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# Combination of PLR, MLR, MWR, and Tumor Size Could Significantly Increase the Prognostic Value for Gastrointestinal Stromal Tumors

*Fan Feng, PhD, Yangzi Tian, MD, Shushang Liu, MM, Gaozan Zheng, MM, Zhen Liu, MM, Guanghui Xu, MM, Man Guo, BM, Xiao Lian, MStat, Daiming Fan, PhD, and Hongwei Zhang, PhD*

**Abstract:** Systemic inflammation and immune response were associated with prognosis of tumors. However, data was limited due to the relatively low incidence of gastrointestinal stromal tumors (GISTs). The aim of the present study was to investigate the predictive value of preoperative peripheral blood cells in prognosis of GISTs.

From September 2008 to July 2015, a total of 274 GIST patients in our department were enrolled in the present study. Clinicopathological features of GISTs were recorded. The association between preoperative peripheral blood cells and prognosis of GISTs were analyzed.

Tumor location, tumor size, mitotic index, intratumoral necrosis, and National Institutes of Health (NIH) risk category were associated with prognosis of GISTs. High neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-white blood cell ratio (NWR), monocyte-to-white blood cell ratio (MWR) and low lymphocyte-to-white blood cell ratio (LWR) was associated with poor prognosis of GISTs (76.2% vs 83.7%, $P = 0.010$. 70.5% vs 98.7%, $P = 0.000$. 65.7% vs 96.4%, $P = 0.004$. 78.5% vs 82.5%, $P = 0.044$. 73.5% vs 97.8%, $P = 0.004$. 76.6% vs 83.6%, $P = 0.012$, respectively). However, tumor size was the only independent risk factor for prognosis according to multivariate analysis ($P = 0.006$). Tumor location, tumor size, mitotic index, and NIH risk category were significantly correlated with the above-mentioned parameters (all $P < 0.05$). The prognosis of GISTs with tumor size >5 cm, high MLR, high PLR, and high MWR was significantly lower than the remnant patients ($P = 0.010$).

The peripheral blood routine test is convenient, reproducible, and inexpensive. High NLR, MLR, PLR, NWR, MWR, and low LWR were associated with poor prognosis of GISTs. The association between the above parameters and prognosis of GISTs may be attributed to their correlation with tumor size, mitotic index, and NIH risk category. The combination of tumor size, MLR, PLR, and MWR could further increase the predictive value of prognosis of GISTs.

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From the Department of Digestive Surgery (FF, SL, GZ, ZL, GX, MG, XL, DF, HZ), Xijing Hospital, Fourth Military Medical University; and Department of Dermatology (YT), Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, China.
Correspondence: Hongwei Zhang, Department of Digestive Surgery, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, China (e-mail: zhanghwfmmu@126.com).
FF, YT, and SL contributed equally to this study.
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**Abbreviations**: CI = confidence interval, CT = computed tomography, DFS = disease-free survival, DOG-1 = discovered on GIST 1, EUS = endoscopic ultrasound, GI = gastrointestinal, GIST = gastrointestinal stromal tumor, HPF = high power field, ICC = interstitial cells of Cajal, LWR = lymphocyte-to-white blood cell ratio, MLR = monocyte-to-lymphocyte ratio, MWR = monocyte-to-white blood cell ratio, NIH = National Institutes of Health, NK = natural killer, NLR = neutrophil-to-lymphocyte ratio, NWR = neutrophil-to-white blood cell ratio, PLR = platelet-to-lymphocyte ratio, PWR = platelet-to-white blood cell ratio.

## INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract and represent 1% to 2% of all GI tumors.[1] GISTs are considered to arise from the interstitial cells of Cajal (ICC), the pacemaker cells of the GI tract.[2] GISTs can occur anywhere throughout the GI tract and are seen most commonly in the stomach (40–70%), followed by small intestine (20–40%), and colon and rectum (5–15%).[3] Many clinicopathological features were reported as prognostic factors for GISTs, including tumor location,[4] tumor size, mitotic index,[5] Ki-67,[6] histological types,[7] gene mutations,[8] and so on. However, only tumor size and mitotic index are the best prognostic indicators for determining the malignant potential of GISTs.[9]

Recently, it has been demonstrated that systemic inflammation could promote tumor progression and metastasis by inhibition of apoptosis and promotion of angiogenesis.[10] The neutrophil-to-lymphocyte ratio (NLR) is one of the systemic inflammation markers, and it was reported that high level of NLR was associated with poor prognosis of various tumors.[11] However, investigations on the prognostic value of NLR for GISTs are limited and the results are controversial.[12–16]

The immune response is also an important prognostic factor for GISTs. Natural killer (NK) cells expression of NKp30c isoform[17] and low secretion of interferon-γ by peripheral NK cells[18] both correlated with poor prognosis of GISTs. $CD3^+$ tumor infiltrating lymphocytes were found to be highly activated in GISTs and high density of these cells were associated with a reduced relapse rate.[19] However, the role of preoperative peripheral blood lymphocyte rate in the prognosis of GISTs has not been investigated until now.

Given this situation, we attempted to investigate the association between preoperative peripheral blood cells and prognosis of GISTs.

