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Development of prognostic predictive model with neutrophil–lymphocyte ratio (NLR) in patients with gastric signet ring carcinoma

Shihai Yang, MD, Shangdong Li, MD*

Abstract

The risk factors have not been well-defined for prognosis in gastric signet ring cell carcinoma (GSRC) patients. This study is designed to prognosticate survival in GSRC patients by establishing and verifying a predictive model with neutrophil–lymphocyte ratio (NLR).

A total of 147 GSRC patients from Department of Surgical Oncology, Neimenggu Baogang Hospital, Inner Mongolia Medical University were retrospectively reviewed. A predictive model was established using Cox proportional hazards. The performance of the model was evaluated by ROC curves.

In present study, we found that overall survival (OS) ($P < .001$, Fig. 1A) and tumor recurrence rate ($P = .036$, Fig. 1B) in the NLR $\leq$ 2.8 group were significantly better than those in the NLR $>$ 2.8 group. These results showed that NLR $\leq$ 2.8 was significant prognostic factor related with both OS and tumor recurrence in patients with GSRC. After adjusting for competing risk factors, NLR $\leq$ 2.8 (hazard ratio [HR]: 2.625, 95% confidence interval [CI]: 1.505–5.3166, $P = .003$), tumor size (HR: 3.024, 95% CI: 1.521–4.186, $P = .005$), and tumor metastasis (HR: 3.303, 95% CI: 1.25–4.525, $P = .012$) remained independent predictors of tumor recurrence rate and OS. Our results showed that comparing with the model without NLR (area under ROC curve: 0.798), the model with NLR (area under ROC curve: 0.826) had significant better predictive power than the model without NLR, which further confirmed the value of NLR in predicting prognosis of patients with GSRC.

In conclusion, a high NLR value independently predicts poor survival in patients with GSRC after surgery. The NLR may help oncologists evaluate outcomes of patients received surgical resection and chemotherapy in order to choose alternative therapies for patients with high NLR value.

Abbreviations: AUC = area under ROC curve, CI = confidence interval, EGC = early gastric cancer, ESD = endoscopic submucosal dissection, GC = gastric cancer, GSRC = gastric signet ring cell carcinoma, HR = hazard ratio, NLR = neutrophil–lymphocyte ratio, OS = overall survival, TTR = tumor recurrence rate.

Keywords: GSRC, neutrophil–lymphocyte ratio, prognosis

1. Introduction

Gastric cancer (GC), a high incidence and mortality disease, topped the public health problems worldwide.[1,2] Signet ring cell carcinoma with abundant intracytoplasmic mucin in cells, which to be reported has more aggressive biological behavior and poor prognosis. Although the prevalence of GC has gradually declined in recent decades, the incidence of gastric signet ring cell carcinoma (GSRC) is still increasing.[3–7]

Additionally, the associations of inflammation-based scores with the prognosis of PC have been actively explored. Inflammatory response plays a vital role in tumor progression including initiation, promotion, malignant conversion, invasion, and metastasis. Based on these factors, several inflammations and immune-based prognostic scores such as lymphocyte count, platelet–lymphocyte ratio, and neutrophil–lymphocyte ratio (NLR) have been developed to predict the inflammatory response being associated with poor survival and recurrence in different types of cancer, including GSRC.[8–10] An increasing body of evidence shows that systemic inflammation activation exerted by cancer cells anticipates tumor progression via inducing cancer proliferation and metastasis or promoting angiogenesis.[11,12] The NLR, which has been considered as a member of the marker of the systemic inflammation response, is valuable for predicting the prognosis of various cancers.[13–15] However, these indexes did not comprehensively reflect the balance of host inflammatory and immune status. Challenges remain in order to identify reliable, cost-effective biomarkers to identify which patients are most likely to receive therapeutic benefit from surgery for GCs.

Increasing evidence shows that systemic inflammatory activation caused by cancer cells can induce cancer cell proliferation, metastasis, or promote angiogenesis. NLR is considered to be one of the markers of systemic inflammatory response and is valuable for predicting the prognosis of various cancers. Studies have

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Department of Surgical Oncology, Neimenggu Baogang Hospital, Inner Mongolia Medical University, Baotou, China.

