

Prognostic impact of preoperative neutrophil-lymphocyte ratio for surgically resected gastrointestinal stromal tumors

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Abstract

Neutrophil-lymphocyte ratio (NLR) was shown to be prognostic value in various malignancies. There are limited data about predictive or prognostic role of NLR during gastrointestinal stromal tumors (GISTs) patients. This study evaluated the prognostic significance of preoperative NLR in patients with GIST.

We retrospectively enrolled 72 primary GIST patients who received initial curative surgical resection with or without adjuvant imatinib therapy. The preoperative NLR in the peripheral blood was calculated. Univariate and multivariate Cox proportional hazard regression models were used to identify potential predictors of tumor outcomes.

The NLR cut-off value of 4.18 was selected. Multivariate analysis revealed that high NLR was associated with a unfavorable prognosis of GISTs ($P < .05$). Tumor size, tumor location, and age were significantly correlated with the NLR ($P < .05$).

High NLR was an unfavorable prognostic factor of overall survival in GISTs and may be a useful preoperative biomarker of the prognosis of GISTs.

Abbreviations: GISTs = gastrointestinal stromal tumors, NIH = National Institutes of Health, NLR = neutrophil-lymphocyte ratio, ROC = receiver operating characteristic.

Keywords: biomarker, GIST, neutrophil-to-lymphocyte ratio, overall survival, prognosis, surgery

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal malignancies,^[1] arising from the pacemaker cells of the interstitial cells of Cajal in the gastrointestinal (GI) tract, of which incidence represent approximately 1% to 2% of all GI tumors.^[2,3] GISTs may occur at any site of the alimentary tract and occasionally may be found outside the GI tract. They are seen most commonly primarily in the stomach (50%–60%), followed by small intestine (30%–35%), and colon, rectum and esophagus.^[4–6] Majority of GISTs exist a functional mutation in the KIT (CD117) or PDGFRFA proto-oncogene.^[7,8] These mutations result in the constitutive activation of tyrosine kinase and lay the

foundation for targeted molecular therapy. Hence, with the progress of tyrosine kinase inhibitor imatinib mesylate in clinic use, prognosis has significantly been improved in GISTs.^[9–11] However, estimating of tumor prognosis is of great clinical impact in the management of GIST, because in the era of imatinib treatment, the accurate assessment for tumor prognosis is important to select the optimal patients for adjuvant therapy.

The standard treatment of primary localized GIST is complete operative resection with clear margins, without the dissection of clinically negative lymph nodes.^[12,13] Nonetheless, the risk of recurrence remains, even after complete macroscopic and microscopic clearance.^[14] At present, the prognostic factors of GIST have been well-established, and some specific parameters were reported as prognostic factors for GISTs such as tumor location,^[15] tumor size,^[15] tumor rupture,^[16] tumor necrosis,^[15] mitotic rate,^[17] Ki-67,^[18] gene mutations,^[19] and so on.

It is now widely recognized that systemic inflammation and immune response is closely related to tumor prognosis and metastasis.^[20] One of the most widely studied inflammatory biomarkers in the last few years is the neutrophil-lymphocyte ratio (NLR), which is an accessible, reproducible, and inexpensive indicator that can be used to detect systemic inflammation.^[21,22] It was reported that elevated NLR was an adverse prognostic factor in various types of tumor, such as colorectal,^[23] lung,^[24] pancreatic,^[25] ovarian,^[25] and liver cancers.^[26] However, some studies for investigations on the prognostic ability of NLR for surgically resected primary localized GIST are limited. The relationship between elevated NLR and worse outcomes in GISTs is complex and remains unclear.

In this study, we firstly aimed to investigate whether NLR associates with survival outcomes in GIST patients. Secondly, we evaluated whether NLR can be used as a valuable biomarker to improve the accuracy of prognosis.

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2. Patients and methods

2.1. Study population

A total of 72 GIST patients who underwent curative surgery at the Clinical Center of General Surgery, Gansu Provincial Hospital, between January 2014 and July 2017 were retrospectively reviewed. All patients suffered from histopathologic diagnosis confirmed GIST. The exclusion criteria were listed as follows: patients with non-GIST synchronous malignant tumors; a change in diagnosis based on final immunohistochemistry and genetic test results; incomplete data of blood values; patients who had received preoperative imatinib therapy; without R0 resection; with definitive distant metastasis; and factors potentially influencing the NLR, such as infection and leukocytosis. Figure 1 is a flowchart of the patients' selection in the present study. This study was approved by the Ethics Committee of Gansu Provincial Hospital (No.16GSSY6-10).