## METHODS

This study was performed in the Xijing Hospital of Digestive Diseases affiliated to the Fourth Military Medical

**TABLE 1.** Prognostic Factors for DFS in GIST Patients According to Univariate Analysis

| Prognostic Factors | β | Hazard Ratio (95% CI) | *P* Value |
|---|---|---|---|
| Age (≤60/ > 60) | −0.268 | 0.765 (0.301–1.943) | 0.573 |
| Gender (M/F) | −0.717 | 0.488 (0.185–1.286) | 0.147 |
| Location (gastric/ non-gastric) | −1.123 | 0.325 (0.132–0.801) | 0.015 |
| Tumor size (2/5/10) | 2.333 | 10.313 (4.453–23.883) | 0.000 |
| Mitotic index (≤5/ > 5) | 2.348 | 10.464 (2.399–45.647) | 0.002 |
| Histological type | 0.224 | 1.251 (0.451–3.471) | 0.668 |
| Intratumoral hemorrhage | 0.856 | 2.354 (0.767–7.225) | 0.135 |
| Intratumoral necrosis | 1.601 | 4.958 (1.944–12.643) | 0.001 |
| NIH risk category | 2.694 | 14.785 (2.318–94.323) | 0.004 |
| NLR | 1.263 | 3.535 (1.270–9.838) | 0.016 |
| MLR | 2.113 | 8.270 (1.904–35.919) | 0.005 |
| PLR | 1.494 | 4.454 (1.476–13.440) | 0.008 |
| NWR | 0.975 | 2.652 (1.007–6.989) | 0.048 |
| LWR | −1.223 | 0.294 (0.106–0.820) | 0.019 |
| MWR | 1.883 | 6.576 (1.510–28.642) | 0.012 |
| PWR | 0.396 | 1.487 (0.597–3.700) | 0.394 |

CI = confidence interval, DFS = disease-free survival, GIST = gastrointestinal stromal tumor, LWR = lymphocyte-to-white blood cell ratio, MLR = monocyte-to-lymphocyte ratio, MWR = monocyte-to-white blood cell ratio, NIH = National Institutes of Health, NLR = neutrophil-to-lymphocyte ratio, NWR = neutrophil-to-white blood cell ratio, PLR = platelet-to-lymphocyte ratio, PWR = platelet-to-white blood cell ratio.

**TABLE 2.** Prognostic Factors for DFS in GIST Patients According to Multivariate Analysis

| Prognostic Factors | β | Hazard Ratio (95% CI) | *P* Value |
|---|---|---|---|
| Tumor size (2/5/10) | 1.579 | 4.850 (1.581–14.876) | 0.006 |
| Mitotic index (≤5/ > 5) | 0.792 | 2.208 (0.325–15.008) | 0.418 |
| Intratumoral necrosis | 0.311 | 1.364 (0.406–4.581) | 0.615 |
| NIH risk category | 0.768 | 2.155 (0.185–25.148) | 0.540 |
| NLR | 4.389 | 80.593 (0.000–8.244 × $10^7$) | 0.534 |
| MLR | 1.109 | 3.030 (0.280–32.785) | 0.362 |
| PLR | 0.327 | 1.387 (0.330–5.832) | 0.655 |
| NWR | −0.254 | 0.776 (0.078–7.762) | 0.829 |
| LWR | 3.572 | 35.591 (0.000–3.408 × $10^7$) | 0.611 |
| MWR | 0.662 | 1.939 (0.360–10.454) | 0.441 |

CI = confidence interval, DFS = disease-free survival, GIST = gastrointestinal stromal tumor, LWR = lymphocyte-to-white blood cell ratio, MLR = monocyte-to-lymphocyte ratio, MWR = monocyte-to-white blood cell ratio, NIH = National Institutes of Health, NLR = neutrophil-to-lymphocyte ratio, NWR = neutrophil-to-white blood cell ratio, PLR = platelet-to-lymphocyte ratio.

University. From September 2008 to July 2015, a total of 274 GIST patients in our department were enrolled in the present study. The inclusion criteria were listed as follows: (1) without other malignant tumor, (2) without distant metastasis, (3) without preoperative imatinib therapy, (4) with R0 resection, (5) without signs of infection. This study was approved by the Ethics Committee of Xijing Hospital, and written informed consent was obtained from all patients before surgery.

All the preoperative peripheral blood routine tests were performed within 7 days before surgery. The Blood NLR value was calculated as neutrophil count (number of neutrophils/μL) divided by the lymphocyte count (number of lymphocytes/μL). Low and high NLR values were defined with respect to sample median. The value of monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-white blood cell ratio (NWR), lymphocyte-to-white blood cell ratio (LWR), monocyte-to-white blood cell ratio (MWR), and platelet-to-white blood cell ratio (PWR) were calculated same as NLR.