** Correspondence: Shangdong Li, Department of Surgical Oncology, Neimenggu Baogang Hospital, Inner Mongolia Medical University, Baotou 014040, China (e-mail: zhonglcip@126.com).*

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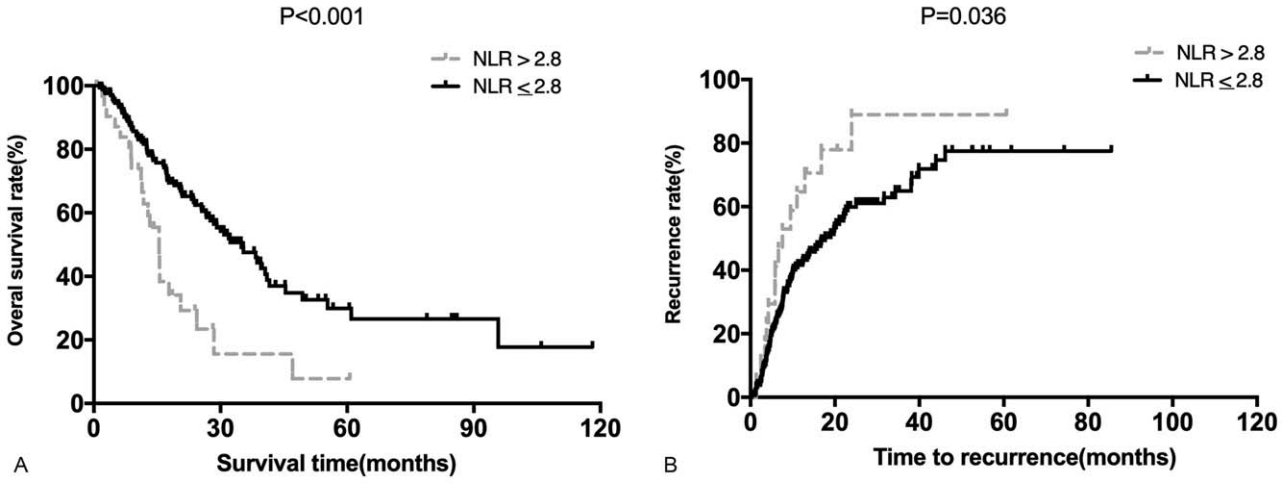

Figure 1. (A) Overall survival (OS) and (B) tumor recurrence rate (TTR) for the different groups divided by NLR. NLR = lymphocyte ratio.

shown that in patients with GSRC who have undergone chemotherapy or surgical resection, elevated NLR before treatment is associated with poor prognosis. In the present study, we evaluated the prognostic value of NLR in patients with GSRC who received curative resection. Moreover, we also analyzed the predictive values between the models with or without NLR.

2. Patients and methods

2.1. Study design and participants

The cohort consisted of 147 consecutive patients with GSRC identified retrospectively from January 1, 2015 to July 30, 2019. The study was approved by the Regional Ethical Review Board for Department of Surgical Oncology, Neimenggu Baogang Hospital, Inner Mongolia Medical University. Patients were treated according to the Declaration of Helsinki's ethical principles for medical research involving human subjects. All patients provided an informed written consent prior to study entry. Patients were required to meet the following inclusion criteria: participants were aged 18 to <80 years; Eastern Cooperative Oncology Group performance status[16] was evaluated; the primary procedure was surgical resection, histologically or cytologically confirmed GSRC. No prior chemotherapy or immunotherapy was allowed. Patients were excluded if they had a concurrent malignancy other than GSRC, a serious, uncontrollable medical condition, or a psychiatric disorder that would limit ability to comply with study requirements.

2.2. Pre-treatment evaluation

Medical history and physical findings were documented in each patient. Each patient also had an ECG, computed tomography of the abdomen and pelvis (and thorax, if needed), serum chemistry and CBC, and urine analysis.

2.3. Procedures

All patients received surgical resection, while 98 patients received adjuvant chemotherapy and number of previous lines of palliative intent chemotherapy were recorded. Adverse events were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE v4.0) and response to treatment was assessed by the Response Evaluation Criteria in Solid Tumors (www.cancer.gov/).