2.2. Data acquisition

Data were collected from medical case notes for individual patients, electronic patient records, and pathology reports. Clinicopathological data including gender, age, tumor location, tumor size, mitotic rate, intratumoral hemorrhage, intratumoral necrosis, National Institutes of Health (NIH) risk category, and imatinib intervention period were recorded. Peripheral blood samples were obtained from each patient in the early morning within 7 days before surgery. The NLR was calculated as the absolute count of neutrophils divided by the absolute count of lymphocytes. Low- and high-NLR values were determined using receiver operating characteristic (ROC) curve. Specimens were fixed in 10% neutral formalin immediately after resection and embedded routinely for histologic examination. Histological type and mitotic rate were detected by hematoxylin and eosin stain. Immunohistochemistry was performed using the standard protocols, including CD117, CD34, and DOG-1 antibodies.^[27]

The patients after operation were followed-up through laboratory and computed tomography (CT) examination every 3 months within the first 3 years to evaluate tumor recurrence and distant metastasis. Overall survival (OS) was defined as the time from operation resection to the time of the last follow up visit or the date of death.

2.3. Statistical analysis

All the statistical analyses and graphics were performed with the SPSS 15.0 statistical software (IBM, New York). Optimal NLR cut-off value was defined that maximized the Youden Index in a ROC analysis. Associations between the NLR and clinicopathological features were assessed by χ^2 test and Fisher's exact test, which were used to analyze continuous and categorical variables. An initial assessment of predictors was performed using univariate analysis and only those variables with significance or clinical implications were included in the multivariate analysis. Evaluation for OS was obtained by the Kaplan–Meier method and log-rank test. Data were expressed by hazard ratio and 95% confidence intervals. The *P* values were considered to be statistically significant at *P* < .05.

3. Results

3.1. NLR cut-off value

The median NLR in 72 patients with GIST was 2.49. We used the continuous variable NLR as the test variable, and OS as the state variable. The area under the ROC curve of NLR was 0.651 (Fig. 2). For all of the GIST patients, NLR=4.18 had a maximizing the Youden index, which was equivalent to highest sensitivity (71.4%) and specificity (75.4%).

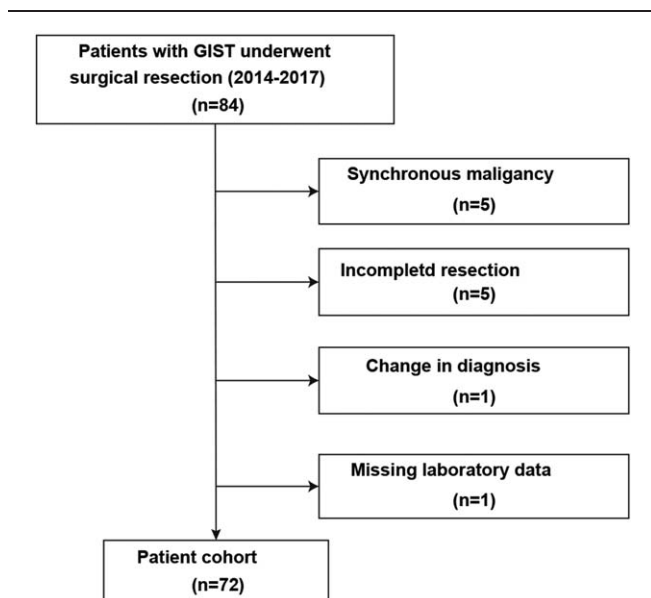


Figure 1. Selection of patients included in the statistical analysis.