Specimens were fixed in 10% neutral formalin immediately after resection and embedded routinely for histologic examination. Histological type and mitotic index were detected

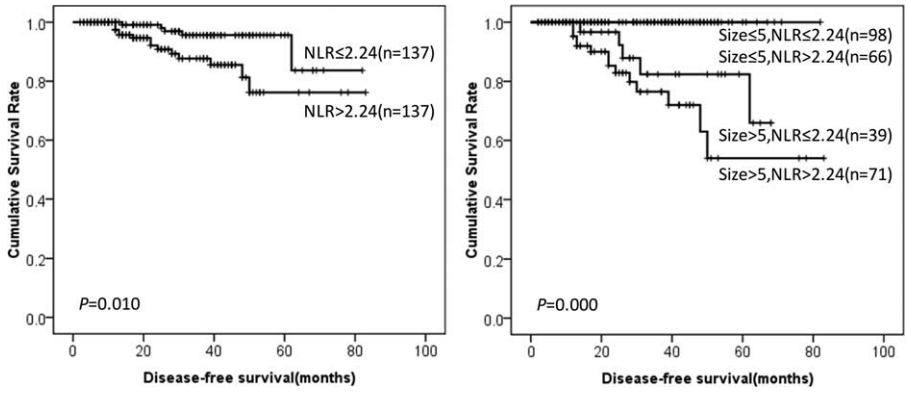


**FIGURE 1.** DFS of GIST patients according to NLR and tumor size. DFS = disease-free survival, GIST = gastrointestinal stromal tumor, NLR = neutrophil-to-lymphocyte ratio.

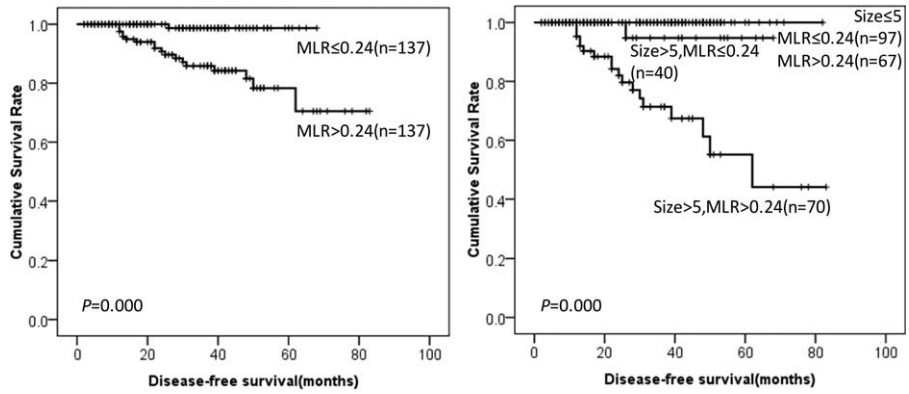


**FIGURE 2.** DFS = disease-free survival, GIST = gastrointestinal stromal tumor, MLR = monocyte-to-lymphocyte ratio.

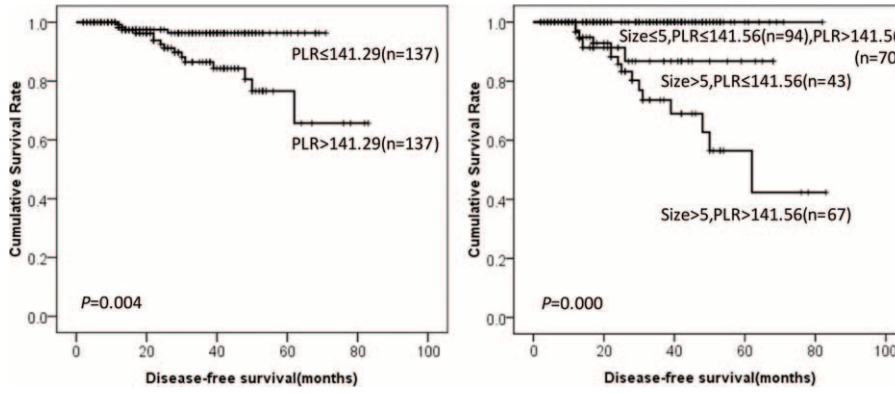


**FIGURE 3.** DFS of GIST patients according to PLR and tumor size. DFS = disease-free survival, GIST = gastrointestinal stromal tumor, PLR = platelet-to-lymphocyte ratio.

by hematoxylin and eosin stain. Immunohistochemistry was performed using the following antibodies: CD117, CD34, and DOG-1 (discovered on GIST 1).

Clinicopathological data including gender, age, blood routine test, location of tumor, tumor size, mitotic index, histological type, intratumoral hemorrhage, intratumoral necrosis, and National Institutes of Health (NIH) risk category were collected. The patients after resection were followed up through endoscopic ultrasound (EUS) and computed tomography (CT) every 6 months to evaluate tumor recurrence and distant metastasis.

Data were processed using SPSS 22.0 for Windows (SPSS Inc, Chicago, IL). Discrete variables were analyzed using the Chi-square test or Fisher's exact test. Significant predictors for

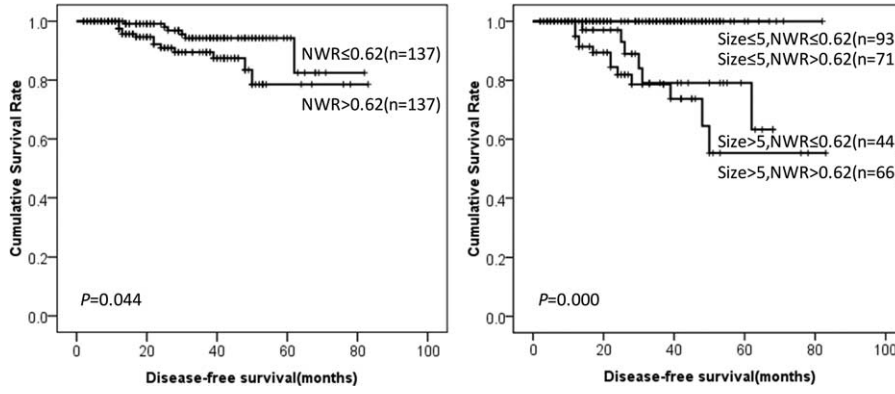


**FIGURE 4.** DFS of GIST patients according to NWR and tumor size. DFS = disease-free survival, GIST = gastrointestinal stromal tumor, NWR = neutrophil-to-white blood cell ratio.