2.4. Survival assessment

Overall survival (OS) was calculated from the time of surgery until death from any cause or last follow-up. Tumor recurrence was calculated as the time from surgery until tumor progression as determined by the treating physician, death from any cause, or last follow-up, whichever occurred first.

2.5. Statistical methods

Continuous variables were expressed as mean ± standard deviation and compared using a two-tailed unpaired Student *t* test; categorical variables were compared using $\chi 2$ or Fisher analysis. The predictive performance of NLR was measured using the area under ROC curve (AUC).[17] Life-table estimates of survival time were calculated according to the Kaplan and Meier methodology.[18] The Greenwood formula was used for the standard deviation. A Cox proportional hazards regression approach[19] was chosen for the evaluation of tumor recurrence rate (TTR) and OS as the primary end-point. Potential prognostic variables were analyzed both univariately with 1 factor taken at a time, and then in a multivariate model combining all factors. Results are reported as hazard ratios (HRs) and their 95% confidence intervals (CIs). A HR >1 indicated an elevated risk with respect to the reference category. A CI which did not include the value 1 indicated statistical significance at the 5% level. All statistical evaluations were carried out using SPSS software (Statistical Package for the Social Science, version 15.0, SPSS Inc., Chicago, IL). A value of $P < 0.05$ was considered to be statistically significant in all the analyses.

3. Results

3.1. Patients' characteristics

The 147 patients GSRC patients were retrospectively enrolled in this study from the hospital cohorts with 66.3% LNM rates,

Table 1

Demographics and clinical characteristics of all patients.

Variable	NLR > 2.8 (N = 110)	NLR ≤ 2.8 (N = 37)	*P* values
Age	52.3 ± 10.5	55.4 ± 12.3	.258
Gender			
Female	35	11	.786
Male	85	26	
ECOG-PS			.504
1	97	29	
2	13	8	
TNM staging			.002
I–II	90	12	
III	20	25	
Treatment group			.137
Adjuvant chemotherapy	87	30	
No chemotherapy	23	7	
Estimated blood loss (mL)	1198.6 ± 863.3	1253.4 ± 943.3	.335
Tumor size (cm)	2.38 ± 3.05	2.41 ± 3.25	.385
Primary site			
Upper	45	11	.749
Middle	35	10	
Lower	25	16	
Lymph node metastasis			.595
Yes	34	7	
No	76	30	
No. site of metastasis			.736
<2	79	18	
>2	31	19	

ECOG-PS = Eastern Cooperative Oncology Group performance status, NLR = lymphocyte ratio.

respectively. Patients tend to be younger age (≤60), poorer tumor grade, bigger tumor size (>2 cm), and primary sites were more commonly located in the middle and lower third of stomach. Patients are more frequently in T1 (36.3%) and T3 (54.1%) status. The detailed clinicopathological information is listed in Table 1.

3.2. Survival analysis of patients with GSRC with respect to NLR

In present study, we found that OS ($P < .001$, Fig. 1A) and TTR ($P = .036$, Fig. 1B) in the NLR ≤ 2.8 group were significantly better than those in the NLR > 2.8 group. These results showed that NLR ≤ 2.8 was significant prognostic factor related with both OS and tumor recurrence in patients with GSRC.

3.3. Predictors associated with clinical outcomes

Cox proportional hazards models were then used to quantify the prognostic significance of risk factors after multivariable adjustment. A multivariable analysis was performed to assess the factors that demonstrated significant effects in univariate analysis. After adjusting for competing risk factors, NLR ≤ 2.8 (HR: 2.625, 95% CI: 1.505–5.3166, $P = .003$), tumor size (HR: 3.024, 95% CI: 1.521–4.186, $P = .005$), and tumor metastasis (HR: 3.303, 95% CI: 1.25–4.525, $P = .012$) remained independent predictors of TTR and OS. The details are shown in Figure 2.

