 300×10^9/L	253	105 (41.5)	148 (58.5)		
⩾ 300×10^9/L	38	26 (68.4)	12 (31.6)		
CEA				2.972	0.085
< 5 ng/mL	178	73 (41.0)	105 (59.0)		
⩾ 5 ng/mL	113	58 (51.3)	55 (48.7)		

NLR: Neutrophil-to-lymphocyte ratio; CEA: Carcinoembryonic antigen.

By contrast, gender, differentiation degree, N staging and CEA values were not significantly different ($P > 0.05$). As the tumour invasion depth increased and clinicopathological staging progressed, the proportion of patients with high NLR correspondingly increased. The patients in the high-NLR group were older and exhibited larger tumours and high platelet counts (Table 1).

Logistic regression analysis was performed to evaluate the clinicopathological factors that likely caused the increased NLR. The results showed that age and tumour size were independent risk factors that possibly increased the NLR ($P < 0.05$; Table 2).

Effects of NLR on the prognosis of GC patients

The five-year survival rate of the high-NLR group was 17.0%, which was significantly lower than that of the low-NLR group (43.6%; $\chi^2 = 32.818$, $P < 0.001$, Figure 1B). The univariate analysis results showed that the five-year survival rate was related to age, tumour size, T staging, N staging, TNM staging, CEA value and NLR ($P < 0.001$). These parameters were then subjected to multivariate analysis. The results showed that TNM staging and NLR were independent prognostic factors for the five-year survival rate of patients ($P < 0.05$; Table 3).

Our data were subjected to further stratification analysis. Our results showed that the five-year survival rates of high- and low-NLR groups of stage Ⅰ patients were not significantly different ($\chi^2 = 0.732$, $P = 0.392$; Figure 1C). By contrast, the five-year survival rate of the high-NLR group of stage Ⅱ and stage Ⅲ patients was significantly lower than that of the low-NLR group ($\chi^2 = 12.299$, $P < 0.001$; $\chi^2 = 7.507$, $P = 0.006$; Figure 1D and E).

DISCUSSION

Abnormal phenotypes of malignant cancer cells likely stimulate the accumulation of inflammatory cells and destroy the tumour-surrounding tissues, thereby causing a series of non-specific inflammatory responses. As a tumour grows, these inflammatory responses likely increase the peripheral blood neutrophil count and decrease the lymphocyte count; as a result, NLR increases. This result is consistent with those of previous studies[15,16,19]. Our study further found that the proportion of patients in the high-NLR group increased as the tumour invasion depth increased and the disease progressed; this finding is

