Prognostic value of systemic immune-inflammation index in patients with gastric cancer

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Abstract

Background: Inflammation-based indexes have been used to predict survival and recurrence in cancer patients. Systemic immune-inflammation index (SII) was reported to be associated with prognosis in some malignant tumors. In the present study, we aimed to explore the association between SII and the prognosis of patients with gastric cancer.

Methods: We retrospectively analyzed data from 444 gastric cancer patients who underwent gastrectomy at the First Affiliated Hospital of Sun Yat-sen University between January 1994 and December 2005. Preoperative SII was calculated. The Chi square test or Fisher’s exact test was used to determine the relationship between preoperative SII and clinicopathologic characteristics. Overall survival (OS) rates were estimated using the Kaplan–Meier method, and the effect of SII on OS was analyzed using the Cox proportional hazards model. Receiver operating characteristic (ROC) curves were used to compare the predictive ability of SII, NLR, and PLR.

Results: SII equal to or higher than 660 was significantly associated with old age, large tumor size, unfavorable Borrmann classification, advanced tumor invasion, lymph node metastasis, distant metastasis, advanced TNM stage, and high carcino-embryonic antigen level, high neutrophil–lymphocyte ratio, and high platelet–lymphocyte ratio (all \( P < 0.05 \)). High SII was significantly associated with unfavorable prognosis (\( P < 0.001 \)) and SII was an independent predictor for OS (\( P = 0.015 \)). Subgroups analysis further showed significant associations between high SII and short OS in stage I, II, III subgroups (all \( P < 0.05 \)). SII was superior to NLR and PLR for predicting OS in patients with gastric cancer.

Conclusion: Preoperative SII level is an independent prognostic factor for OS in patients with gastric cancer.

Keywords: Gastric cancer, Preoperative systemic immune-inflammation index, Prognosis

Background

Gastric cancer is the fifth most common cancer and the second leading cause of cancer-related death worldwide [1]. It was estimated that 679,100 new cases of gastric cancer were diagnosed and 498,000 related deaths occurred in China in 2015 [2]. Despite the development of new surgical techniques and the use of chemotherapy and radiotherapy, gastric cancer is still an extremely deadly disease, and patients with gastric cancer have a generally unfavorable prognosis [3]. However, simple, low-cost, and effective methods in predicting the prognosis of patients with gastric cancer are still lacking, and it is important to identify a reliable biomarker to predict the prognosis.

Systemic inflammatory responses have been shown to involve in DNA damage, angiogenesis promotion, and tumor invasion and migration [4–7]. Moreover, a study indicated that circulating lymphocytes could reflect a patient’s inflammatory status [8]. Thus, some inflammation-based parameters, such as lymphocyte count, neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), have been used to predict survival and recurrence.
in cancer patients [9–13]. SII, a parameter combining lymphocyte, neutrophil, and platelet counts, has shown to be more accurate than NLR and PLR in predicting the prognosis of patients with hepatocellular carcinoma [12] and small-cell lung cancer [13]. However, the significance of SII as a predictor of survival in patients with gastric cancer has not been assessed in our center. In this study, we aimed to evaluate the prognostic value of SII for survival in patients with gastric cancer who underwent surgery.

Patients and methods

Patients

We reviewed the records of patients with gastric cancer who underwent gastrectomy between January 1994 and December 2005 at the First Affiliated Hospital of Sun Yat-sen University in Guangzhou, China. All patients were diagnosed with pathologic examination. Patients were excluded if they met the following criteria: history of other malignant tumors, receipt of neoadjuvant therapy, lack of blood test results, lost to follow-up, lymphatic system disorders, acute coronary syndromes, valvular heart diseases, autoimmune thyroid diseases, and systematic inflammatory diseases. Tumor stage was defined according to the 2010 American Joint Committee on Cancer TNM staging system and the Japanese classification of gastric carcinoma, Borrmann classification.

Clinical data collecting and processing

Baseline data, including demographic information, routine blood test results, tumor markers, and gastrectomy history, were reviewed. Following clinical and pathologic data were collected: sex, age, tumor location, tumor size, pathologic type, Borrmann classification, depth of invasion, lymph node metastasis, distant metastasis, and TNM stage.

SII, NLR, and PLR were calculated as follows: SII = P \times N/L; NLR = N/L; and PLR = P/L, where P, N, and L stood for platelet, neutrophil, and lymphocyte counts, respectively [14, 15]. Optimal cutoff values of SII (low, < 660; high, ≥ 660); NLR (low, < 2.10; high, ≥ 2.10); and PLR (low, < 120; high, ≥ 120) were determined according to previous studies [14–16]. Cutoff values of age, tumor size, and carcino-embryonic antigen (CEA) were adopted from previous studies [17, 18].

Follow-up

Patients were followed up every 3 months during the first year and every 6 months thereafter. Phone calls were made and letters were sent to patients and their relatives according to the National Comprehensive Cancer Network follow-up guidelines. Follow-ups were ended after December 2013.