3.4. Prognosis predictive model for patients with GSRC

We then used the results from Cox proportional hazards models to predict the OS of patients with GSRC. We measured the AUC

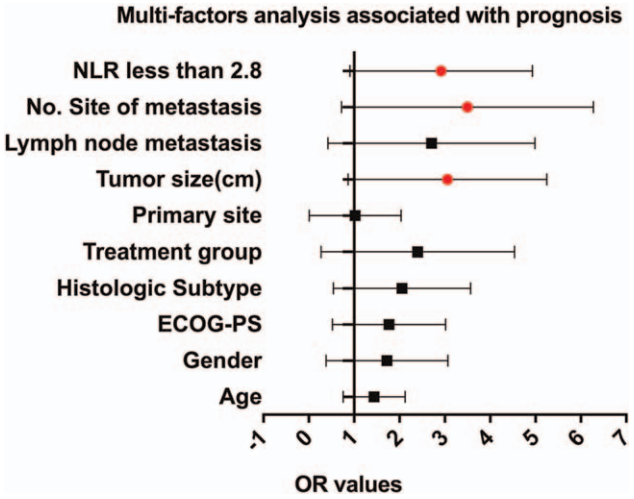

Figure 2. Cox proportional hazards models were then used to quantify the prognostic significance of risk factors after multivariable adjustment.

to confirm the predictive values of different models with/without the variable of NLR. Our results showed that comparing with the model without NLR (AUC: 0.798), the model with NLR (AUC: 0.826) had significant better predictive power than the model without NLR (Fig. 3), which further confirmed the value of NLR in predicting prognosis of patients with GSRC.

4. Discussion

Consistent with previous conclusions, GSRC patients pretended to be more advanced stages with a large proportion of T3 and T4 (SEER cohort: 71.3%; YJS cohort: 65.9%). Prior studies reported that GSRC histology was independently associated with LNM status, patients of which have a significantly worse 5-year survival outcome than other types of GC, and have larger lesions and deeper infiltration and higher LNM rates than non-GSRC in advanced stage.[20–23] Chen et al observed that GSRC patients have a high LNM rate (94.1%, 32/34) in advanced stage. Zu et al reported that the LNM rate of advanced GSRC was 56.8% (25/44). In our study, the LNM rate of GSRC patients in T2–4 stages was 75.9% (1558/2052), which was similar to previous conclusions.[4,24] Recent studies showed that patients with lesions ≥2 cm account for the majority proportion in early GSRC patients. Our research found that 60.8% (293/482) and 80.3% (2036/2534) patients had lesions >2 cm in T1 and all patients in SEER cohort, respectively. Deeper infiltration and larger lesions had been reported to be independent risk factors of LNM in early GSRC patients. Naruhiko et al demonstrated that depth of infiltration and NLNE were independent predictors of LNM in T1–2 GC patients. Chen et al reported that deeper infiltration and larger lesions were independent risk factors of LNM in advanced GC patients (5). Our findings were similar to above conclusions.[25,26]

Endoscopic resection for early gastric cancer (EGC) with low recurrence rates, has been widely used in Asian countries, and endoscopic submucosal dissection (ESD) is increasingly being considered for EGC in America. Endoscopic resection for EGC in NCCN guideline meets following criteria: well or moderately differentiated, ≤2 cm in diameter, negative margins (lateral and deep margins), lacking lymphovascular invasion, and limited to