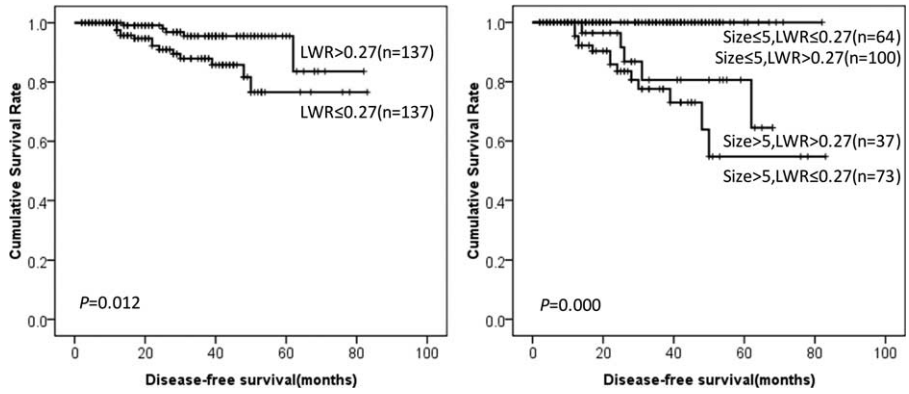


**FIGURE 5.** DFS = disease-free survival, GIST = gastrointestinal stromal tumor, LWR = lymphocyte-to-white blood cell ratio.

survival identified by univariate analysis were further assessed by multivariate analysis using logistic regression analysis. Evaluation for disease-free survival (DFS) was obtained by the Kaplan–Meier method. The *P* values were considered to be statistically significant at 5% level.

## RESULTS

There were 138 male (50.4%) and 136 female (49.6%). The patient age ranged from 19 to 86 years (median, 56 years; mean, 56.6 years). The most common location was stomach (71.2%), followed by small intestine (16.4%), duodenum (4.4%), colorectum (1.8%), esophagus (1.5%), and extra-gastrointestinal sites (4.7%). The tumors ranged from 0.3 to 30 cm in maximum diameter (median, 4.5 cm; mean, 5.5 cm). The mitotic index of 124 patients exceeded 5/50 high power field (HPF) (45.3%). According to NIH risk classification, 50 patients were classified as very low risk (18.2%), 74 patients were classified as low risk (27.1%), 51 patients were classified as intermediate risk (18.6%), and 99 patients were classified as high risk (36.1%). The follow up time ranged from 2 to 83 months (mean, 31.6 months; median, 30.0 months). Nineteen patients showed recurrence or metastasis; 8 patients suffered from GIST related deaths. The 1-, 3- and 5-year survival rate of DFS was 98.7%, 91.8% and 80.2%, respectively.

Prognostic factors for DFS in GIST patients according to univariate analysis were summarized in Table 1. The results showed that location, tumor size, mitotic index, intratumoral necrosis, NIH risk category, NLR, MLR, PLR, NWR, LWR, and MWR were associated with prognosis of GIST patients. It was worth mentioning that high NLR, MLR, PLR, NWR, and MWR were associated with poor prognosis of GISTs (76.2% vs 83.7%, $P = 0.010$. 70.5% vs 98.7%, $P = 0.000$. 65.7% vs 96.4%, $P = 0.004$. 78.5% vs 82.5%, $P = 0.044$. 73.5% vs 97.8%, $P = 0.004$, respectively). However, low LWR was associated with poor prognosis of GISTs (76.6% vs 83.6%, $P = 0.012$). Tumor size was the only independent risk factor for prognosis according to multivariate analysis (Table 2). The DFS of GISTs according to NLR, MLR, PLR, NWR, LWR, MWR, and tumor size were shown in Figures 1–6, respectively.

The clinicopathological features between high and low group of NLR, MLR, PLR, NWR, LWR, and MWR were analyzed and summarized in Tables 3–8, respectively. The results showed that location, tumor size, mitotic index, and NIH risk category were significantly correlated with the above-mentioned parameters (all $P < 0.05$). This indicated that the correlation between the above parameters and prognosis may be attributed to their correlation with tumor size, mitotic index, and NIH risk category.

