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Prognostic Prediction Model Development Using Neutrophil–Lymphocyte Ratio (NLR) in Gastric Signet Ring Cell Carcinoma

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Abstract

The prognostic determinants for gastric signet ring cell carcinoma (GSRC) remain inadequately characterized. This study aimed to predict survival outcomes in GSRC patients by developing and validating a model incorporating the neutrophil–lymphocyte ratio (NLR). We retrospectively analyzed 147 GSRC patients treated at the Department of Surgical Oncology, Neimenggu Baogang Hospital, Inner Mongolia Medical University. Using Cox proportional hazards regression, a predictive model was constructed, and its accuracy was assessed via ROC curves. Our analysis revealed that patients with NLR ≤ 2.8 had significantly improved overall survival (OS) (P < .001, **(Figure 1a)**) and lower rates of tumor recurrence (P = .036, **(Figure 1b)**) compared to those with NLR > 2.8. Multivariate analysis confirmed that NLR ≤ 2.8 (HR: 2.625, 95% CI: 1.505–5.3166, P = .003), larger 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) independently predicted both OS and tumor recurrence. Incorporating NLR enhanced model performance (AUC: 0.826 vs. 0.798 without NLR), highlighting its prognostic relevance. These findings suggest that elevated NLR is an independent indicator of poor prognosis post-surgery and may assist clinicians in selecting optimal therapeutic strategies for high-risk GSRC patients.

Keywords: GSRC, Neutrophil–lymphocyte ratio, Prognosis, Gastric cancer (GC)

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Introduction

Gastric cancer (GC) remains a leading global health challenge due to its high incidence and mortality rates [1, 2]. Among its subtypes, gastric signet ring cell carcinoma (GSRC), characterized by abundant mucin within tumor cells, exhibits particularly aggressive behavior and poor survival outcomes. Although the overall incidence of GC has declined over recent decades, GSRC cases continue to rise [3–7].

Emerging evidence has underscored the role of systemic inflammation in cancer progression, encompassing tumor initiation, growth, invasion, and metastasis. Consequently, various inflammation- and immune-based prognostic indices—including lymphocyte counts, platelet–lymphocyte ratios, and neutrophil–lymphocyte ratios (NLR)—have been evaluated in multiple cancers, including GSRC, as potential predictors of recurrence and survival [8–10]. Cancer-driven systemic inflammation may facilitate tumor proliferation, metastasis, and

angiogenesis [11, 12]. Among these markers, NLR is widely recognized as an accessible indicator of systemic inflammatory status and has shown prognostic value across diverse malignancies [13–15]. Nevertheless, current indices may not fully capture the interplay between host immunity and tumor-induced inflammation, and reliable, cost-effective biomarkers are needed to guide treatment decisions in GSRC.

Prior studies indicate that elevated preoperative NLR correlates with worse outcomes in GSRC patients receiving surgery or chemotherapy. Building on these findings, the present study aimed to assess the prognostic significance of NLR in GSRC patients undergoing curative resection and to evaluate the predictive capacity of models with versus without NLR.

Materials and Methods

Study population

This retrospective cohort included 147 patients with histologically confirmed GSRC treated between January 1, 2015, and July 30, 2019. The study protocol was approved by the Regional Ethical Review Board of the Department of Surgical Oncology, Neimenggu Baogang Hospital, Inner Mongolia Medical University, and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants. Eligible patients were aged 18–79 years, had an Eastern Cooperative Oncology Group performance status evaluated [16], and underwent primary surgical resection. Exclusion criteria included prior chemotherapy or immunotherapy, concurrent malignancies, uncontrolled comorbidities, or psychiatric conditions impeding compliance.

Baseline assessment

Patient evaluation included medical history, physical examination, electrocardiography, abdominal and pelvic computed tomography (and thoracic imaging when indicated), serum biochemistry, complete blood counts, and urinalysis.

Treatment procedures

All patients underwent surgical resection; 98 patients received adjuvant chemotherapy. Prior lines of palliative chemotherapy were recorded. Adverse events were graded according to NCI-CTCAE v4.0, and tumor response was assessed using RECIST criteria (www.cancer.gov/).

Outcome measures

Overall survival (OS) was defined from the date of surgery to death from any cause or last follow-up. Tumor recurrence was measured from surgery to progression, death, or last follow-up, whichever occurred first.