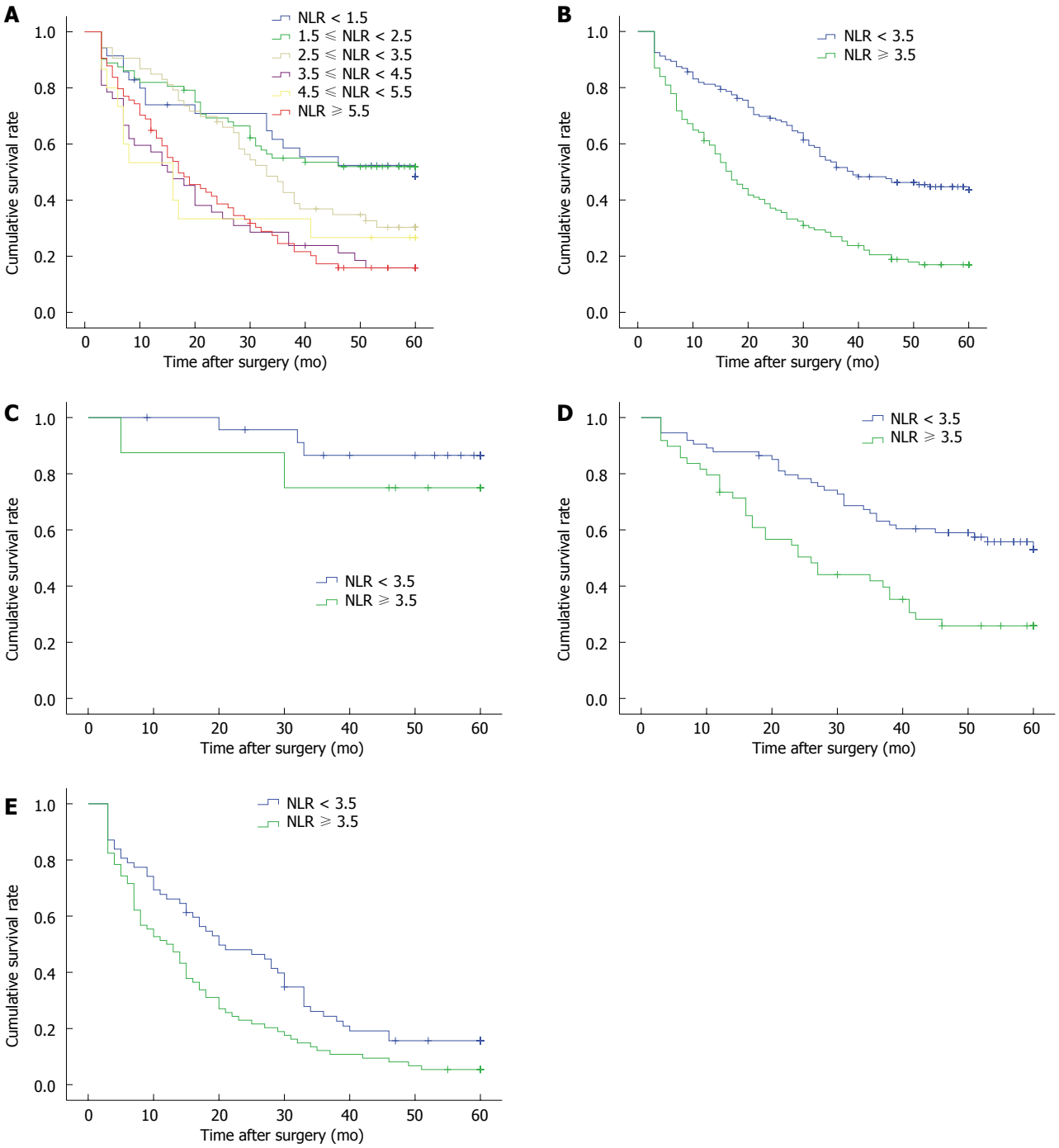

Figure 1 Five-year survival curves. A: All patients; B: High- and low-neutrophil-to-lymphocyte ratio groups; C: Stage Ⅰ patients; D: Stage Ⅱ patients; E: Stage Ⅲ patients. NLR: Neutrophil-to-lymphocyte ratio.

also consistent with those in previous studies. Shimada *et al*[15] performed a logistical regression analysis of clinicopathological factors that likely influence the increase in NLR and found that old age and high blood platelet count are independent risk factors of high NLR; the data of the present study showed that age and tumour size were independent risk factors that likely affected the increase in NLR.

High NLR is related to poor prognosis of patients with various malignant tumours[9,10,12,14]. Hirashima *et al*[17] revealed that NLR is related to the prognosis of patients with GC in the early stage; however, they did not further analyse whether NLR is an independent factor affecting the prognosis of GC patients. Jung *et al*[16] investigated patients with stage Ⅲ and Ⅳ GC and found that the overall survival rate of the high-NLR group (⩾ 2.0) was significantly lower than that of the low-NLR group. Indeed, NLR is an independent factor affecting patient's overall survival rate. Shimada *et al*[15] studied 1028 GC cases subjected to radical

Table 2 Multivariate analysis of neutrophil-to-lymphocyte ratio-associated risk factors

Clinicopathological feature	HR	95%CI	*P* value
Gender (M/F)	1.219	0.693-2.146	0.492
Age (yr)	1.036	1.014-1.059	0.002
Tumor size	2.690	1.584-4.565	0.000
Differentiation degree	0.966	0.575-1.622	0.895
T staging	1.269	0.705-2.287	0.427
N staging	0.743	0.453-1.219	0.239
TNM staging	1.732	0.680-4.409	0.249
Platelet counting	0.999	0.996-1.002	0.395
CEA	1.001	0.998-1.003	0.630

M/F: Male/female; CEA: Carcinoembryonic antigen; HR: Hazard ratio.

surgery and found that the five-year survival rate of patients with high NLR (≥ 4.0) was significantly lower than that of patients with low NLR. Similarly, Shimada *et al*[15] found that NLR is an independent factor affecting patient's five-year survival rate. Other scholars[20,21] also investigated patients with advanced GC treated with chemotherapy and found that high NLR is an independent risk factor influencing patient's disease-free survival period and overall survival rate. In our study, the effect on five-year survival rate of the patients with NLR ≥ 3.5 was apparent compared with that of patients with NLR < 3.5 possibly because NLR was related to the development of GC. Multivariate analysis results showed that NLR was an independent factor that likely affected the patient's five-year survival rate. Therefore, high preoperative NLR is an indicator of the poor prognosis of patients with GC.