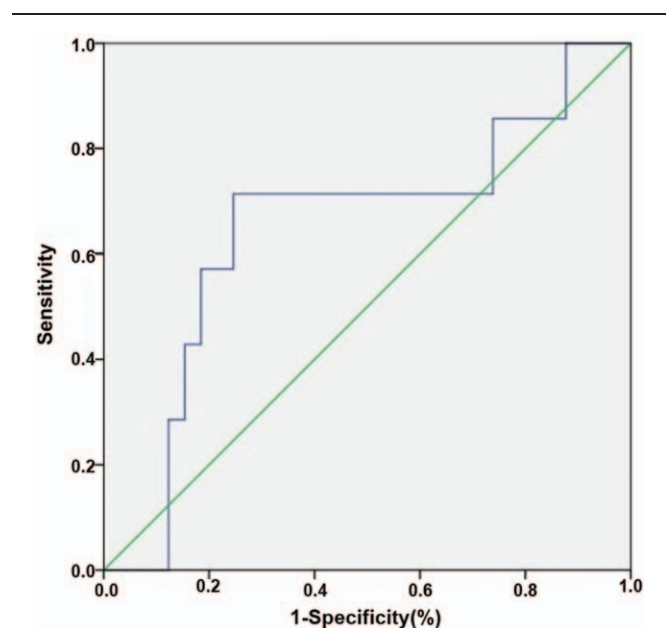


Figure 2. ROC curves for NLR to predict OS. A receiver-operating characteristic graph was constructed to estimate the optimal cut-off value. The green line represents the reference line. The blue line represents NLR. NLR=neutrophil-lymphocyte ratio, OS=overall survival, ROC=receiver operating characteristic.

3.2. Patient characteristics

There were 43 males (59.7%) and 29 females (40.3%). The median age of the 72 patients was 56 years (range: 28–74). The median tumor size was 60 mm (range: 5–250), and the mitotic rate of 45 patients exceeded 5/50 high power field (HPF) (62.5%). The most common primary tumor site was stomach (56.9%; 41/72), followed by mesenterium (11.1%; 8/72), colorectum (9.7%; 7/72), small intestine (9.7%; 7/72), duodenum (4.2%, 3/72), and extragastrointestinal sites (8.3%; 6/72). The median follow-up time of all patients was 20 months (range: 6–46). Two patients showed recurrence or metastasis; 7 patients suffered from GIST related deaths. The 1- and 3-year survival rate of OS was 95.4% and 85.5%, respectively. cKIT immunohistochemistry positivity was present in 62 patients (86.1%). Twenty-three patients (31.9%) had undergone adjuvant imatinib therapy.

All patient demographics and clinicopathologic features with a low NLR (< 4.18) and those with a high (≥4.18) NLR were comparable (Table 1). Tumors with high NLR were significantly likely to be in over 50 year old patients ($P=.04$). Significantly more patients in the high NLR group (76.2%) had a tumor size exceeding 50 mm than in the low NLR group (45.1%) ($P=.02$). The patients with high NLR were non-gastric in location than the patients with low NLR ($P=.01$). Further subgroup analysis revealed that GIST patients with high NLR was more likely to be the small intestine and others (including 8 in mesenterium, 4 in omentum, 1 in pelvic and 1 in unknown location) in nongastric location. In contrast, gender, mitotic rate, intratumoral

hemorrhage, intratumoral necrosis, NIH risk category were not significantly correlated with the NLR.

3.3. Survival analysis

High NLR group was significantly associated with shorter overall survival, although the median OS was not reached in these patients ($P<.05$; Fig. 3). The patients were divided into 4subgroups and analyzed: high NIH risk group; without received imatinib treatment group; tumor size exceeding 50 mm group; mitotic rate exceeding 5/50 HPF group. In the mitotic rate exceeding 5/50 HPF group, the elevated NLR suggested shorter OS ($P=.02$; Fig. 4). Moreover, there is a tendency that increased level NLR is unfavorable to OS in high NIH risk group ($P=.89$; Fig. 5), without received imatinib treatment group ($P=.15$; Fig. 6), and tumor size exceeding 50 mm group, respectively ($P=.35$; Fig. 7). In addition, the numbers of patients in the low and intermediate NIH risk groups, received imatinib treatment group, tumor size <50 mm group, and mitotic rate <5/50 HPF group were not adequate for Kaplan–Meier survival analysis.

3.4. Predictors of survival with GIST patients

Univariate and multivariate logistic regression analysis for predictors associated with GISTs are presented in Table 2. Univariate and multivariate analyses showed that NLR was the only significant independent prognostic indicator for survival. Elevated NLR was detected as an independent adverse prognostic factor.

Table 1
Relationship between clinicopathological features of GIST patients and preoperative NLR.

