Peripheral Venous Blood Platelet-to-Lymphocyte Ratio (PLR) for Predicting the Survival of Patients With Gastric Cancer Treated With SOX or XELOX Regimen Neoadjuvant Chemotherapy

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Abstract

Background: Inflammation plays an important role in tumor progression. Predicting survival is remarkably difficult in patients with gastric cancer receiving neoadjuvant chemotherapy. The aim of the present study is to investigate the potential prognostic significance of the platelet-to-lymphocyte ratio in patients with gastric cancer receiving S-1 plus oxaliplatin or oxaliplatin and capecitabine regimen. Methods: Ninety-one patients with gastric cancer treated with neoadjuvant chemotherapy were enrolled in this study and then underwent operation. The optimal cutoff value was calculated using receiver-operating characteristic curve analyses. The optimal cutoff value of platelet-to-lymphocyte ratio was divided into low platelet-to-lymphocyte ratio <162 group and high platelet-to-lymphocyte ratio ≥162 group. Kaplan-Meier method and log-rank test were used to analyze the survival curves. The independent prognostic factors and prognostic value of the platelet-to-lymphocyte ratio were assessed by univariate and multivariate Cox proportional hazards regression model. The toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria. Results: Kaplan-Meier analyses revealed that patients with low platelet-to-lymphocyte ratio correlated remarkably with better mean disease-free survival and mean overall survival than those with high platelet-to-lymphocyte ratio (mean disease-free survival 47.33 and 33.62 months, respectively; mean overall survival 51.21 and 36.80 months, respectively). The results demonstrated that platelet-to-lymphocyte ratio had prognostic significance using the cutoff value of 162 on disease-free survival and overall survival, and the mean disease-free survival and overall survival time for patients with low platelet-to-lymphocyte ratio were longer than those with high platelet-to-lymphocyte ratio (mean disease-free survival 47.33 and 33.62 months, respectively; mean overall survival 51.21 and 36.80 months, respectively). The results demonstrated that platelet-to-lymphocyte ratio had prognostic significance using the cutoff value of 162 on disease-free survival and overall survival, and the mean disease-free survival and overall survival time for patients with low platelet-to-lymphocyte ratio were longer than those with high platelet-to-lymphocyte ratio. Meanwhile, patients with gastric cancer who had lower platelet-to-lymphocyte ratio had longer 1-, 3-, and 5-year rates of disease-free survival and overall survival. Moreover, patients with low platelet-to-lymphocyte ratio had longer mean disease-free survival and overall survival than those with high platelet-to-lymphocyte ratio in receiving S-1 plus oxaliplatin or oxaliplatin and capecitabine regimen. Conclusions: The preoperative platelet-to-lymphocyte ratio may be a promising and convenient prognostic biomarker for patients gastric cancer receiving S-1 plus oxaliplatin or oxaliplatin and capecitabine regimen neoadjuvant chemotherapy. It may be useful to help the doctors identify the high-risk patients for taking efficient treatment strategy decisions.

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Introduction

Gastric cancer is one of the common malignant tumors and is considered a major public health threat all over the world. Nowadays, although the incidence rate of gastric cancer has been decreasing globally, the prognosis of gastric cancer remains poor. Most patients with gastric cancer are from Asia, and more than half patients come from China. Although the early-stage gastric cancer is without symptoms, majority of patients have advanced-stage gastric cancer when diagnosed. Moreover, recurrence and metastasis are the common factors that lead to the low level of 5-year survival rate in gastric cancer. It is urgent that the gastric cancer should be diagnosed early. Thus, it is important to explore the potential prognostic biomarkers that can distinguish patients who may benefit from the therapeutic regimen from those who may not.

In recent years, neoadjuvant chemotherapy has been proved to be effective in the treatment of gastric cancer. Many researches have indicated that the neoadjuvant chemotherapy may decrease the tumor stage and increase the R0 resection rate without increasing surgical morbidity and mortality, compared with taking surgical treatment alone. The neoadjuvant chemotherapy may result in increased pathological complete response (path CR) with tolerable side effects and lower negative pathological nodes. For the past several decades, the neotype chemotherapeutics have been emerging markedly, and the S-1 plus oxaliplatin (SOX) and oxaliplatin and capecitabine (XELOX) regimens are commonly used in clinical practice. Radical surgery with D2 lymph–node dissection and neoadjuvant chemotherapy regimens have significantly improved the survival rate of patients with gastric cancer. Thus, it is of importance to look for more precise biomarkers to improve better survival outcome for patients with gastric cancer.

Cancer-related inflammation is considered the seventh hallmark of cancer and acts as a main component and plays a critical role in cancer development and progression. Nowadays, it is well known that inflammation plays pivotal roles in tumor carcinogenesis and progression. Recently, the systemic inflammatory response (SIR) is closely correlated with prognosis of many tumors. Tumor–inflammation interaction might represent a possible therapeutic target for the neoplastic therapy. Moreover, the relationship between SIR and malignant tumors has been hotly researched. Accumulated studies have reported that C-reactive protein (CRP), white blood cell, neutrophil (N), lymphocyte, monocyte, platelet counts, as well as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) might influence the tumor carcinogenesis and metastasis.

Studies have reported that the PLR is a useful predictor in gastric cancer. However, the PLR is described rarely in patients undergoing neoadjuvant chemotherapy for gastric carcinoma, especially receiving SOX or XELOX neoadjuvant chemotherapy regimen. In this study, 91 patients with gastric cancer receiving the regimens were enrolled. The aim of the present study is to evaluate the prognostic significance of PLR in patients with gastric cancer receiving SOX or XELOX neoadjuvant chemotherapy regimen.