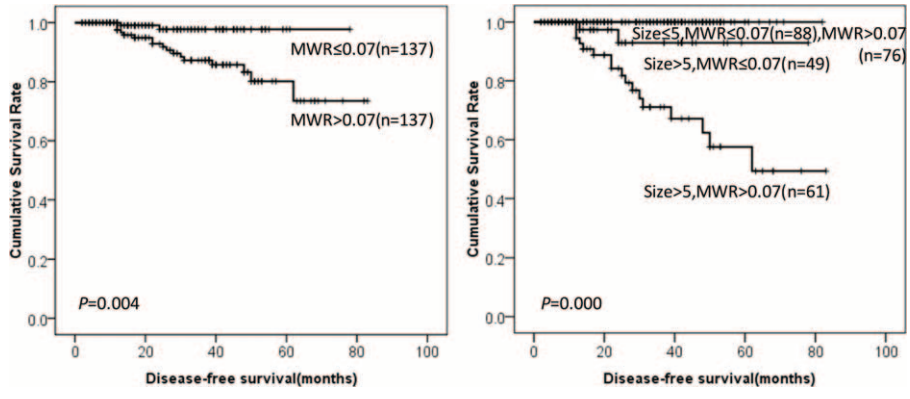


**FIGURE 6.** DFS of GIST patients according to MWR and tumor size. DFS = disease-free survival, GIST = gastrointestinal stromal tumor, MWR = monocyte-to-white blood cell ratio.

**TABLE 3.** Clinicopathological Features of GIST Patients Stratified by Preoperative NLR

| Characteristics | Low NLR (≤2.24) | High NLR (>2.24) | *P* Value |
|---|---|---|---|
| Age | | | 0.265 |
| ≤60 | 88 | 79 | |
| >60 | 49 | 58 | |
| Gender | | | 0.091 |
| Male | 62 | 76 | |
| Female | 75 | 61 | |
| Location | | | 0.011 |
| Gastric | 107 | 88 | |
| Extra-gastric | 30 | 49 | |
| Tumor size | | | 0.000 |
| ≤2cm | 46 | 13 | |
| 2.1–5 cm | 52 | 53 | |
| 5.1–10 cm | 27 | 49 | |
| >10 cm | 12 | 22 | |
| Mitotic index | | | 0.002 |
| ≤5 | 88 | 62 | |
| >5 | 49 | 75 | |
| Histological type | | | 0.259 |
| Spindle | 131 | 126 | |
| Epithelioid | 0 | 2 | |
| Mixed | 6 | 9 | |
| Intratumoral hemorrhage | | | 0.393 |
| Yes | 10 | 14 | |
| No | 127 | 123 | |
| Intratumoral necrosis | | | 0.132 |
| Yes | 12 | 20 | |
| No | 125 | 117 | |
| NIH risk category | | | <0.001 |
| Very low risk | 39 | 11 | |
| Low risk | 45 | 29 | |
| Intermediate risk | 19 | 32 | |
| High risk | 34 | 65 | |

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

**TABLE 4.** Clinicopathological Features of GIST Patients Stratified by Preoperative MLR

| Characteristics | Low MLR (≤0.24) | High MLR (>0.24) | *P* Value |
|---|---|---|---|
| Age | | | 0.386 |
| ≤60 | 87 | 80 | |
| >60 | 50 | 57 | |
| Gender | | | 0.004 |
| Male | 57 | 81 | |
| Female | 80 | 56 | |
| Location | | | 0.002 |
| Gastric | 109 | 86 | |
| Extra-gastric | 28 | 51 | |
| Tumor size | | | 0.000 |
| ≤2cm | 41 | 18 | |
| 2.1–5 cm | 56 | 49 | |
| 5.1–10 cm | 32 | 44 | |
| >10 cm | 8 | 26 | |
| Mitotic index | | | 0.015 |
| ≤5 | 85 | 65 | |
| >5 | 52 | 72 | |
| Histological type | | | 0.728 |
| Spindle | 130 | 127 | |
| Epithelioid | 1 | 1 | |
| Mixed | 6 | 9 | |
| Intratumoral hemorrhage | | | 0.522 |
| Yes | 10 | 14 | |
| No | 127 | 123 | |
| Intratumoral necrosis | | | 0.008 |
| Yes | 9 | 23 | |
| No | 128 | 114 | |
| NIH risk category | | | 0.000 |
| Very low risk | 36 | 14 | |
| Low risk | 38 | 36 | |
| Intermediate risk | 40 | 21 | |
| High risk | 33 | 66 | |

GIST = gastrointestinal stromal tumor, MLR = monocyte-to-lymphocyte ratio.

Among NLR, MLR, PLR, NWR, LWR, and MWR, the predictive values of MLR, PLR, and MWR are superior to NLR, NWR, and LWR. Furthermore, all the recurrence occurred in GIST patients with tumor size larger than 5 cm in our present study. Thus, GIST patients with tumor size >5 cm were divided into 4 groups—Group 1: low MLR, low PLR, and low MWR; Group 2: high MLR, low PLR, low MWR, or low MLR, high PLR, low MWR, or low MLR, low PLR, high MWR; Group 3: high MLR, high PLR, low MWR, or low MLR, high PLR, high MWR, or high MLR, low PLR, high MWR; Group 4: high MLR, high PLR, and high MWR. The prognosis of group 4 was significantly lower than Group 1, Group 2, and Group 3 (28.2% vs 100.0% vs 89.1% vs 86.3%, $P = 0.010$, Figure 7).