Variables	Patients (n)	Low NLR (%) n=51	High NLR (%) n=21	P-value
Gender				.81
Male	43	30 (58.8)	13 (61.9)	
Female	29	21 (41.2)	8 (38.1)	
Age, years				.04
≤50	25	22 (43.1)	3 (14.3)	
>50	47	29 (56.9)	18 (85.7)	
Tumor size, cm				.02
≤5	33	28 (54.9)	5 (23.8)	
>5	39	23 (45.1)	16 (76.2)	
Tumor location				.01
Stomach	41	33 (64.7)	8 (38.1)	
Duodenum	3	2 (3.9)	1 (4.8)	
Small intestine	7	2 (3.9)	5 (23.8)	
Colorectum	7	7 (13.7)	0 (0.0)	
Others	14	7 (13.7)	7 (33.3)	
Mitotic index (per 50 HPFs)				.95
≤5	27	19 (37.3)	8 (38.1)	
>5	45	32 (62.7)	13 (61.9)	
Intratumoral hemorrhage				.15
Yes	22	13 (25.5)	9 (42.9)	
No	50	38 (74.5)	12 (57.1)	
Intratumoral necrosis				.55
Yes	27	18 (35.3)	9 (42.9)	
No	45	33 (64.7)	12 (57.1)	
NIH risk category				.17
Very low and low	17	13 (25.5)	4 (19.0)	
Intermediate	11	10 (19.6)	1 (4.8)	
High	44	28 (54.9)	16 (76.2)	

GIST = gastrointestinal stromal tumor, HPFs = high-power fields, NIH = National Institutes of Health, NLR = neutrophil-to-lymphocyte ratio.

4. Discussion

The introduction of targeted therapies based on advances in both biology and pathogenesis of GISTs has revolutionized GIST patients' outcome. Surgical resection remains the primary treatment modality for primary localized GISTs; however, despite improvement in prognosis, there remains a high recurrence rate postoperatively.^[14,28] Several studies have investigated the contribution of prognostic factors in predicting

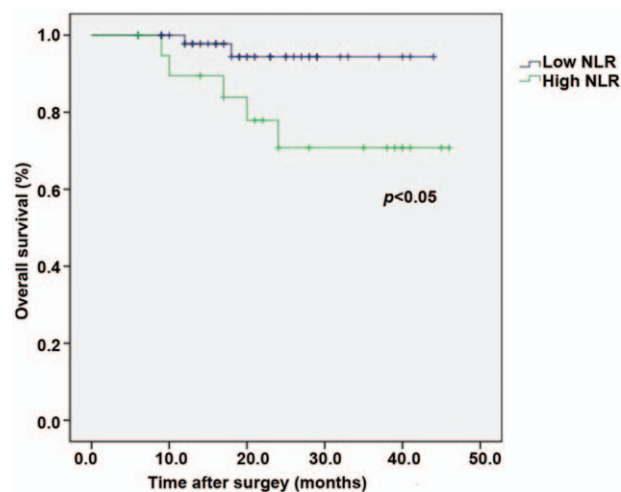


Figure 3. Overall survival (OS) of GIST patients classified by NLR. Kaplan–Meier estimate of the censoring time distribution in 72 GIST patients. The P-value was calculated by using the log-rank test. GISTs = gastrointestinal stromal tumors, NLR = neutrophil-lymphocyte ratio, OS = overall survival.

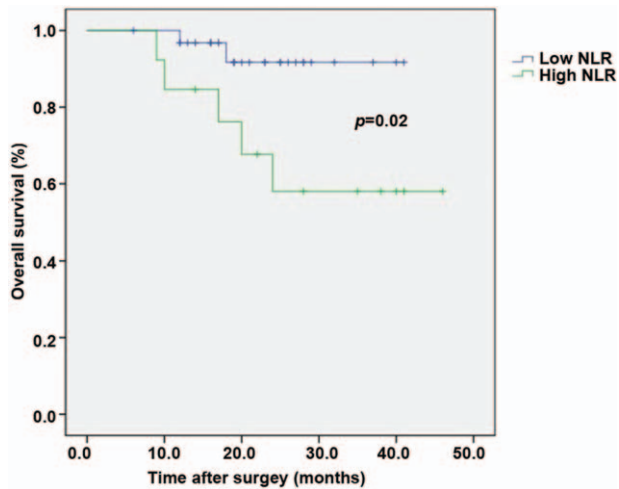


Figure 4. OS of mitotic rate over 5/50 HPF GIST patients classified by NLR. In the study of 45 GIST patients with mitotic rate exceeding 5/50 HPF, elevated NLR suggested shorter OS. GISTs=gastrointestinal stromal tumors, HPF=high-power field, NLR=neutrophil-lymphocyte ratio, OS=overall survival.

