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Original Article

Neutrophil-to-lymphocyte ratio predicts the outcome of recurrent gastric cancer

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Abstract: The neutrophil-to-lymphocyte ratio (NLR) was identified to be an independent factor for several solid tumors; however, its role in the recurrent gastric cancer (RGC) remains unclear. The aim of this study was to investigate the prognostic value of NLR in RGC. Total of 62 RGC patients who received surgical treatment from March 2006 to March 2009 was enrolled. The clinical-pathological data and survival time were retrospectively reviewed. The NLR was calculated when the recurrence was confirmed, and the patients were divided into two groups based on the pretreatment NLR. The prognostic significance of NLR for RGC was explored through univariate and multivariate analyses. The pretreatment NLR was elevated (NLR≥4.15) in 38.7% RGC patients (n=24; E-NLR). The elevated NLR was significantly associated with larger tumor size (P=0.021), worse histology (P=0.001) and lymph node metastasis (P=0.001). The median survival time for RGC was significantly worse in the E-NLR group compared to normal NLR group (5.1 months vs. 11.5 months, P=0.002). And the NLR (HR=1.787, P=0.010), histology (HR=1.954, P=0.005) were independent prognostic factors for RGC. In summary, the elevated NLR predicted aggressive pathological character and poor long-term outcome, which might be used as a prognostic marker for RGC patients.

Keywords: Gastric cancer, inflammation, prognosis, neutrophil to lymphocyte ratio

Introduction

Gastric cancer (GC) is one of the most common tumors worldwide, as most of the GC patients were at advanced stage when the diagnosis was confirmed, the mortality of GC remains high [1]. For these GC patients who received radical gastrectomy, more than 60% GC patients would undergo tumor recurrence [2, 3]. In the recent years, many clinical and basic researches have investigated the characteristics, treatment and prognosis of recurrent gastric cancer (RGC) [4-7]. However, the ideal predictive factors were lacking, and the standard treatment for RGC was not established [8, 9]. What's worse, the long-term survival of RGC was not improved in the past years. It is urgent and important to identify the precisely predictive factors and establish the effective treatment for RGC.

The association between inflammation and cancer was identified by many studies, which showed that the inflammation could contribute to cancer progression and metastasis [10]. The role of many nonspecific serum inflammatory markers was studied in solid tumors [10-12]. NLR, one of the inflammatory markers, was found was associated with survival in colorectal cancer, gastric cancer and lung cancer [13-15]. However, there were limited papers showing the predictive value of inflammatory factors for RGC, and the role of NLR in RGC remains unclear.

In the present study, we explored the association between NLR and clinical, pathological characteristics, and investigated its prognostic role through univariable and multivariable Cox regression models in RGC patients.

Patients and methods

Total of 62 RGC patients who underwent surgical treatment from March 2006 to March 2009 were enrolled. The clinical-pathological, surviv-

Table 1. The association between NLR and Clinical-pathological characteristics (n=62)

	Number	E-NLR group (n=24)	N-NLR group (n=38)	*P* value
Age (years)				0.294
Mean		62.4±8.8	59.6±5.3	
Gender (%)				0.066
Male	50	16 (66.7%)	34 (89.5%)	
Female	12	8 (33.3%)	4 (10.5%)	
Tumor Size (cm)				0.021
<5	17	4 (16.7%)	13 (34.2%)	
≥5	45	20 (83.3%)	25 (65.8%)	
Location of tumor				0.043
Lower	23	6 (25.0%)	17 (44.8%)	
Middle	8	4 (16.7%)	4 (10.4%)	
Upper	31	14 (58.3%)	17 (44.8%)	
Lymph node metastasis				0.001
No	35	6 (25.0%)	29 (76.3%)	
Yes	27	18 (75.0%)	9 (23.7%)	
Histology				0.001
Well differentiated	35	7 (29.2%)	28 (73.7%)	
Worse differentiated	27	17 (70.8%)	10 (26.3%)	
Patterns of Recurrence				0.441
Locoregional recurrence	14	6 (25.0%)	8 (21.1%)	
Peritoneal seeding	25	10 (41.7%)	15 (39.4%)	
Hematogenous recurrence	13	6 (25.0%)	7 (18.4%)	
Others*	10	2 (8.3%)	8 (21.1%)	
Chemotherapy				0.302
No	10	3 (12.5%)	7 (18.4%)	
Yes	52	21 (87.5%)	31 (81.6%)	

*The patterns of recurrence involved at least two patterns.