## DISCUSSION

The peripheral blood routine test is convenient, reproducible, and inexpensive. Data about the association between peripheral blood cell and prognosis of GISTs were limited and also controversial. Therefore, we evaluated the prognostic value of peripheral blood cell for GISTs. We found that high NLR, MLR, PLR, NWR, MWR, and low LWR were associated with poor prognosis of GISTs. However, none of them was an independent risk factor for prognosis of GISTs.

Peripheral blood neutrophil is one of the markers for acute and chronic inflammation.[20] For the first time, we found that high NWR was associated with poor prognosis of GISTs. The mechanism of the association between NWR and prognosis of GISTs remains unclear. It was reported that neutrophils could inhibit the immune system by suppressing the activity of NK cells, lymphocytes, and activated T cells.[21–23] On the other hand, neutrophils could promote the angiogenesis and progression of tumor by producing the vascular endothelial growth factor[24] and matrix metalloproteinase-9.[25]

Lymphocytes play critical roles in host immune response. The increased level of lymphocyte was associated with improved prognosis of a variety of tumors.[26] Rusakiewicz et al reported that high densities of $CD3^+$ tumor tissue infiltrating lymphocytes

**TABLE 5.** Clinicopathological Features of GIST Patients Stratified by Preoperative PLR

| Characteristics | Low PLR (≤141.29) | High PLR (>141.29) | *P* Value |
|---|---|---|---|
| Age | | | 0.265 |
| ≤60 | 88 | 79 | |
| >60 | 49 | 58 | |
| Gender | | | 0.334 |
| Male | 73 | 65 | |
| Female | 64 | 72 | |
| Location | | | 0.000 |
| Gastric | 20 | 59 | |
| Extra-gastric | 117 | 78 | |
| Tumor size | | | 0.000 |
| ≤2cm | 45 | 14 | |
| 2.1–5 cm | 49 | 56 | |
| 5.1–10 cm | 32 | 44 | |
| >10 cm | 11 | 23 | |
| Mitotic index | | | 0.015 |
| ≤5 | 85 | 65 | |
| >5 | 52 | 72 | |
| Histological type | | | 0.728 |
| Spindle | 130 | 127 | |
| Epithelioid | 1 | 1 | |
| Mixed | 6 | 9 | |
| Intratumoral hemorrhage | | | 0.393 |
| Yes | 10 | 14 | |
| No | 127 | 123 | |
| Intratumoral necrosis | | | 0.003 |
| Yes | 8 | 24 | |
| No | 129 | 113 | |
| NIH risk category | | | 0.000 |
| Very low risk | 38 | 12 | |
| Low risk | 40 | 34 | |
| Intermediate risk | 23 | 28 | |
| High risk | 36 | 63 | |

GIST = gastrointestinal stromal tumor, PLR = platelet-to-lymphocyte ratio.

**TABLE 6.** Clinicopathological Features of GIST Patients Stratified by Preoperative NWR

| Characteristics | Low NWR (≤0.62) | High NWR (>0.62) | *P* Value |
|---|---|---|---|
| Age | | | 0.265 |
| ≤60 | 88 | 79 | |
| >60 | 49 | 58 | |
| Gender | | | 0.053 |
| Male | 61 | 77 | |
| Female | 76 | 60 | |
| Location | | | 0.033 |
| Gastric | 106 | 89 | |
| Extra-gastric | 31 | 48 | |
| Tumor size | | | 0.001 |
| ≤2 cm | 43 | 16 | |
| 2.1–5 cm | 50 | 55 | |
| 5.1–10 cm | 31 | 45 | |
| >10 cm | 13 | 21 | |
| Mitotic index | | | 0.011 |
| ≤5 | 86 | 64 | |
| >5 | 51 | 73 | |
| Histological type | | | 0.350 |
| Spindle | 130 | 127 | |
| Epithelioid | 0 | 2 | |
| Mixed | 7 | 8 | |
| Intratumoral hemorrhage | | | 0.285 |
| Yes | 9 | 15 | |
| No | 128 | 122 | |
| Intratumoral necrosis | | | 0.132 |
| Yes | 12 | 20 | |
| No | 125 | 117 | |
| NIH risk category | | | 0.000 |
| Very low risk | 36 | 14 | |
| Low risk | 42 | 32 | |
| Intermediate risk | 22 | 29 | |
| High risk | 37 | 62 | |

GIST = gastrointestinal stromal tumor, NWR = neutrophil-to-white blood cell ratio.

predicted progression-free survival of GISTs.[19] However, the correlation between peripheral blood LWR and prognosis of GISTs has not been investigated before. Our present study showed that low LWR was associated with poor prognosis of prognosis of GISTs.

NLR could be considered as a combined marker for inflammatory and immune status in vivo. Increased level of NLR may reflect increased inflammation or/and decreased immune reaction. Thus, high level of NLR was associated with poor prognosis of various tumors.[11] Previously, there were only 5 studies investigate the association between NLR and prognosis of GISTs. The results of the 5 studies were summarized in Table 9. Among them, Perez et al[12] Atila et al,[13] Kargin et al,[15] and Goh et al[16] showed that high level of NLR was correlated with poor prognosis of GISTs. No correlation between NLR and prognosis of GISTs was found in the study reported by Racz et al.[14] This may attribute to the relatively small sample size of the study. In our present study, we also found that high NLR was associated with poor prognosis of GISTs.