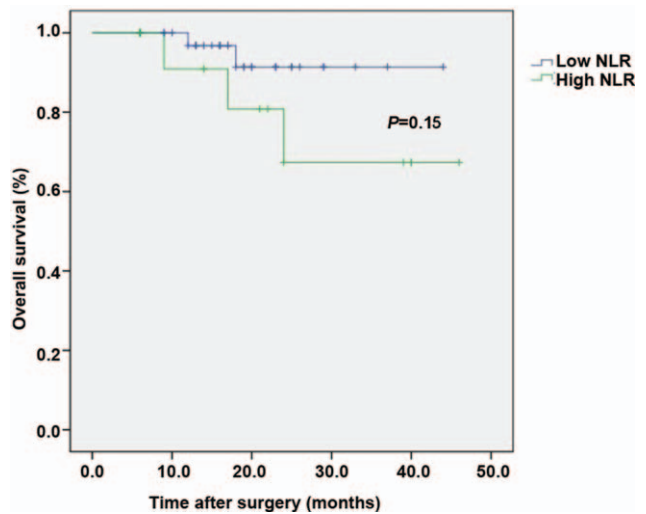


Figure 6. OS of GIST patients without receive imatinib treatment classified by NLR. In the subgroup analysis of 49 patients who did not receive imatinib treatment, a tendency showed that an increased NLR was inimical to OS. GISTs=gastrointestinal stromal tumors, NLR=neutrophil-lymphocyte ratio, OS=overall survival.

disease recurrence so that it can provide clinicians with better guide decisions and surveillance protocols regarding individualized treatment of patients. Currently, the NIH tumor size and tumor risk category are used as independent prognostic criteria.^[29,30] However, clinicians can only roughly assess risk stratification according to the tumor size before operation; therefore, the addition of novel variables may improve the accuracy of predicting prognosis, which will lead in turn to improved treatment strategies and patient outcomes.

Previous studies have well demonstrated the prognostic ability of NLR for various malignancies. In this study, we observed the prognostic impact of NLR in 72 patients undergoing surgical treatment for primary GIST. It is interesting that diverse cut-off NLRs for GISTs were reported. Feng et al^[31] chose the sample median NLR as a cut-off value. We used ROC to determine the

optimal cut-off value, as this method has been commonly used in the literature to study indicators of the systemic inflammatory response.

The recently published study by Rutkowski et al^[32] reported on the association between NLR and OS for 385 patients with metastatic/unresectable GIST treated initially with imatinib between 2001 and 2016. In their series, elevated NLR was significantly associated with poorer OS. The authors concluded that the usefulness of NLR as a prognostic and predictive marker as well as marker for treatment monitoring in patients with advanced GIST treated with imatinib. In their study, patients had advanced stage disease and high risk of recurrence. However, our work included patients with various malignant potential. We

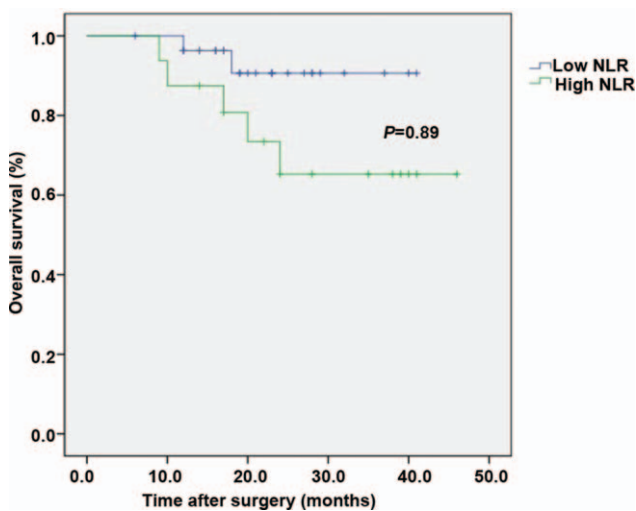


Figure 5. OS of GIST patients in high NIH risk classified by NLR. In the patients with high NIH risk, a tendency showed that an increased NLR was unfavorable to OS. GISTs=gastrointestinal stromal tumors, NIH=National Institutes of Health, NLR=neutrophil-lymphocyte ratio, OS=overall survival.