Materials and Methods

Patient Selection

We retrospectively enrolled 91 patients who were treated at Harbin Medical University Cancer Hospital between August 2008 and September 2015. All patients had stage II/III gastric carcinoma and are treated with neoadjuvant chemotherapy. All cases were diagnosed and confirmed gastric cancer in accordance with pathological evidence, and the clinical stage was determined as II/III according to tumor–node–metastasis (TNM) staging system. Our study was approved by Harbin Medical University Cancer Hospital Ethics Committee (approval no. KY2013-05). All patients provided written informed consent prior to enrollment in the study. All procedures were performed in accordance with the standards of the 1964 Helsinki Declaration and its later amendments. The clinical and demographic data were extracted from the patients’ medical records. Inclusion criteria were as follows: (1) histologically confirmed, locally advanced gastric cancer; (2) patients with a good performance status, with Eastern Cooperative Oncology Group performance status ranging from 0 to 2 and Karnofsky performance status ≥80; (3) survival time for more than 3 months; and (4) without chemoradiation, targeted therapy, Chinese traditional treatment, and so forth. Exclusion
Table 1. Demographic and Clinicopathological Characteristics of 91 Patients With Advanced Gastric Cancer.

| Parameters                      | Low PLR <162 | High PLR ≥162 | $\chi^2/t$ | $P$ Value |
|---------------------------------|--------------|---------------|------------|-----------|
| Cases (n)                       | 91           | 40            | 51         |           |
| Age (years)                     |              |               |            |           |
| <57                             | 45 (49.5%)   | 21 (52.5%)    | 24 (47.1%) | 0.266     | 0.606     |
| ≥57                             | 46 (50.5%)   | 19 (47.5%)    | 27 (52.9%) |           |           |
| Gender                          |              |               |            |           |
| Male                            | 70 (76.9%)   | 32 (80.0%)    | 38 (74.5%) | 0.381     | 0.537     |
| Female                          | 21 (23.1%)   | 8 (20.0%)     | 13 (25.5%) |           |           |
| BMI                             |              |               |            |           |
| <22.32                          | 45 (49.5%)   | 25 (62.5%)    | 20 (39.2%) | 4.862     | 0.027     |
| ≥22.32                          | 46 (50.5%)   | 15 (37.5%)    | 31 (60.8%) |           |           |
| ABO blood type                  |              |               |            |           |
| A                               | 23 (25.3%)   | 12 (30.0%)    | 11 (21.6%) | 4.543     | 0.235*    |
| B                               | 32 (35.2%)   | 17 (42.5%)    | 15 (29.4%) |           |           |
| O                               | 27 (29.7%)   | 9 (22.5%)     | 18 (35.3%) |           |           |
| AB                              | 9 (9.9%)     | 2 (5.0%)      | 7 (13.7%)  |           |           |
| Blood pressure (before chemotherapy) |          |               |            |           |
| High value                      | 126 ± 21     | 128 ± 23      | 124 ± 20   | 0.954     | 0.343     |
| Low value                       | 77 ± 12      | 78 ± 14       | 76 ± 11    | 0.857     | 0.394     |
| Blood pressure (before surgery) |              |               |            |           |
| High value                      | 123 ± 15     | 123 ± 13      | 122 ± 15   | 0.407     | 0.685     |
| Low value                       | 77 ± 9       | 78 ± 9        | 75 ± 9     | 1.750     | 0.084     |
| Chemotherapy regimen            |              |               |            |           |
| SOX                             | 35 (38.5%)   | 18 (45.0%)    | 17 (33.3%) | 1.289     | 0.256     |
| XELOX                           | 56 (61.5%)   | 22 (55.0%)    | 34 (66.7%) |           |           |
| Radical resection               |              |               |            |           |
| R0                              | 51 (56.0%)   | 26 (65.0%)    | 25 (49.0%) | 3.066     | 0.216     |
| R1                              | 21 (23.1%)   | 6 (15.0%)     | 15 (29.4%) |           |           |
| R2                              | 19 (20.9%)   | 8 (20.0%)     | 11 (21.6%) |           |           |
| Type of surgery                 |              |               |            |           |
| Distal gastrectomy              | 52 (57.1%)   | 23 (57.5%)    | 29 (56.9%) | 0.232     | 1.000*    |
| Proximal gastrectomy            | 6 (6.6%)     | 3 (7.5%)      | 3 (5.9%)   |           |           |
| Total gastrectomy               | 33 (36.3%)   | 14 (35.0%)    | 19 (37.2%) |           |           |
| Differentiation                 |              |               |            |           |
| Poorly differentiated           | 54 (59.3%)   | 24 (60.0%)    | 30 (58.8%) | 1.159     | 0.549*    |
| Moderately differentiated       | 32 (35.2%)   | 15 (37.5%)    | 17 (33.3%) |           |           |
| Well differentiated             | 5 (5.5%)     | 1 (2.5%)      | 4 (7.9%)   |           |           |
| Primary tumor site              |              |               |            |           |
| Upper 1/3                       | 11 (12.1%)   | 4 (10.0%)     | 7 (13.7%)  | 2.118     | 0.374*    |
| Middle 1/3                      | 31 (34.1%)   | 11 (27.5%)    | 20 (39.2%) |           |           |
| Low 1/3                         | 49 (53.8%)   | 25 (62.5%)    | 24 (47.1%) |           |           |
| Pathology                       |              |               |            |           |
| Normal (Tis)                    | 5 (5.5%)     | 3 (7.5%)      | 2 (4.0%)   | 1.881     | 0.626*    |
| Adenocarcinoma                  | 63 (69.2%)   | 26 (65.0%)    | 37 (72.6%) |           |           |
| Mucinous carcinoma              | 10 (11.0%)   | 4 (10.0%)     | 6 (11.8%)  |           |           |
| Signet ring cell carcinoma      | 12 (13.2%)   | 7 (17.5%)     | 5 (9.8%)   |           |           |
| Others                          | 1 (1.1%)     | 0 (0.0%)      | 1 (2.0%)   |           |           |
| Clinical TNM classification     |              |               |            |           |
| T stage                         |              |               |            |           |
| T3                              | 6 (6.6%)     | 3 (7.5%)      | 3 (5.9%)   |           |           |
| T4                              | 85 (93.4%)   | 37 (92.5%)    | 48 (94.1%) |           |           |
| N stage                         |              |               |            |           |
| N0                              | 24 (26.4%)   | 11 (27.5%)    | 13 (25.5%) | 0.432     | 0.806     |
| N1                              | 51 (56.0%)   | 21 (52.5%)    | 30 (58.8%) |           |           |
| N2                              | 16 (17.6%)   | 8 (20.0%)     | 8 (15.7%)  |           |           |
| TNM stage                       |              |               |            |           |
| II                              | 2 (2.2%)     | 2 (5.0%)      | 0 (0.0%)   | 0.190*    |           |
| III                             | 89 (97.8%)   | 38 (95.0%)    | 51 (100.0%)|           |           |