PLR has also been demonstrated as prognostic factors for several solid malignancies.[14] Furthermore, superiority of PLR over NLR as an independent prognostic factor has been demonstrated in ovarian,[27] colon,[28] and esophageal cancer.[29]

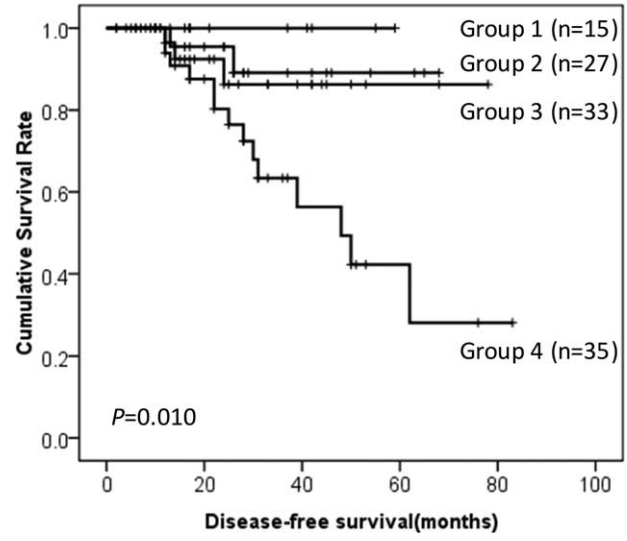


**FIGURE 7.** DFS of GIST patients according to the combination of tumor size, PLR, MLR, and MWR. DFS = disease-free survival, GIST = gastrointestinal stromal tumor, NLR = neutrophil-to-lymphocyte ratio, MLR = monocyte-to-lymphocyte ratio, MWR = monocyte-to-white blood cell ratio, PLR = platelet-to-lymphocyte ratio.

**TABLE 7.** Clinicopathological Features of GIST Patients Stratified by Preoperative LWR

| Characteristics | Low LWR (≤0.27) | High LWR (>0.27) | *P* Value |
|---|---|---|---|
| Age | | | 0.107 |
| ≤60 | 77 | 90 | |
| >60 | 60 | 47 | |
| Gender | | | 0.147 |
| Male | 75 | 63 | |
| Female | 62 | 74 | |
| Location | | | 0.011 |
| Gastric | 88 | 107 | |
| Extra-gastric | 49 | 30 | |
| Tumor size | | | 0.000 |
| ≤2 cm | 12 | 47 | |
| 2.1–5 cm | 52 | 53 | |
| 5.1–10 cm | 50 | 26 | |
| >10 cm | 23 | 11 | |
| Mitotic index | | | 0.000 |
| ≤5 | 59 | 91 | |
| >5 | 78 | 46 | |
| Histological type | | | 0.260 |
| Spindle | 126 | 131 | |
| Epithelioid | 2 | 0 | |
| Mixed | 9 | 6 | |
| Intratumoral hemorrhage | | | 0.393 |
| Yes | 14 | 10 | |
| No | 123 | 127 | |
| Intratumoral necrosis | | | 0.060 |
| Yes | 21 | 11 | |
| No | 116 | 126 | |
| NIH risk category | | | 0.000 |
| Very low risk | 10 | 40 | |
| Low risk | 26 | 48 | |
| Intermediate risk | 34 | 17 | |
| High risk | 67 | 32 | |

GIST = gastrointestinal stromal tumor, LWR = lymphocyte-to-white blood cell ratio.

**TABLE 8.** Clinicopathological Features of GIST Patients Stratified by Preoperative MWR

| Characteristics | Low MWR (≤0.07) | High MWR (>0.07) | *P* Value |
|---|---|---|---|
| Age | | | 0.620 |
| ≤60 | 86 | 81 | |
| >60 | 51 | 56 | |
| Gender | | | 0.016 |
| Male | 59 | 79 | |
| Female | 78 | 58 | |
| Location | | | 0.023 |
| Gastric | 106 | 89 | |
| Extra-gastric | 31 | 48 | |
| Tumor size | | | 0.144 |
| ≤2cm | 30 | 29 | |
| 2.1–5 cm | 58 | 47 | |
| 5.1–10 cm | 38 | 38 | |
| >10 cm | 11 | 23 | |
| Mitotic index | | | 0.225 |
| ≤5 | 80 | 70 | |
| >5 | 57 | 67 | |
| Histological type | | | 0.260 |
| Spindle | 126 | 131 | |
| Epithelioid | 2 | 0 | |
| Mixed | 9 | 6 | |
| Intratumoral hemorrhage | | | 0. 393 |
| Yes | 10 | 14 | |
| No | 127 | 123 | |
| Intratumoral necrosis | | | 0.060 |
| Yes | 11 | 21 | |
| No | 126 | 116 | |
| NIH risk category | | | 0.004 |
| Very low risk | 28 | 22 | |
| Low risk | 31 | 43 | |
| Intermediate risk | 36 | 15 | |
| High risk | 42 | 57 | |

GIST = gastrointestinal stromal tumor, MWR = monocyte-to-white blood cell ratio.