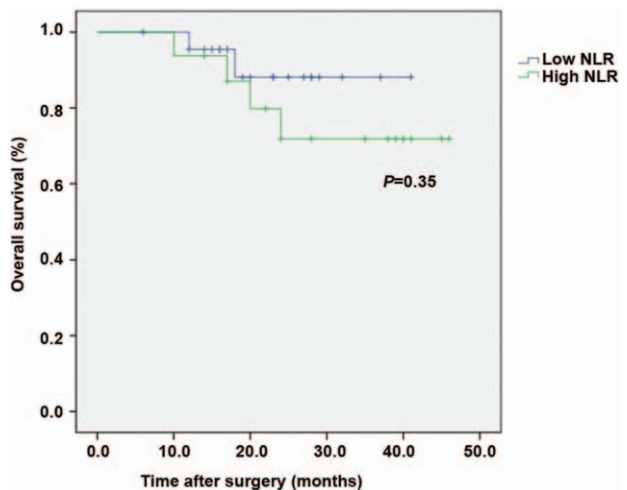


Figure 7. OS of GIST patients in tumor size exceeding 50mm classified by NLR. In the patients with tumor size over 50mm, a tendency showed that an increased NLR was unfavorable to OS. GISTs=gastrointestinal stromal tumors, HPF=high-power field, NLR=neutrophil-lymphocyte ratio, OS=overall survival.

Table 2
Cox regression analysis for overall survival.

Variables	Univariate	Multivariate		
	P-value	HR	95%CI	P-value
NLR	.027	0.189	0.036–0.983	.048
Low				
High				
Tumor size, cm	.505	—	—	—
≤5				
>5				
Tumor location	.810	—	—	—
Gastric				
Extra-gastric				
Mitotic rate (per 50 HPFs)	.054	—	—	—
≤5				
>5				
Intratatumoral hemorrhage	.934	—	—	—
Yes				
No				
Intratatumoral necrosis	.078	—	—	—
Yes				
No				
NIH risk category	.476	—	—	—
Very low and low				
Intermediate				
High				
Adjuvant imatinib therapy	.500	—	—	—
Yes				
No				

CI=confidence interval, HPFs=high-power fields, HR=hazard ratio, NIH=National Institutes of Health, NLR=neutrophil-to-lymphocyte ratio.

discovered that higher NLR was associated with larger tumor size, increased incidence of nongastric tumor and older age. Our data are consistent with the fact that increased NLR was associated with tumor features.^[33]

The exact mechanisms of the prognostic impact of NLR in GISTs are unclear. It has been suggested that cross-talk exists between the inflammatory response and tumor progression.^[20,34] In addition, high neutrophil counts inhibit the immune system via restraining the cytolytic activity of immune cells such as lymphocytes, activated T cells, and natural killer cells.^[35] Lymphocytes play a critical role in the cell-mediated antitumor immune response. The lymphocyte count reflects the degree of responsiveness of the immune system of the host^[36,37] Taken together, elevated NLR indicates a relative increased neutrophil and decreased lymphocyte, breaking the balance in favor of pro-tumor inflammatory status, and generating poor outcome of patients with GISTs. Our study demonstrated that NLR was a significant independent prognostic indicator for OS in surgically resected primary GIST via multivariate analyses (odds ratio, 0.19; 95% confidence interval, 0.04–0.98; $P=.048$). In addition, subgroup analyses found that a significant association between elevated NLR and shorter OS within greater mitotic count GIST patients. This means a high NLR provides important prognostic information before operation, which would be especially important in the preoperative assessment of patients. As a convenient and inexpensive biomarker, NLR might be combined with current prognostic factors in order to forecast the therapeutic effect and prognosis in GIST, and incorporated into routine clinical practice.

This study had several limitations. It was a retrospective and nonrandomized study of a single center’s experience. A small

sample size might have led to the failure of the traditionally considered prognostic factors such as tumor size, location, and mitotic rate. Given the relatively short follow-up duration in our study, median survival was not achieved. In addition, according to the National Comprehensive Cancer Network (NCCN) guideline, adjuvant imatinib therapy prolongs RFS and may improve OS.^[38] However, in our clinical practice, only 23 patients (31.9%) were treated with imatinib adjuvant therapy. The main reasons maybe the lack of medical insurance coverage in Gansu province between 2014 and 2017 and the inability of most patients to afford expensive drugs. So, not all patients eligible for imatinib treatment received imatinib or were treated with a standard course. This may affect the prognostic ability of imatinib on GISTs.

5. Conclusion

The NLR is an independent factor associated with adverse survival in GIST and may serve as a valuable prognostic biomarker for patients with primary and localized GIST. The NLR could contribute to treatment decision making early and supplement existing tools to improve the accuracy of prognosis. Large scale prospective studies are needed to confirm the usefulness of NLR in improving current risk-stratification systems for GIST.

Author contributions

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Writing – review & editing: JiaYu Xu, Yan Zhang.

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