(continued)
criteria were as follows: (1) with another malignant disease or distant metastases; (2) with any form of acute and chronic inflammatory disease; (3) serious complications, such as lung infection, active bleeding, and intestinal obstruction; and (4) blood transfusion within a month before neoadjuvant chemotherapy.

**Treatment Protocols**

The SOX regimen consisted of oxaliplatin 130 mg/m² (intravenous infusion administered in 500 mL of 5% glucose over a period of 2 hours) combined with S-1 60 mg (orally administered twice a day for 14 days). The XELOX regimen consisted of oxaliplatin 130 mg/m² (intravenous infusion administered in 500 mL of 5% glucose over a period of 2 hours) combined with capecitabine 1500 mg (orally administered twice a day for 14 days). A cycle of the 2 regimens was repeated every 3 weeks.

**Response Evaluation**

The treatment efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors guidelines. The clinical response included 4 groups: CR, partial response (PR), stable disease (SD), and progression of disease (PD). Pathological CR was defined as the absence of tumor cells in primary site. The CR and PR were defined as clinical objective response, and the SD or PD as nonclinical response.

**Table 1. (continued)**

| Parameters | Low PLR <162 | High PLR ≥162 | $\chi^2/t$ | $P$ Value |
|------------|-------------|---------------|----------|----------|
| Pathological TNM classification | | | | |
| Tis | 5 (5.5%) | 3 (7.5%) | 2 (3.9%) | 1.515 | 0.736a |
| T1 | 7 (7.7%) | 3 (7.5%) | 4 (7.8%) | |
| T2 | 14 (15.4%) | 5 (12.5%) | 9 (17.7%) | |
| T3 | 43 (47.3%) | 21 (52.5%) | 22 (43.1%) | |
| T4 | 22 (24.2%) | 8 (20.0%) | 14 (27.5%) | |
| N0 | 24 (26.4%) | 11 (27.5%) | 13 (25.5%) | 2.623 | 0.623 |
| N1 | 23 (25.3%) | 13 (32.5%) | 10 (19.6%) | |
| N2 | 15 (16.5%) | 5 (12.5%) | 10 (19.6%) | |
| N3 | 29 (31.8%) | 11 (27.5%) | 18 (35.3%) | |
| TNM stage | | | | |
| Tis | 5 (5.5%) | 3 (7.5%) | 2 (3.9%) | 1.001 | 0.923a |
| I | 9 (9.9%) | 4 (10.0%) | 5 (9.8%) | |
| II | 29 (31.8%) | 14 (35.0%) | 15 (29.4%) | |
| III | 45 (49.5%) | 18 (45.0%) | 27 (53.0%) | |
| IV | 3 (3.3%) | 1 (2.5%) | 2 (3.9%) | |
| Total lymph nodes | | | | |
| <27 | 45 (49.5%) | 18 (45.0%) | 27 (52.9%) | 0.566 | 0.452 |
| ≥27 | 46 (50.5%) | 22 (55.0%) | 24 (47.1%) | |
| Positive lymph nodes | | | | |
| 0 | 25 (27.5%) | 11 (27.5%) | 14 (27.5%) | 4.000 | 0.135 |
| <3 | 19 (20.9%) | 12 (30.0%) | 7 (13.7%) | |
| ≥3 | 47 (51.6%) | 17 (42.5%) | 30 (58.8%) | |
| HER-2 | | | | |
| 0-+ | 54 (59.3%) | 25 (62.5%) | 29 (56.9%) | 0.295 | 0.587 |
| +++++ | 37 (40.7%) | 15 (37.5%) | 22 (43.1%) | |
| Platelet (P) | | | | |
| <294 | 45 (49.5%) | 33 (82.5%) | 12 (23.5%) | 31.187 | <0.001 |
| ≥294 | 46 (50.5%) | 7 (17.5%) | 39 (76.5%) | |
| Lymphocyte (L) | | | | |
| <1.68 | 43 (47.3%) | 14 (35.0%) | 29 (56.9%) | 4.299 | 0.038 |
| ≥1.68 | 48 (52.7%) | 26 (65.0%) | 22 (43.1%) | |
| Response | | | | |
| CR | 5 (5.5%) | 3 (7.5%) | 2 (3.9%) | 1.534 | 0.725a |
| PR | 65 (71.4%) | 28 (70.0%) | 37 (72.6%) | |
| SD | 7 (7.7%) | 4 (10.0%) | 3 (5.8%) | |
| PD | 14 (15.4%) | 5 (12.5%) | 9 (17.7%) | |

Abbreviations: BMI, body mass index; CR, complete response; N, neutrophil; PD, progression of disease PLR, platelet-to-lymphocyte ratio; PR, partial response; SD, stable disease; SOX, S-1 plus oxaliplatin; TNM, tumor–node–metastasis; XELOX, oxaliplatin and capecitabine.