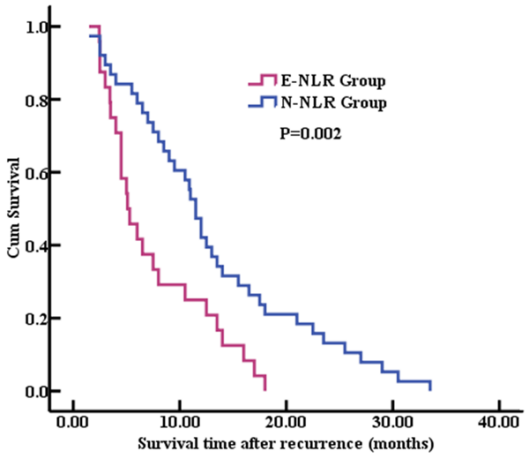

Figure 1. The survival time after recurrence for RGC patients. The median survival time after recurrence was significantly shorter in the E-NLR group than N-NLR group (5.1 months vs. 11.5 months, P=0.002).

al data were retrospectively reviewed and collected. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. And the patients were divided into two groups based on the pretreatment NLR cut-off point (≥4.15 or <4.15) [16]. Patients with concurrent infection were excluded. 8 RGC patients underwent a total gastrectomy, and 52 patients received adjuvant chemotherapy after surgery. The survival time was defined as time from the recurrence confirmed to the date of death or last visit. This study was approved by the Research Ethics Committee of Tianjin First Center Hospital, China. Written informed consents were obtained from all the patients enrolled in the study.

Statistical analysis

The analyses were conducted with SPSS version 18.0 (SPSS, Chicago, IL, United States). The categorical variables were analyzed by a chi-squared test; the survival curve was drawn using the Kaplan-Meier method and log-rank tests. And the prognostic value of the NLR was identified through the Multivariate analyses. Significance was defined as *P*-Values <0.05.

Results

Patient clinical-pathological characteristics

As the **Table 1** showed, 50 males and 12 females with RGC were enrolled in our study. The mean age was 61.0 years. For these RGC patients, 10 patients had at least two recurrence patterns concurrently. Among these recurrence patterns, the peritoneal seeding was the most common recurrence pattern, followed by locoregional recurrence (n=14) and hema-

Table 2. Univariate and multivariate analysis for RGC survival

Variable	Univariate analysis	Multivariate Cox regression		
	p-Value	HR	95% CI	*P*-Value
NLR	0.002	1.787	1.209-3.059	0.010
Lymph node metastasis	0.018	1.585	1.218-2.314	0.124
Tumor location	0.224	-	-	-
Tumor size	0.089	-	-	-
Histology	0.005	1.954	1.249-2.901	0.005
The therapy	0.041	2.307	1.119-3.847	0.077

HR hazard ratio, CI confidence interval.

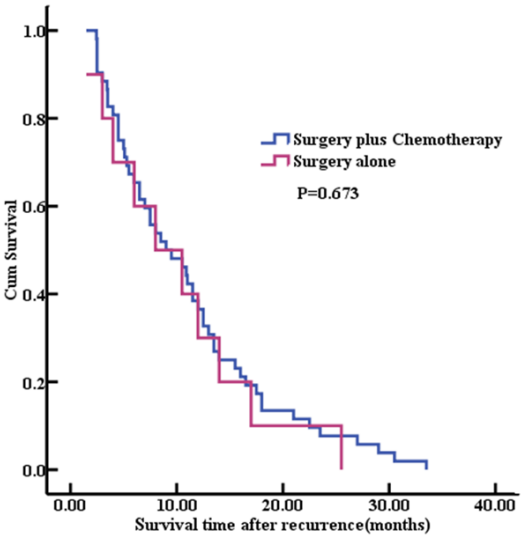

Figure 2. The effect of treatment on the survival of RGC. As the figure showed, the prognosis of RGC patients who received surgery plus chemotherapy treatment was not better than surgery alone (P=0.673).

togenous recurrence (n=13) (showed in the **Table 1**). The median follow-up time for all RGC patients was 60 months.