Statistical analysis

Continuous variables are reported as mean ± standard deviation and compared using two-tailed unpaired t-tests, while categorical variables were compared using χ^2 or Fisher's exact tests. ROC curves were used to assess NLR predictive performance [17]. Kaplan–Meier methodology estimated survival curves [18], with standard deviations calculated using the Greenwood formula. Cox proportional hazards regression was applied to evaluate tumor recurrence and OS [19], with univariate analysis followed by multivariate modeling. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported; HR >1 indicated increased risk, and CIs excluding 1 were considered statistically significant ($P < 0.05$). Analyses were performed using SPSS v15.0 (SPSS Inc., Chicago, IL).

Results and Discussion

Patient characteristics

Among the 147 GSRC patients, lymph node metastasis was observed in 66.3%. The majority were ≤60 years old, had poorly differentiated tumors, tumor sizes >2 cm, and tumors primarily located in the middle or lower stomach. T-stage distribution showed predominance in T1 (36.3%) and T3 (54.1%). Detailed clinicopathological features are presented in **Table 1**.

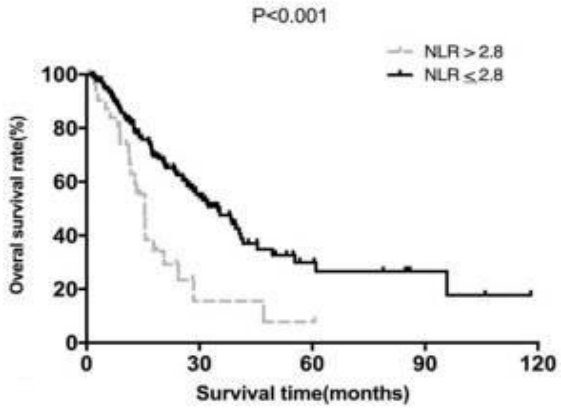
Table 1. Demographics and clinical characteristics of all patients.

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	

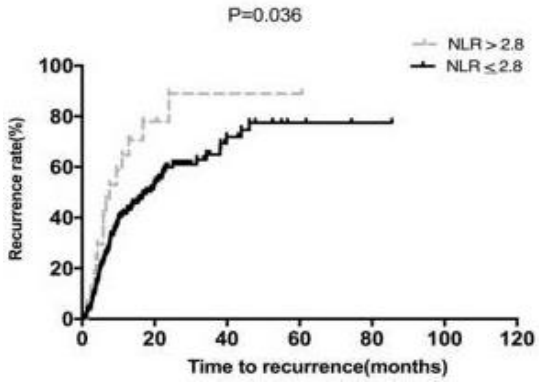
TNM staging			.002
I–II	90	12	
III	20	25	
Treatment group			.137
Adjuvant chemotherapy	87	30	
No chemotherapy	23	7	
Estimated blood loss (mL)	1198.6±863.3	1253.4±943.3	.335
Tumor size (cm)	2.38±3.05	2.41±3.25	.385
Primary site			
Upper	45	11	.749
Middle	35	10	
Lower	25	16	
Lymph node metastasis			.595
Yes	34	7	
No	76	30	
No. site of metastasis			.736
<2	79	18	
>2	31	19	

Survival analysis according to NLR

Our analysis demonstrated that patients with NLR ≤ 2.8 experienced significantly improved overall survival (OS) (P<.001, **(Figure 1a)**) and longer time to tumor recurrence (TTR) (P=.036, **(Figure 1b)**) compared with those whose NLR exceeded 2.8. These findings indicate that a lower NLR (≤ 2.8) serves as an important prognostic indicator for both OS and tumor recurrence in GSRC patients.



a)



b)

Figure 1. (a) Overall survival (OS) and (b) time to tumor recurrence (TTR) curves for patient groups stratified by neutrophil-to-lymphocyte ratio (NLR) levels. (Note: NLR refers to the neutrophil-to-lymphocyte ratio.)

Independent prognostic factors for clinical outcomes

Cox proportional hazards regression models were employed to evaluate the prognostic value of various risk factors following multivariable adjustment. Multivariable analysis was conducted on factors that showed significance in univariate testing. After controlling for confounding variables, an NLR ≤ 2.8 (hazard ratio [HR]: 2.625, 95% confidence interval [CI]: 1.505–5.316, P = .003), larger tumor size (HR: 3.024, 95 percent CI: 1.521–4.186, P = .005), and presence of tumor metastasis (HR:

3.303, 95 percent CI: 1.25–4.525, P = .012) emerged as independent predictors of both poorer time to tumor recurrence (TTR) and overall survival (OS). Further details are presented in **Figure 2**.