*Performed using the Fisher exact test.
Table 2. Univariate and Multivariate Cox Regression Analyses of DFS and OS in 91 Patients With Advanced Gastric Cancer.

| Parameters                        | DFS Univariate Analysis | DFS Multivariate Analysis | OS Univariate Analysis | OS Multivariate Analysis |
|-----------------------------------|-------------------------|---------------------------|------------------------|--------------------------|
|                                   | Hazard Ratio (95% CI)   | P Value                   | Hazard Ratio (95% CI)   | P Value                   |
| Age (years)                       |                         |                           |                         |                           |
| <57                               | 1 (reference)           | 0.011                     | 1 (reference)           | 0.006                     |
| ≥77                               | 0.304 (0.121-0.764)     | 0.027                     | 0.271 (0.107-0.683)     | 0.020                     |
| Gender                            | 1 (reference)           | 0.185                     | 1 (reference)           | 0.181                     |
| Male                              | 2.346 (0.665-8.274)     | 0.690                     | 2.251 (0.685-7.398)     | 0.768                     |
| Female                            | 1 (reference)           | 0.045                     | 1 (reference)           | 0.236                     |
| BMI                               |                         |                           |                         |                           |
| <22.32                            | 1 (reference)           | 0.014                     | 1 (reference)           | 0.001                     |
| ≥22.32                            | 1.198 (0.493-2.914)     | 0.069                     | 1.141 (0.474-2.749)     | 0.001                     |
| ABO blood type                    |                         |                           |                         |                           |
| A                                 | 1 (reference)           | 0.397                     | 1 (reference)           | 0.101                     |
| B                                 | 0.198 (0.036-1.091)     | 0.645 (0.234-1.780)       | 0.430 (0.145-1.278)     | 0.247                     |
| O                                 | 1.118 (0.221-5.663)     | 0.217 (0.064-0.739)       | 0.973 (0.200-4.744)     | 0.247                     |
| AB                                | 1.083 (0.211-5.567)     | 0.275 (0.045-1.662)       | 0.955 (0.197-4.632)     | 0.247                     |
| Chemotherapy regimen              |                         |                           |                         |                           |
| SOX                               | 1 (reference)           | 0.400                     | 1 (reference)           | 0.101                     |
| XELOX                             | 0.645 (0.234-1.780)     | 0.250 (0.047-1.303)       | 0.340 (0.145-0.789)     | 0.247                     |
| Radical resection                 |                         |                           |                         |                           |
| R0                                | 1 (reference)           | 0.007                     | 1 (reference)           | 0.013                     |
| R1                                | 0.069 (0.022-0.216)     | 0.025 (0.007-0.088)       | 0.137 (0.067-0.281)     | 0.013                     |
| R2                                | 0.132 (0.034-0.506)     | 0.342 (0.158-0.741)       | 0.247 (0.112-0.541)     | 0.247                     |
| Type of surgery                   |                         |                           |                         |                           |
| Distal gastrectomy                | 1 (reference)           | 0.007                     | 1 (reference)           | 0.007                     |
| Proximal gastrectomy              | 7.889 (2.115-29.498)    | 5.420 (1.567-18.752)      | 16.779 (4.356-64.633)   | 8.314 (2.687-25.727)      |
| Total gastrectomy                 | 11.205 (1.057-118.803)  | 11.239 (1.595-79.199)     | 17.96 (1.628-198.948)   | 10.026 (1.458-68.960)     |
| Differentiation                   |                         |                           |                         |                           |
| Poorly differentiated             | 1 (reference)           | 0.001                     | 1 (reference)           | 0.001                     |
| Moderately differentiated         | 51.745 (6.039-443.373)  | 9.880 (2.280-42.804)      | 39.273 (4.999-308.532)  | 6.843 (1.827-25.634)      |
| Well differentiated               | 11.721 (1.640-83.761)   | 4.000 (0.938-17.059)      | 18.85 (2.901-122.490)   | 4.018 (1.043-15.474)      |
| Primary tumor site                |                         |                           |                         |                           |
| Upper 1/3                         | 1 (reference)           | 0.001                     | 1 (reference)           | 0.005                     |
| Middle 1/3                        | 26.380 (3.996-174.154)  | 6.242 (1.563-24.924)      | 27.713 (4.014-191.332)  | 4.688 (1.366-16.093)      |
| Low 1/3                           | 14.535 (2.919-72.359)   | 6.435 (1.735-23.865)      | 24.647 (4.785-126.948)  | 6.520 (1.974-21.534)      |
| Pathology                         |                         |                           |                         |                           |
| Normal (Tis) + adenocarcinoma      | 1 (reference)           | 0.662                     | 1 (reference)           | 0.617                     |
| Mucinous + signet ring cell carcinoma + others | 1.255 (0.453-3.478) | 1.309 (0.455-3.770)       |                           |                           |
| Clinical TNM classification        |                         |                           |                         |                           |
| T stage                           | 0.170                   | 0.177                     | 0.184 (0.009-2.363)     | 0.495                     |
| T4                                | 0.130 (0.007-2.394)     | 0.184 (0.009-2.363)       | 0.148 (0.009-2.363)     | 0.495                     |
| N stage                           | 0.170                   | 0.177                     | 0.184 (0.009-2.363)     | 0.495                     |
| N0                                | 1 (reference)           | 0.170                     | 1 (reference)           | 0.177                     |