However, these studies did not provide a reasonable explanation for the results. The results in our present study showed that high level of PLR was associated with poor prognosis of GISTs. This was consistent with the studies reported by Racz et al[14] and Goh et al.[16]

Monocytes were reported to be associated with prognosis of a variety of tumors. High level of preoperative monocyte is independently predictive of poor survival of T3N0M0 rectal cancer without neoadjuvant chemoradiotherapy.[30] Preoperative circulating monocyte has also been identified as an independent unfavorable prognostic parameter for survival in breast cancer patients.[31] In vitro, monocyte could induce prostate cancer cell invasion through increased level of chemokine ligand 2 and nuclear factor-κB activity.[32] Amedei et al reported that tumor-infiltrating T cells had the potential to express helper function for MMP-2, MMP-9, and VEGF production by monocytes, which play an important role in angiogenesis, invasion, and metastasis.[33] In our present study, we found that both high level of MWR and MLR were associated with poor prognosis of GISTs. Monocyte was considered to be the critical component of inflammation system and might directly stimulate tumor cell growth through producing proinflammatory cytokines, including tumor necrosis factor, interleukin-1, and interleukin-6.[34] In addition, monocytes could differentiate into tumor-associated macrophages via cytokines and chemokines produced by tumor cells.[35] Tumor-associated macrophages could promote growth, migration, and metastasis of tumor cells.[36] These may, in part, explain the prognostic value of MWR and MLR in the prognosis of GISTs in our present study.

Although all the parameters mentioned above could predict the prognosis of GISTs, the predictive values were different from each other. We found that the predictive values of MLR, PLR, and MWR are superior to NLR, NWR, and LWR. Thus, we wonder whether combination of MLR, PLR, and MWR could increase the predictive value of prognosis of GISTs or not. Considering tumor size was the only independent risk factor for prognosis of GISTs, and all the recurrence occurred in GIST patients with tumor size >5 cm in our present study. Thus, we

**TABLE 9.** Evaluation of Correlation Between NLR/PLR and Prognosis in GISTs

| Literature | No. | Location (n) | Parameter | Cut-Off Value | Statistical Analysis |
|---|---|---|---|---|---|
| Perez et al 2013 | 335 | Stomach (119), Small intestine (30) Rectum (5), Others (6) | NLR | 2.7 (median) | Univariate: $P = 0.003$ Multivariate: $P = 0.120$ |
| Atila et al 2014 | 67 | Esophagus (1), Stomach (37) Duodenum (5), Small intestine (10) Colon (2), Rectum (6), Omentum (1), Uterus (1) Retroperitoneum (2) Unknown (2) | NLR | 1.92 (median) | Univariate: $P = 0.045$ Multivariate: $P > 0.05$ |
| Racz et al 2015 | 93 | Stomach (60), Duodenum (13) Small intestine (19), Other (1) | NLR | 2.043 (recursive partitioning method) | Univariate: $P = 0.2139$ Multivariate: Not done |
| | | | PLR | 245.2 (recursive partitioning method) | Univariate: $P = 0.0393$ Multivariate: Not done |
| Kargin et al 2015 | 78 | Esophagus (2), Stomach (35) Duodenum (1), Small intestine (20) Colon (5), Rectum (2), Appendix (1), Adrenal gland (1) Retroperitoneum (11) | NLR | 3.5 (median) | Pearson correlation: $P = 0.009$ |
| Goh et al 2015 | 300 | Stomach (199), Small intestine (80) Colorectum (15), Others (6) | NLR | 3.0 (median) | Univariate: $P < 0.001$ Multivariate: $P = 0.012$ |
| | | | PLR | 275.0 (median) | Univariate: $P < 0.001$ Multivariate: $P = 0.010$ |

GIST = gastrointestinal stromal tumor, NLR = neutrophil-to-lymphocyte ratio, No = number, PLR = platelet-to-lymphocyte ratio.

compared the prognosis of GISTs >5 cm with high MLR, high PLR, and high MWR with the remnant GISTs >5 cm. We found that the combination of tumor size, MLR, PLR, and MWR could further increase the predictive value of prognosis of GISTs.

There are several limitations in our present study. First, it was a retrospective study of a single center's experience. Prospective studies are needed to verify the predictive value of these parameters. Second, the sample size was not large enough and the incidence of recurrence and metastasis was relatively low, which may result in bias during analysis. Third, the cut-off value of parameters were defined with respect to sample median, which could only be obtained retrospectively. Furthermore, the cut-off values of our present and previous studies were different from each other. Thus, a reasonable cut-off value which could be used to predict prognosis of GISTs prospectively should be identified. Fourth, tumor location was an independent risk factor for prognosis of GISTs. Because of the relatively small sample size, we did not analyze the predictive value of different parameters under the condition of particular tumor locations. Fifth, we only analyze the predictive value of parameters in primary, localized and operable GISTs. Whether these parameters have a predictive value in inoperable GISTs with imatinib therapy needs further investigation.

## CONCLUSIONS

The peripheral blood routine test is convenient, reproducible, and inexpensive. Data about the association between peripheral blood cell and prognosis of GISTs were limited and also controversial. Therefore, we evaluated the prognostic value of peripheral blood cell for GISTs. We found that high NLR, MLR, PLR, NWR, MWR, and low LWR were associated with poor prognosis of GISTs. The combination of tumor size, MLR, PLR, and MWR could further increase the predictive value of prognosis of GISTs.

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