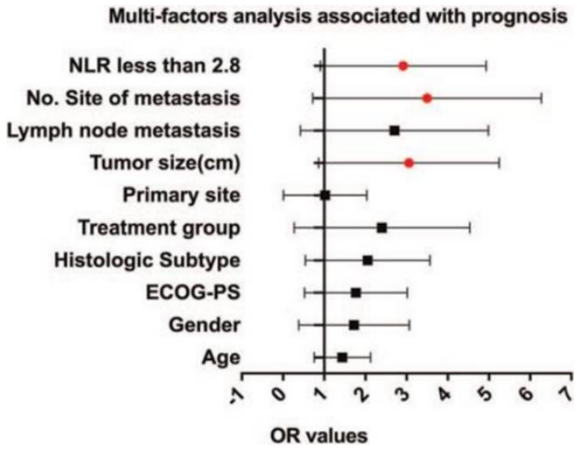
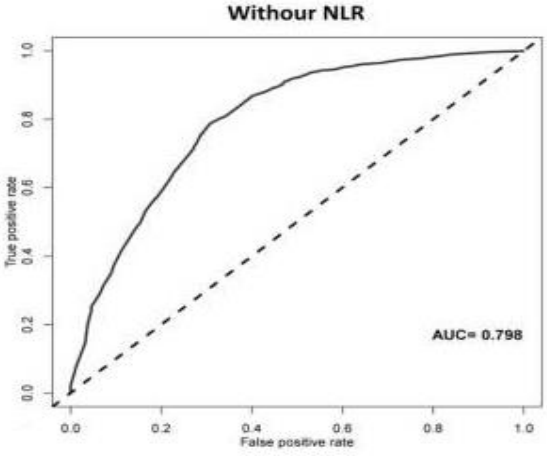


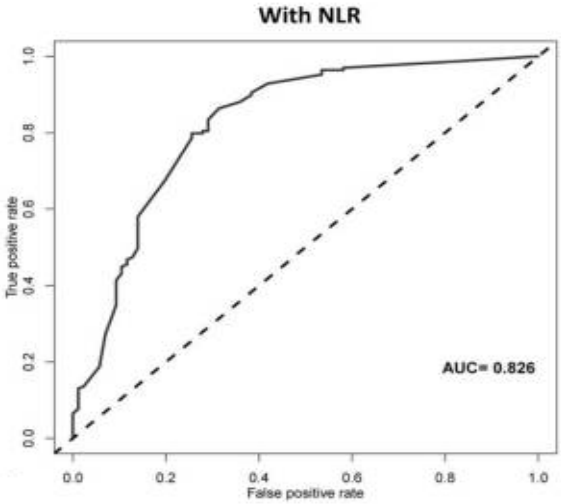
Figure 2. Multivariable Cox proportional hazards analysis illustrating the independent prognostic significance of risk factors after adjustment for confounders.

Development of a prognostic model for GSRC

Using the outcomes from the multivariate Cox regression, we constructed a model to predict overall survival (OS) in patients with GSRC. To evaluate the predictive performance, the area under the ROC curve (AUC) was calculated for models including or excluding NLR. The analysis revealed that the inclusion of NLR improved model accuracy, with an AUC of 0.826 compared with 0.798 for the model without NLR **(Figure 3)**. These results emphasize that NLR enhances the prognostic capability of survival models for GSRC, reinforcing its clinical relevance in outcome prediction.



a)



b)

Figure 3. Comparison of the area under the ROC curve (AUROC) for Cox proportional hazards models predicting overall survival in GSRC patients: (a) model excluding NLR and (b) model including NLR. GSRC = gastric signet ring cell carcinoma; NLR = neutrophil–lymphocyte ratio.

Consistent with prior reports, GSRC patients often present at more advanced stages, with a high prevalence of T3 and T4 tumors (SEER cohort: 71.3%; YJS cohort: 65.9%). Previous studies have demonstrated that GSRC histology independently correlates with lymph node metastasis (LNM), and affected patients experience significantly worse five-year survival compared with other gastric cancer subtypes, as well as larger tumors, deeper invasion, and higher rates of LNM in advanced stages [20–23]. For instance, Chen *et al*. reported a 94.1% LNM rate (32/34) in advanced GSRC, while Zu *et al*. found a 56.8% LNM rate (25/44). In our cohort, T2–T4 stage GSRC patients exhibited an LNM rate of 75.9% (1558/2052), aligning with these previous observations [4, 24].

Early GSRC frequently presents with lesions ≥2 cm. In our study, 60.8% (293/482) of T1 patients and 80.3% (2036/2534) of all SEER cohort patients had tumors exceeding 2 cm. Prior research has identified tumor depth and size as independent predictors of LNM in both early and advanced GSRC. Naruhiko *et al*. found that depth of invasion and the number of lymph nodes examined (NLNE) independently predicted LNM in T1–T2 gastric cancer, while Chen *et al*. observed that deeper invasion and larger tumor size were risk factors in advanced disease [25, 26]. Our findings are consistent with these results.