(continued)
### Table 2. (continued)

| Parameters                                      | DFS Univariate Analysis | DFS Multivariate Analysis | OS Univariate Analysis | OS Multivariate Analysis |
|-------------------------------------------------|-------------------------|---------------------------|------------------------|--------------------------|
| N1                                              | 0.516 (0.146-1.821)    | 0.483 (0.132-1.775)      | 0.550 (0.173-1.752)    |                          |
| N2                                              | 0.743 (0.237-2.330)    |                           |                        |                          |
| TNM stage                                       |                         |                           |                        |                          |
| II                                              | 1 (reference)           | 1 (reference)             |                        |                          |
| III                                             | 26.759 (0.398-1798.221) | 35.945 (0.699-1849.658)  |                        |                          |
| Pathological TNM classification                 |                         |                           |                        |                          |
| T stage                                         |                         |                           |                        |                          |
| Tis + Tl                                        | 0.140                   | 0.435                     |                        |                          |
| T2                                              | 0.898 (0.046-17.496)   | 0.237 (0.013-4.429)      | 1.624 (0.270-9.770)    | 1.310 (0.283-6.055)     |
| T3                                              | 6.411 (0.867-43.498)   | 0.929 (0.057-15.107)     | 2.339 (0.734-7.454)    | 2.278 (1.020-5.087)     |
| T4                                              | 3.225 (0.741-14.031)   |                           |                        |                          |
| N stage                                         |                         |                           |                        |                          |
| N0                                              | 1 (reference)           | 0.081 (0.003-1.990)      | 0.929 (0.057-15.107)   | 1.078 (0.400-2.901)     |
| N1                                              | 0.191 (0.008-4.763)    | 0.273 (0.013-4.429)      | 1.624 (0.270-9.770)    | 1.310 (0.283-6.055)     |
| N2                                              | 1.521 (0.091-25.302)   |                           |                        |                          |
| N3                                              | 1.772 (0.572-5.485)    |                           |                        |                          |
| TNM stage                                       |                         |                           |                        |                          |
| Tis + I                                         | 0.024 <0.001           | 0.035 <0.001             |                        |                          |
| II                                              | 1 (reference)           | 0.849 (0.093-7.161)      | 1.589 (0.341-7.408)    | 2.278 (1.020-5.087)     |
| III                                             | 2.115 (0.458-9.755)    | 2.066 (0.269-25.260)     | 6.685 (1.593-28.060)   |                          |
| IV                                              | 7.941 (1.896-33.590)   | 7.423 (0.705-78.387)     | 14.815 (2.294-95.680)  |                          |
| Total lymph nodes                               | 0.791 0.647            |                           |                        |                          |
| <27                                             | 1.133 (0.449-2.862)    | 1.235 (0.500-3.051)      |                        |                          |
| ≥27                                             | 0.762 0.992            |                           |                        |                          |
| Positive lymph nodes                            |                         |                           |                        |                          |
| <3                                              | 1.462 (0.125-17.084)   | 0.988 (0.084-11.616)     |                        |                          |
| ≥3                                              | 1.462 (0.125-17.084)   | 0.988 (0.084-11.616)     |                        |                          |
| HER-2                                           | 0.445 0.789            |                           |                        |                          |
| 0+                                              | 1.398 (0.592-3.303)    | 1.127 (0.469-2.712)      |                        |                          |
| Platelet (P)                                    | <0.001 0.004           |                           | <0.001 <0.001          |                          |
| <294                                            | 1 (reference)           | 1 (reference)             | 1 (reference)          | 1 (reference)            |
| ≥294                                            | 13.979 (3.172-61.602)   | 3.947 (1.543-10.096)     | 23.553 (5.352-103.658) | 5.949 (2.356-15.017)    |
| Lymphocyte (L)                                  | 0.003 0.019            |                           |                        |                          |
| <1.68                                           | 0.165 (0.050-0.541)    | 0.271 (0.091-0.808)      | 0.558 (0.293-1.064)    |                          |
| ≥1.68                                           | 0.002 0.025            |                           |                        |                          |
| PLR                                             |                         |                           |                        |                          |
| <162                                            | 1 (reference)           | 1 (reference)             | 1 (reference)          | 1 (reference)            |
| ≥162                                            | 0.133 (0.037-0.483)    | 0.345 (0.135-0.877)      | 0.151 (0.045-0.508)    | 0.304 (0.123-0.752)     |

Abbreviations: BMI, body mass index; CI, confidence interval; DFS, disease-free survival; N, neutrophil; OR, odds ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; TNM, tumor–node–metastasis; SOX, S-1 plus oxaliplatin; XELOX, oxaliplatin and capecitabine.
Peripheral Venous Blood Sample

Peripheral venous blood samples were routinely obtained and measured within 1 week before neoadjuvant chemotherapy treatment. Hematological parameters were analyzed by XE-2100 hematology analyzer (Sysmex, Kobe, Japan).

Follow-Up

All patients were routinely followed up in inpatient and outpatient every 3 months during the first 2 years after surgery, every 6-month interval thereafter, and until death. Follow-up assessments included laboratory tests, physical examination, multislice computed tomography, gastroscopy, and some other examinations as it fits. Disease-free survival (DFS) is defined as the time from surgery to relapse (local recurrence and distant metastases). Overall survival (OS) is defined as the time from surgery to death for any cause or last follow-up. Follow-up was terminated on December 3, 2016.