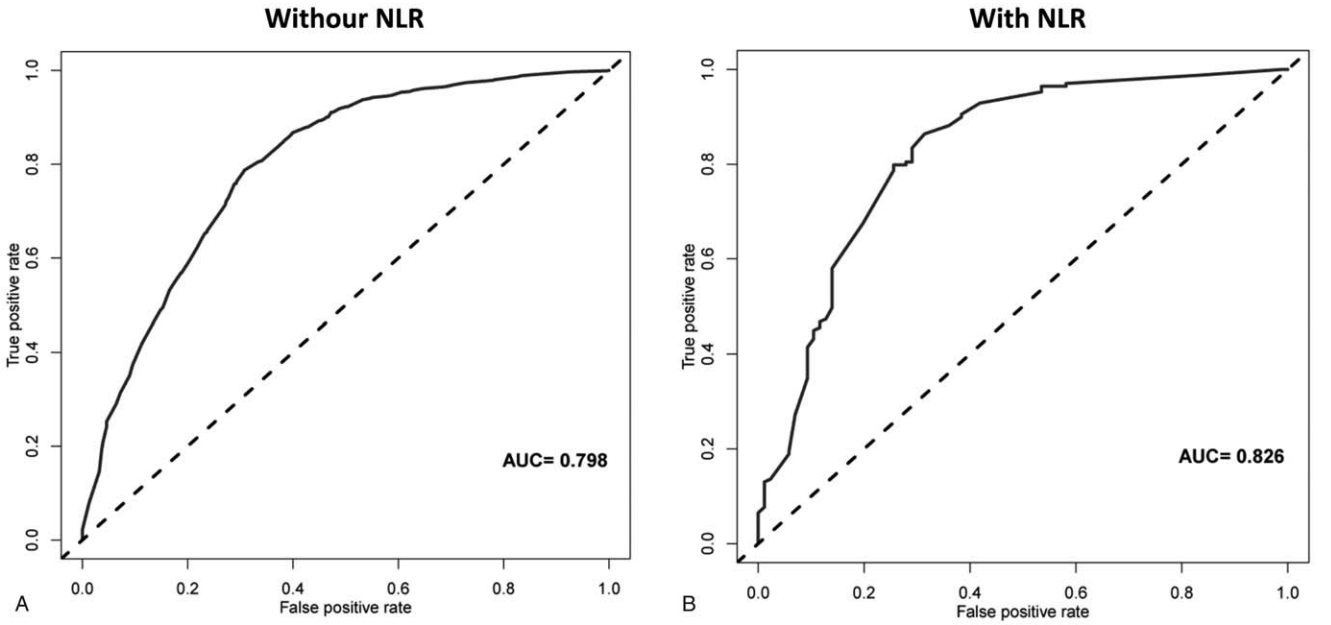

Figure 3. Comparison of AUROC of Cox proportional hazards models without NLR (A) and with NLR (B) in predicting overall survival of patients with GSRC. GSRC = gastric signet ring cell carcinoma, NLR = lymphocyte ratio.

the superficial submucosa. Therefore, poor and undifferentiated GSRC (account for 97.3%) in the SEER cohort is not suitable for endoscopic resection. Signet ring cell carcinoma is defined as an undifferentiated carcinoma in Japan. Association Japanese Gastric Cancer demonstrated that the LNM rate of T1a undifferentiated GC (≤2 cm) without and with ulcer were 0% (0/310, 95% CI = 0%–0.96%) and 2.9% (8/271, 95% CI = 1.2%–5.7%) in Japanese cohort, respectively. The former subgroup met the expanded indication for ESD; however, the latter subgroup was not recommended for ESD. Pokala et al pointed out that the LNM rate of T1a GSRC (<2 cm) was 5.4%, and proposed that endoscopic resection could be considered for this cohort.

The mechanism underlying the potential prognostic value of NLR is mainly due to the significance of the infiltrated neutrophils and lymphocytes. The systemic inflammatory response from cancer cells promotes the infiltration of neutrophils, which benefits cancer progression via secreting interleukin-2, interleukin-6, interleukin-10, tumor necrosis factor α, and vascular endothelia growth factor.[27,28] Vascular endothelia growth factor is a proangiogenic factor contributes to cancer development especially through angiogenesis. Moreover, increased tumor necrosis factor α and interleukin-10 issue in lymphocyte count decrease and lymphocyte dysfunction also.[29] It is well known that lymphocyte depletion is likely reflection of an impaired T-lymphocyte-mediated antitumor response, which represents an adverse prognostic trait.[30] In general, the relative ratio of elevated neutrophils and decreased lymphocytes could be a scientific marker for evaluating the systemic inflammatory response and outcome of individuals. And so, NLR is valuable as a potential indicator of prognosis to some degree.

By the way, there were several limitations of this study: on one hand, this is a study with small sample size and retrospective design. On the other hand, the relationship between survival and change of NLR after treatment apart from pre-treatment can be investigated in future studies.

In conclusion, a high NLR value independently predicts poor survival in patients with GSRC after surgery. The NLR may help oncologists evaluate outcomes of patients received surgical resection and chemotherapy in order to choose alternative therapies for patients with high NLR value.

Author contributions

Conceptualization: Shihai Yang, Shangdong Li.
Data curation: Shihai Yang.
Formal analysis: Shihai Yang.
Methodology: Shihai Yang.
Writing – original draft: Shihai Yang, Shangdong Li.
Writing – review & editing: Shihai Yang, Shangdong Li.

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