Endoscopic resection, particularly endoscopic submucosal dissection (ESD), has become a widely adopted treatment for early gastric cancer (EGC) in Asia and is gaining consideration in Western countries. According to NCCN guidelines, EGC suitable for endoscopic resection should be well or moderately differentiated, ≤2 cm, confined to the superficial submucosa, have negative margins, and

lack lymphovascular invasion. Consequently, poorly differentiated or undifferentiated GSRC—which represents 97.3% of the SEER cohort—is generally unsuitable for endoscopic therapy. In Japan, signet ring cell carcinoma is classified as undifferentiated. Data from the Japanese Gastric Cancer Association show that T1a undifferentiated GC ≤2 cm without ulceration has a 0% LNM rate (0/310, 95% CI 0%–0.96%), whereas lesions with ulceration show a 2.9% rate (8/271, 95% CI 1.2%–5.7%). Only the former group meets expanded ESD indications, while the latter is not recommended for ESD. Pokala *et al*. reported a 5.4% LNM rate for T1a GSRC <2 cm, suggesting that select patients could be considered for endoscopic resection.

The prognostic relevance of NLR is primarily linked to the roles of neutrophils and lymphocytes in the tumor microenvironment. Tumor-driven systemic inflammation recruits neutrophils, which secrete cytokines such as interleukin-2, interleukin-6, interleukin-10, tumor necrosis factor-α, and vascular endothelial growth factor (VEGF), all of which promote tumor progression and angiogenesis [27, 28]. Elevated TNF-α and IL-10 can also reduce lymphocyte counts and impair lymphocyte function [29]. Lymphopenia reflects a weakened T-cell-mediated antitumor response and is associated with poor prognosis [30]. Therefore, the ratio of neutrophils to lymphocytes provides a meaningful measure of systemic inflammation and can serve as a prognostic biomarker, supporting the clinical utility of NLR.

This study has limitations. First, its retrospective design and modest sample size may limit generalizability. Second, the potential prognostic significance of post-treatment NLR dynamics was not examined and warrants future investigation.

Conclusion

In conclusion, elevated preoperative NLR independently predicts worse survival in GSRC patients undergoing surgery. Assessment of NLR may assist clinicians in identifying high-risk patients who could benefit from alternative or intensified therapeutic strategies.

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Ethics statement: None

References

1. Li Y, Zhu Z, Ma F, Xue L, Tian Y. Improving survival of stage II–III primary gastric signet ring cell carcinoma by adjuvant chemoradiotherapy. Cancer Med. 2020;9(18):6617–28.
2. Lin CL, Zhu GW, Huang YJ, Zheng W, Yang SG, Ye JX. Operable gastric adenocarcinoma with different histological subtypes: cancer-specific survival in the United States. Saudi J Gastroenterol. 2020;26(1):46–52.
3. Choi BH, Song HS, An YS, Han SU, Kim JH, Yoon JK. Relation between fluorodeoxyglucose uptake and glucose transporter-1 expression in gastric signet ring cell carcinoma. Nucl Med Mol Imaging. 2011;45(1):30–5.
4. Tabouret T, Dhooge M, Rouquette A, Mariette C, Bouché O, Leteurtre E, et al. Gastric signet ring cell adenocarcinoma: a distinct entity. Presse Med. 2014;43(4 Pt 1):353–7.
5. Fourgeaud C, Derieux S, Mirshahi S, Fourgeaud J, Mirshahi M, Benderitter M, et al. Expression of heparanase in cancer as biomarker of malignancies: overexpression in aggressive poor-survival gastric signet ring cell carcinoma. Thromb Res. 2016;140(Suppl 1):S184–5.
6. Fung BM, Patel M, Patel N, Brown AF, Ostrzega NL, Tabibian JH. Signet ring cell gastric carcinoma: clinical epidemiology and outcomes in a predominantly Latino county hospital population. Dig Dis Sci. 2021;66(4):1240–8.
7. Li Y, Zhu Z, Ma F, Xue L, Tian Y. Gastric signet ring cell carcinoma: current management and future challenges. Cancer Manag Res. 2020;12(1):7973–81.
8. Vartolomei MD, Ferro M, Cantiello F, Lucarelli G, Di Stasi S, Hurle R, et al. Validation of neutrophil-to-lymphocyte ratio in a multi-institutional cohort of patients with T1G3 non-muscle-invasive bladder cancer. Clin Genitourin Cancer. 2018;16(6):445–52.
9. Vartolomei MD, Porav-Hodade D, Ferro M, Mathieu R, Abufaraj M, Foerster B, et al. Prognostic role of pretreatment neutrophil-to-lymphocyte ratio in patients with non-muscle-invasive bladder cancer: a systematic review and meta-analysis. Urol Oncol. 2018;36(9):389–99.
10. Vartolomei MD, Mathieu R, Margulis V, Karakiewicz PI, Roupret M, Shariat SF, et al. Promising role of preoperative neutrophil-to-lymphocyte ratio in patients treated with radical nephroureterectomy. World J Urol. 2017;35(1):121–30.
11. Hainaut P, Plymoth A. Targeting the hallmarks of cancer: towards a rational approach to next-generation cancer therapy. Curr Opin Oncol. 2013;25(1):50–1.
12. Jaiswal M, LaRusso NF, Burgart LJ, Gores GJ. Inflammatory cytokines induce DNA damage and

inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide–dependent mechanism. Cancer Res. 2000;60(1):184–90.
13. He W, Yin C, Guo G, Jiang C, Wang F, Qiu H, et al. Initial neutrophil lymphocyte ratio is superior to platelet lymphocyte ratio as an adverse prognostic and predictive factor in metastatic colorectal cancer. Med Oncol. 2013;30(1):439.
14. Kobayashi N, Usui S, Kikuchi S, Goto Y, Sakai M, Onizuka M, et al. Preoperative lymphocyte count is an independent prognostic factor in node-negative non-small cell lung cancer. Lung Cancer. 2012;75(2):223–7.
15. Jung MR, Park YK, Jeong O, Seon JW, Ryu SY, Kim DY. Elevated preoperative neutrophil to lymphocyte ratio predicts poor survival following resection in late stage gastric cancer. J Surg Oncol. 2011;104(5):504–10.
16. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649–55.
17. Hanley JA. Receiver operating characteristic (ROC) methodology: the state of the art. Crit Rev Diagn Imaging. 1989;29(3):307–35.
18. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53(282):457–81.
19. Cox DR. Regression models and life-tables. J R Stat Soc Series B. 1972;34(2):187–220.
20. Bleaney CW, Barrow M, Hayes S, Ang Y. The relevance and implications of signet-ring cell adenocarcinoma of the oesophagus. J Clin Pathol. 2018;71(3):201–6.
21. de Aguiar VG, Segatelli V, Macedo ALV, Nunes TA, Silva AR, Begnami MD, et al. Signet ring cell component, not the Lauren subtype, predicts poor survival: an analysis of 198 cases of gastric cancer. Future Oncol. 2019;15(4):401–8.
22. Khan MR, Farooqi NB, Shahzad N. Is proximal gastric cancer a different entity from distal gastric cancer? Anatomical site distribution of signet ring cell carcinoma and its association with Helicobacter pylori infection. J Ayub Med Coll Abbottabad. 2020;32(2):194–7.
23. Lee YM, Kang SH, Kim JS, Kim BW, Kim JH, Kim JH, et al. Subepithelial spread of early gastric signet ring cell carcinoma: how far they can reach? Dig Dis. 2020;38(6):442–8.
24. He CL, Chen P, Xia BL, Xiao Q, Cai FL. Breast metastasis of gastric signet-ring cell carcinoma: a case report and literature review. World J Surg Oncol. 2015;13(1):120.
25. Schröder W, Bruns C. Gastric signet ring cell carcinoma: new aspects for long-range prognosis. Chirurg. 2017;88(8):710.
26. Xiong ZF, Shi J, Fu ZH, Wan HP, Tu LX. Phenotypic classification of gastric signet ring cell carcinoma and its relationship with K-ras mutation. Genet Mol Res. 2017;16(1):gmr16019402.
27. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001;357(9255):539–45.
28. Kusumanto YH, Dam WA, Hospers GA, Meijer C, Mulder NH. Platelets and granulocytes, in particular neutrophils, form important compartments for circulating vascular endothelial growth factor. Angiogenesis. 2003;6(4):283–7.
29. Salazar-Onfray F, Lopez MN, Mendoza-Naranjo A. Paradoxical effects of cytokines in tumor immune surveillance and tumor immune escape. Cytokine Growth Factor Rev. 2007;18(1–2):171–82.
30. Kobayashi N, Hiraoka N, Yamagami W, Ojima H, Kanai Y, Kosuge T, et al. FOXP3+ regulatory T cells affect the development and progression of hepatocarcinogenesis. Clin Cancer Res. 2007;13(3):902–11.