Statistical Analysis

Statistical analyses were performed by using the SPSS software (version 17.0; SPSS Inc, Chicago, Illinois). The optimal cutoff value for PLR was calculated by using receiver operating characteristic (ROC) curve analyses. The area under the curve (AUC) was used to assess the predictive value. The ratio closest to the point with maximum sensitivity and specificity was defined as the optimal cutoff value. The differences in clinicopathological database of patients were analyzed using Fisher exact test. The patients’ baseline characteristics were expressed as the mean ± standard error for the qualitative variables and compared using Student t test. The DFS and OS were compared using Kaplan-Meier method and log-rank test. The independent prognostic factors and prognostic value of the PLR were assessed by univariate and multivariate Cox proportional hazards regression model. Two-tailed P <0.05 was considered to indicate a statistically significant difference.

Results

Demographic and Clinicopathological Characteristics of Patients

We used the ROC curve to determine an optimal cutoff value of the PLR. The AUC of PLR was 0.566, and the optimal cutoff value was 162. The patients were stratified into 2 groups by the optimal cutoff value of PLR: a low PLR group (PLR <162) and a high PLR group (PLR ≥162). The baseline demographic and clinicopathological characteristics of enrolled 91 patients, 70 males and 21 females with a median age of 57 years (range 32-73 years), were listed in Table 1. The median body mass index (BMI) was 22.32, ranging from 17.06 to 34.08. We found that patients with low baseline PLR level were more likely to improve demographic and clinicopathological characteristics, including BMI (χ² = 4.862, P = 0.027), platelet (χ² = 31.187, P < 0.001), lymphocyte (χ² = 4.299, P = 0.038).

Univariate and Multivariate Cox Regression Survival Analyses

As regard to DFS, based on univariate analysis, the significant prognostic factors were age, ABO blood type, radical resection, type of surgery, differentiation, primary tumor site, pathological TNM stage, platelet, lymphocyte, and PLR. Based on the multivariate Cox regression analysis, the factors associated with DFS were age, radical resection, type of surgery, differentiation, primary tumor site, pathological TNM stage, platelet, lymphocyte, and PLR (Table 2). Based on univariate analysis, the significant prognostic factors for OS were age, radical resection, type of surgery, differentiation, primary tumor site, pathological N stage, pathological TNM stage, platelet, lymphocyte, and PLR. Based on the multivariate Cox regression analysis, the factors...
associated with OS were age, radical resection, type of surgery, differentiation, primary tumor site, pathological N stage, pathological TNM stage, platelet, and PLR (Table 2).

Survival and Evaluation of the Prognostic Factors

Univariate and multivariate Cox proportional hazards regression model were used to evaluate the independent prognostic factors and prognostic value of the PLR. We found that PLR had prognostic significance using the cutoff value of 162 on DFS and OS before neoadjuvant chemotherapy. In univariate analysis, low PLR was associated with prolonged DFS and OS ($P = 0.002$, hazard ratio [HR]: 0.133, 95% confidence interval [CI]: 0.037-0.483; $P = 0.002$, HR: 0.151, 95% CI: 0.045-0.508, respectively). In multivariate analysis, low PLR was associated with prolonged DFS and OS ($P = 0.025$, HR: 0.345, 95% CI: 0.135-0.877; $P = 0.010$, HR: 0.304, 95% CI: 0.123-0.752, respectively; Table 2). The mean DFS and OS for patients with low PLR were 47.33 and 51.21 months, respectively. The mean DFS and OS for patients with high PLR were 33.62 and 36.80 months, respectively. By using log-rank test, the mean DFS and OS time for patients with low PLR were longer than those with high PLR ($\chi^2 = 2.777$, $P = 0.096$ and $\chi^2 = 1.793$, $P = 0.181$, respectively; Figure 1A and B).

Survival and Evaluation of the Prognostic Significance of PLR

For all enrolled patients, the 1-, 3-, and 5-year rates of DFS and OS were 75.8% (69/91), 23.1% (21/91), and 7.7% (7/91) and 87.9% (80/91), 26.4% (24/91), and 11.0% (10/91), respectively. Moreover, the 1-, 3-, and 5-year rates of DFS and OS in low PLR were 82.5% (33/40), 27.5% (11/40), and 10.0% (4/40) and 90.0% (36/40), 27.5% (11/40), and 15.0% (6/40), respectively. The patients with low PLR had better 1-, 3-, and 5-year rates of DFS and OS than those with high PLR. Patients with gastric cancer who had lower PLR were more likely to have longer DFS and OS (Table 3, Figure 2A and B).

Association of Platelet Counts and PLR in Patients With Gastric Cancer

With low platelet counts, the median DFS and OS for patients with low PLR were 23.73 and 26.87 months and that of for patients with high PLR were 16.50 and 16.50 months, respectively. The results indicated that patients with
low PLR had longer DFS and OS than those with high PLR and low platelet counts ($\chi^2 = 1.283$, $P = 0.257$ and $\chi^2 = 1.680$, $P = 0.195$, respectively; Figure 3A and B). With high platelet counts, the median DFS and OS for patients with low PLR were 32.54 and 36.40 months and that of for patients with high PLR were 20.47 and 26.80 months, respectively. Meanwhile, patients with low PLR had longer DFS and OS than those with high PLR and high platelet counts ($\chi^2 = 5.758$, $P = 0.016$ and $\chi^2 = 5.184$, $P = 0.023$, respectively; Figure 3C and D).

**Association of Lymphocyte Counts and PLR in Patients With Gastric Cancer**

With low lymphocyte counts, the median DFS and OS for patients with low PLR were 16.40 and 21.03 months and that of for patients with high PLR were 26.80 and 29.37 months, respectively. The results indicated that patients with high PLR had longer DFS and OS than those with low PLR and low lymphocyte counts ($\chi^2 = 0.844$, $P = 0.358$ and $\chi^2 = 0.997$, $P = 0.318$, respectively; Figure 4A and B). With high lymphocyte counts, the median DFS and OS for patients with low PLR were 57.94 and 62.52 months and that of for patients with high PLR were 26.87 and 30.91 months, respectively. Patients with low PLR had longer DFS and OS than those with high PLR and high lymphocyte counts ($\chi^2 = 9.130$, $P = 0.003$ and $\chi^2 = 6.867$, $P = 0.009$, respectively; Figure 4C and D).