Association between NLR and clinical-pathological characteristics

The clinical and pathological characteristics of RGC were shown in **Table 1**. The NLR was elevated (NLR≥4.15) in 38.7% RGC patients (n=24; E-NLR), while 38 patients (61.3%) were within the normal range (n=38; N-NLR). We further explored the association between NLR and Clinical-pathological characteristics. Our data showed that the elevated NLR was associated with larger tumor size (P=0.021), worse histology (P=0.001) and lymph node metastasis (P=0.001). In addition, we found there were more recurrences in the proximal stomach in the E-NLR group (P=0.043).

Survival outcomes

In the present study, our data showed that the median survival time after the recurrence was 9.5 months. And as the **Figure 1** showed, the prognosis of RGC patients with elevated NLR was significantly worse compared to those RGC patients with normal level (5.1 months vs. 11.5 months, P=0.002).

In order to explore the independent prognostic factors for RGC prognosis, the univariate and multivariate were conducted. Our univariate analysis found the NLR (P=0.002), histology (P=0.005), Lymph node metastasis (P=0.018) and the therapy (P=0.005) were associated with the survival of RGC. The further multivariate analysis identified that the NLR (HR=1.787, P=0.010), histology (HR=1.954, P=0.005) were independent prognostic factors for RGC (Showed in the **Table 2**).

Discussion

The prognosis of GC has been improved by early detection and accurate treatment in the recent years. However, the tumor recurrence and metastasis contributed to the high mortality and poor long-term outcome. For the GC patients who underwent surgery, the tumor recurrence mostly occurred within 2 years [3]. As mentioned above, the accurate prognostic markers, potential treatment targets for RGC were deficient, and the effective treatment for RGC was not established yet [4, 8]. This study investigated the potential prognostic value of NLR in RGC patients. We identified that the high NLR was associated with poor prognosis of RGC, which might be used as a novel maker predicting the RGC outcome.

Many reports confirmed the correlation between chronic inflammation and tumor progression. And these studies also reported that NLR was associated with poor prognosis in esophageal squamous cell carcinoma, breast cancer, non-small cell lung cancer, combined small cell lung cancer and gastric cancer [14, 16-18]. In this study, we first explored the prognostic value of NLR in RGC patients. Consistent with these previous reports, our data revealed that the RGC patients in the E-NLR group had worse long-term prognosis than the RGC patients with normal NLR (5.1 months vs. 11.5 months,

P=0.002) (Showed in **Figure 1**). In addition, the elevated NLR (HR=1.787, P=0.010) and histology (HR=1.954, P=0.005) were identified as independent prognostic factors for RGC. These results reinforced the prognostic significance of NLR in solid tumors.

The association between NLR and clinical-pathological factors was also investigated in the present study. As the **Table 1** showed, the RGC patients with elevated NLR had larger tumor size (P=0.021), worse histology (P=0.001) and more lymph node metastasis (P=0.001). These data indicated that the high NLR was associated with aggressive pathological features. However, the potential molecular mechanism involved in these results were unclear, the further experiment is needed to be conducted to fully understand.

As there was no specific treatment to prevent the GC recurrence occurring, the early detection and properly treatment for RGC would improve the long-term prognosis. For the RGC patients who underwent complete resection, the long-term survival could be improved [19]. In addition, some studies found the concurrent treatment (surgery plus chemotherapy) prolonged the prognosis of RGC compared to the RGC patients who were treated with systemic chemotherapy alone [4, 20]. In the present study, we could not confirm these results. Our data showed that RGC patients after resection received chemotherapy had no longer prognosis compared to surgery alone (P=0.673, showed in the **Figure 2**). As the population in our study was small, this result needs large scale and multicenter studies to confirm.

Conclusions

Our study revealed that the elevated NLR was associated with larger tumor size and worse histology. And the NLR was identified as an independent prognostic factor, which might be used as a novel prognostic marker for RGC.

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Disclosure of conflict of interest

None.

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