Several explanations have been provided regarding the relationship of high NLR and poor prognosis. For instance, high NLR corresponds to an enhanced response of neutrophils to tumour inflammation; neutrophils secrete angiogenic factors, such as vascular endothelial growth factor, thereby stimulating angiogenesis and promoting tumour growth and metastasis[22]. Alternatively, peripheral blood lymphocytes are decreased, leading to reduced lymphocyte-mediated anti-tumour immune responses, which would accelerate disease progression. Furthermore, systemic inflammation is closely related to nutritional status and decreased organ function in cancer patients; thus, poor prognosis is observed[23].

High preoperative NLR indicated poor cancer prognosis; this result is very significant for cancer prevention and treatment. Moreover, the effects of anti-inflammatory drugs on tumour occurrence and development have been investigated extensively. For example, the prophylactic application of non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the incidence of colon cancer by 40% to 50%; NSAIDs elicit the same preventive effects on lung cancer, oesophageal cancer and stomach cancer[24,25]. In addition, vaccination has been administered to promote an immune response of lymphocytes against

Table 3 Univariate and multivariate survival analysis results

Clinicopathological feature	Univariate-analyzed *P* value	Multivariate analysis	
		P value	HR (95%CI)
Gender	0.611		
Male			
Female			
Age	0.000	0.096	
< 65 yr			0.774 (0.573-1.046)
≥ 65 yr			1.000
Tumor size	0.000	0.122	
< 5 cm			0.784 (0.576-1.067)
≥ 5 cm			1.000
Differentiation degree	0.108		
Middle and high differentiation			
Low differentiation			
T staging	0.000	0.583	
T1		0.898	0.879 (0.122-6.338)
T2		0.579	0.797 (0.358-1.776)
T3		0.170	0.739 (0.480-1.138)
T4			1.000
N staging	0.000	0.080	
N0		0.303	0.622 (0.252-1.535)
N1		0.910	1.037 (0.556-1.934)
N2		0.091	0.678 (0.433-1.063)
N3			1.000
TNM staging	0.000	0.008	
Stage Ⅰ		0.030	0.134 (0.022-0.822)
Stage Ⅱ		0.004	0.387 (0.204-0.735)
Stage Ⅲ			1.000
Platelet counting	0.382		
< 300 × 10^9/L			
≥ 300 × 10^9/L			
CEA	0.000	0.547	
< 5 ng/mL			0.912 (0.675-1.231)
≥ 5 ng/mL			1.000
NLR	0.000	0.003	
< 3.5			0.626 (0.460-0.852)
≥ 3.5			1.000

NLR: Neutrophil-to-lymphocyte ratio; CEA: Carcinoembryonic antigen; HR: Hazard ratio.

tumours, thereby improving patient prognosis[26]. Indeed, patients with high preoperative NLR should be considered as high-risk patients who should be integrated with multi-mode anti-tumour therapies, such as chemotherapy, radiotherapy and immune therapy.

In summary, preoperative NLR was closely related to the prognosis of GC; in particular, a high NLR was an indicator that could be used to determine the poor prognosis of patients with GC. NLR could be determined using a simple, rapid and cost-effective detection technique; this technique could be applied efficiently to predict the prognosis of GC patients and to provide a reference for the integrated treatment of GC for broad applications.

COMMENTS

Background

Gastric cancer (GC) is one of the most common types of gastrointestinal

cancers; however, the prognosis of GC is poor. The body's inflammatory response plays an important role in tumour development. The neutrophil-to-lymphocyte ratio (NLR), which indicates the systemic inflammatory state of the body, is closely related to the prognosis of GC.

Research frontiers

NLR is closely related to the prognosis of various malignant tumours, such as liver cancer, colorectal cancer, breast cancer, bladder cancer and non-small cell lung cancer. However, few studies have investigated the relationships of NLR and prognosis of GC patients.

Innovations and breakthroughs

This study revealed that NLR was an independent risk factor that likely affected the five-year survival rate of GC patients.

Applications

A high NLR was one indicator that could be used to evaluate the poor prognosis of patients with GC. This finding suggested that NLR might provide a reference of the integrated treatment for patients with GC. NLR could be determined using a simple, rapid and cost-effective technique; thus, this technique could be used to predict the prognosis of patients with GC.

Terminology

The neutrophil-to-lymphocyte ratio, calculated as neutrophil counts divided by lymphocyte counts, is a possible marker of general immune responses to various stress stimuli.

Peer-review

This study investigated the significance of NLR retrospectively in patients who received surgical therapy to treat GC. The results are significant and applicable to clinical practices and studies.

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