**Association of SOX or XELOX Regimen and PLR in Patients With Gastric Cancer**

In order to further investigate the prognostic efficiency of PLR, the PLR was analyzed by SOX or XELOX regimen. With SOX regimen, the results indicated that the mean DFS and OS for patients with low PLR were 40.83 and 41.44 months and that of for patients with high PLR were 29.41 and 39.38 months, respectively. We found that patients with low PLR had longer DFS and OS than those with high PLR ($\chi^2 = 0.932$, $P = 0.334$ and $\chi^2 = 0.251$, $P = 0.617$, respectively; Figure 5A and B). With XELOX regimen, the results indicated that the mean DFS and OS for patients with low PLR were 42.05 and 46.38 months and that of for patients with high PLR were 31.26 and 33.92 months, respectively. We found that patients with low PLR had longer DFS and OS than those with high PLR in receiving XELOX regimen ($\chi^2 = 1.364$, $P = 0.243$ and $\chi^2 = 0.992$, $P = 0.319$, respectively; Figure 5C and D).
Correlation Between PLR and Toxicity Assessment

For all patients, we analyzed the toxicities after neoadjuvant chemotherapy for 2 cycles. The most common toxicities were hematologic after neoadjuvant chemotherapy. The National Cancer Institute Common Toxicity Criteria grades 1 and 2 anemia, leucopenia, neutropenia, and thrombocytopenia of all cases were recorded in 33/91 (36.3%), 18/91 (19.8%), 21/91 (23.1%), and 4/91 (4.4%), respectively (Table 4). In the present study, there were no chemotherapy-related deaths. To further study the PLR in toxicity assessment, we found that there were no difference using the cutoff value 162 of PLR on leucopenia, neutropenia, and thrombocytopenia (P > 0.05), except anemia (P < 0.05; Table 4).

Discussion

Over the past several decades, with the rapid advances in surgical techniques and multimodal therapy, including chemotherapy, radiotherapy, and targeted therapy, it has greatly prolonged survival time and improved quality of life for patients with gastric cancer. Gastric cancer is one of the diseases with the highest tumor burden. Although some immunological and histological biomarkers associated with poor prognosis in patients with gastric cancer have been identified, these biomarkers largely depend on expensive equipment, difficult technology, time-consuming, and some of them obtained after resection of the primary tumor. Therefore, looking for reliable and affordable prognostic factors in patients with gastric cancer is still needed and ongoing.

Dozens of studies have shown that inflammation is associated with the development and progression of many tumors. As we all know, the tumor cells could influence pro-inflammatory mediators; stimulate the production of CRP; increase peripheral blood N, monocyte, and platelet counts; and decrease lymphocyte counts. On the basis of these theories, we may use the cellular components of SIR in peripheral venous blood to predict survival condition and prognosis in many malignancies. However, the mechanisms by which inflammatory response induces a poor outcome remain controversial and poorly understood. Several inflammatory markers in peripheral venous blood as prognostic factors have been studied in some malignant tumors, such as NLR, MLR, PLR, CRP, neutrophil-to-white blood cell ratio, lymphocyte-to-white blood cell ratio,
Figure 5. Disease-free survival (DFS) and overall survival (OS) for the PLR of patients with gastric cancer in SOX or XELOX regimen. (A) Kaplan-Meier analysis of DFS for the PLR of patients with gastric cancer in SOX regimen; (B) Kaplan-Meier analysis of OS for the PLR of patients with gastric cancer in SOX regimen; (C) Kaplan-Meier analysis of DFS for the PLR of patients with gastric cancer in XELOX regimen; (D) Kaplan-Meier analysis of OS for the PLR of patients with gastric cancer in XELOX regimen. PLR indicates platelet-to-lymphocyte ratio; SOX, S-1 plus oxaliplatin; XELOX, oxaliplatin and capecitabine.

Table 4. Main Toxicities According to NCI-CTC Scale of the Patients With Advanced Gastric Cancer Undergoing Neoadjuvant Chemotherapy.

| Parameters       | Number (%) | Low PLR <162 | High PLR ≥162 | \( \chi^2 \) | \( P \) Value |
|------------------|------------|--------------|---------------|--------------|--------------|
| Case (n)         |            | 91           | 40            | 51           |              |
| Anemia           |            | Low PLR <162 | High PLR ≥162 |              |              |
| Grade 0          |            | 58 (63.7)    | 33 (82.5)     | 25 (49.0)    | 10.872       | 0.001        |
| Grade 1-2        |            | 33 (36.3)    | 7 (17.5)      | 26 (51.0)    |              |              |
| Grade 3-4        |            | 0 (0.0)      | 0 (0.0)       | 0 (0.0)      |              |              |
| Leucopenia       |            | Low PLR <162 | High PLR ≥162 |              |              |
| Grade 0          |            | 73 (80.2)    | 35 (87.5)     | 38 (74.5)    | 2.384        | 0.123        |
| Grade 1-2        |            | 18 (19.8)    | 5 (12.5)      | 13 (25.5)    |              |              |
| Grade 3-4        |            | 0 (0.0)      | 0 (0.0)       | 0 (0.0)      |              |              |
| Neutropenia      |            | Low PLR <162 | High PLR ≥162 |              |              |
| Grade 0          |            | 67 (73.6)    | 33 (82.5)     | 34 (66.7)    | 0.185        |              |
| Grade 1-2        |            | 21 (23.1)    | 5 (12.5)      | 16 (31.3)    |              |              |
| Grade 3-4        |            | 3 (3.3)      | 2 (5.0)       | 1 (2.0)      |              |              |
| Thrombocytopenia |            | Low PLR <162 | High PLR ≥162 |              |              |
| Grade 0          |            | 87 (95.6)    | 38 (95.0)     | 49 (96.1)    | 1.000        |              |
| Grade 1-2        |            | 4 (4.4)      | 2 (5.0)       | 2 (3.9)      |              |              |
| Grade 3-4        |            | 0 (0.0)      | 0 (0.0)       | 0 (0.0)      |              |              |

Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; PLR, platelet-to-lymphocyte ratio.

*Fisher exact test.
and monocyte-to-white blood cell ratio. Nevertheless, the PLR with regard to DFS and OS in patients with gastric cancer undergoing neoadjuvant chemotherapy of SOX or XELOX regimen has been rarely studied.

Platelets play a key role in tumor development and progression and are associated with poor survival in patients with various types of malignancies, but the potential mechanisms remain unknown. Some potential mechanisms may be used to explain that high PLR is associated with poor survival time and prognosis. Platelets can promote increasing angiogenesis via cytokine vascular endothelial growth factor and inhibit the immune system in the bloodstream, such as immune attack. Some researches indicate that platelets may help the communication between primary tumor cells and bone remodeling alterations before tumor metastasis. Platelets can shield circulating tumor cells (CTCs) from immune attack and destruction by activated platelets, which in turn protect the CTCs from shearing stresses during circulation. The lymphocytes are known to play a critical role in tumor immune surveillance and defense of tumor cells by inducing cytotoxic cell death as well as inhibiting proliferation and migration of tumor cells. What’s more, the increased lymphocyte levels are associated with better prognosis in some solid tumors and can improve the host’s anticancer immunity and impair cancer immune surveillance. Combined with these findings, we found that an increase in the platelet count and decrease in the lymphocyte count in the peripheral venous blood have been related to tumor growth and progression. Therefore, the PLR may help to predict prognosis and reflect the degree of tumor progression in gastric cancer.

The baseline demographic and clinicopathological characteristics of the enrolled 91 patients were analyzed. We found that low baseline PLR was more likely to improve demographic and clinicopathological characteristics, including BMI, platelet, and lymphocyte count. Based on univariate and multivariate Cox regression analysis, the significant prognostic factors predicting improved DFS and OS were age, radical resection, type of surgery, differentiation, primary tumor site, pathological TNM stage, platelet, and PLR. The results demonstrated that PLR had prognostic significance using the cutoff value of 162 on DFS and OS, and the mean DFS and OS time for patients with low PLR were longer than those with high PLR. Meanwhile, the 1-, 3-, and 5-year rates of DFS and OS were analyzed. The results indicated that patients with gastric cancer who had lower PLR were more likely to have longer 1-, 3-, and 5-year rates of DFS and OS.

In addition, we analyzed the PLR in different platelet or lymphocyte counts group. The results also indicated that the patients with low PLR and high lymphocyte counts or low platelet counts had better median DFS and OS. Furthermore, we also analyzed the relationship between PLR and SOX or XELOX regimen. The results indicated that patients with low PLR had longer DFS and OS than those with high PLR in receiving SOX or XELOX regimen. Moreover, the relationship between PLR and toxicity assessment was also analyzed. All patients could tolerate the neoadjuvant chemotherapy toxicities, and the regimens were safety and effective. The most common toxicities were hematologic after neoadjuvant chemotherapy, and there was no difference in PLR in toxicity assessment using the cutoff value of 162 on these toxicities, except anemia.

As far as we are concerned, the PLR value with DFS and OS in patients with gastric cancer undergoing neoadjuvant chemotherapy is rarely discussed. The present study suggests that the PLR level may help to predict prognosis in gastric cancer. With a view to the high gastric cancer morbidity and unbalanced medical condition in China, it is very important to consider these convenient, simple, cheap, reproducible, and noninvasive biomarkers for the prevention and treatment of gastric cancer. Hence, a comprehensive understanding of hematologic parameter may find new targets for individual treatment. Thus, the present study may provide critical information for the treatment of gastric cancer.

All in all, SOX and XELOX regimens were well tolerated by all patients who received. The results of present study explain the reason for elevated PLR enhancing tumor progression, and the low PLR may be a more favorable prognosis. However, there were several limitations in the present study. First, the number of patients was small sample size. Second, this was a retrospective single-center study. Therefore, larger numbers of patients with gastric cancer was treated with neoadjuvant chemotherapy and multicenter study should be enrolled. The differences in the cutoff value of PLR among the studies may be attributable to the differences in the cumulative number of patients and the disease stage among the studies. In our study, whether the cutoff value of 162 for PLR is correct requires further prospective and well-designed, randomized controlled trial investigation.

Conclusions

In conclusion, our data suggest that the PLR qualifies as a convenient, noninvasive, cost-effective, and easily measured prognostic indicator for patients with gastric cancer treated with neoadjuvant chemotherapy. Low PLR may help clinicians to identify those patients who will benefit from neoadjuvant chemotherapy. However, more studies are needed to verify the changes in inflammatory markers in larger groups of patients with gastric cancer.

Authors’ Note

L.C. edited and conducted the statistical analyses; Y.H., X.C., and M.Z. collected the data; S.L. and L.Z. conducted the statistical analyses; and H.S. and Y.X. provided technical help and fruitful discussion. L.C., Y.H., and M.Z. contributed equally to this work. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.
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