Statistical analysis

SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA) was used for data analysis. Relationships between SII and clinicopathologic factors were analyzed using the Chi square test or Fisher’s exact test. OS was defined as the interval from gastrectomy to last follow-up or the date of death. Mean overall survival (OS) with 95% confidence interval (CI) were compared using the analysis of variance (ANOVA). Kaplan–Meier survival curves were constructed, and the log-rank test was used to compare survival rate. Censored data were used for patients who were alive at last follow-up or lost to follow-up. Univariate and multivariate analysis was performed using the Cox proportional hazards model. Variables in univariate analysis with P values less than 0.05 were included in multivariate analysis. Receiver operating characteristic (ROC) curves and area under the ROC curve (AUC) were used to assess the sensitivity and specificity of SII, NLR, and PLR in predicting the prognosis of patients with gastric cancer. For all analyses, P values less than 0.05 were considered statistically significant.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or national research committees and with the 1964 Helsinki Declaration, its later amendments, or similar ethical standards.

Results

Patient characteristics

The clinical and pathologic characteristics are shown in Table 1. In the present study, we included 444 patients; 281 (63.3%) were men and 163 (36.7%) were women. Median age was 56 years (range 21–87 years). Median follow-up duration was 45 months (range 1–185 months). At the last follow-up, 277 (62.4%) patients died, and 167 (37.6%) were still alive. Tumor location, tumor size, Borrmann classification, tumor invasion, lymph node metastasis, distant metastasis, TNM stage, CEA, and SII were significantly associated with OS of patients with gastric cancer (all P < 0.05).

Relationship between SII and clinicopathologic characteristics

As shown in Table 2, high SII was associated with old age, large tumor size, unfavorable Borrmann classification, advanced tumor invasion, lymph node metastasis, distant metastasis, advanced TNM stage, high CEA level, high NLR, and high PLR (all P < 0.05).

Association of SII with OS

Patients were divided into two groups according to SII values. Five-year OS rates were 46.1% and 29.4% in the
We further assessed the prognostic value of SII in different TNM stage groups. The results showed that preoperative SII was a prognostic indicator in patients with stage I ($P = 0.035$; Fig. 2a), stage II ($P = 0.012$; Fig. 2b), and stage III ($P < 0.001$; Fig. 2c) gastric cancer. However, for patients with stage IV gastric cancer, no significant association of SII with OS was identified ($P = 0.177$; Fig. 2d).

Univariate and multivariate Cox regression analysis for OS
As shown in Table 3, in univariate analysis, age, tumor location, Borrmann classification, TNM stage, CEA, SII, NLR, and PLR were significant prognostic factors (all $P < 0.05$), whereas sex ($P = 0.420$) and pathologic type ($P = 0.758$) were not significant prognostic factors.

Significant variables in univariate analysis were included in multivariate Cox regression analysis. We found that OS was independently associated with age (HR = 1.356, 95% CI 1.059–1.735, $P = 0.026$), Borrmann classification (HR = 1.521, 95% CI 1.279–1.810, $P < 0.001$), TNM stage (HR = 2.081, 95% CI 1.772–2.443, $P < 0.001$), CEA (HR = 1.431, 95% CI 1.006–2.035, $P = 0.045$), and SII (HR = 1.530, 95% CI 1.208–1.940, $P < 0.001$).
Table 2  Association of SII with clinicopathologic characteristics in patients with gastric cancer

| Characteristic                  | SII < 660 [cases (%)] | SII ≥ 660 [cases (%)] | $\chi^2$ value | $P$ value |
|--------------------------------|------------------------|------------------------|----------------|-----------|
| Total                          | 283                    | 161                    |                |           |
| Sex                            |                        |                        | 0.051          | 0.821     |
| Men                            | 178 (62.9)             | 103 (64.0)             |                |           |
| Women                          | 105 (37.1)             | 58 (36.0)              |                |           |
| Age (years)                    |                        |                        | 9.250          | 0.002     |
| <60                            | 174 (61.5)             | 75 (46.6)              |                |           |
| ≥60                            | 109 (38.5)             | 86 (53.4)              |                |           |
| Tumor location                 |                        |                        | 5.667          | 0.059     |
| Upper stomach                  | 82 (29.0)              | 58 (36.0)              |                |           |
| Middle stomach                 | 83 (29.3)              | 54 (33.5)              |                |           |
| Lower stomach                  | 118 (41.7)             | 49 (30.4)              |                |           |
| Tumor size (cm)                |                        |                        | 20.867         | <0.001    |
| <5                             | 164 (58.0)             | 57 (35.4)              |                |           |
| ≥5                             | 119 (42.0)             | 104 (64.6)             |                |           |
| Pathologic type                 |                        |                        | 4.642          | 0.326     |
| Adenocarcinoma                 | 236 (83.4)             | 131 (81.4)             |                |           |
| Squamous carcinoma             | 12 (4.2)               | 13 (8.1)               |                |           |
| Adenosquamous carcinoma        | 3 (1.1)                | 0 (0.0)                |                |           |
| Ring cell carcinoma            | 26 (9.2)               | 13 (8.1)               |                |           |
| Undifferentiated carcinoma     | 6 (2.1)                | 4 (2.5)                |                |           |
| Borrmann classification        |                        |                        | 10.079         | 0.039     |
| 1                              | 15 (5.3)               | 15 (9.3)               |                |           |
| 2                              | 74 (26.1)              | 24 (14.9)              |                |           |
| 3                              | 161 (56.9)             | 98 (60.9)              |                |           |
| 4                              | 28 (9.9)               | 22 (13.7)              |                |           |
| 5                              | 5 (1.8)                | 2 (1.2)                |                |           |
| pT                             |                        |                        | 23.504         | <0.001    |
| 1                              | 46 (16.3)              | 7 (4.3)                |                |           |
| 2                              | 30 (10.6)              | 11 (6.8)               |                |           |
| 3                              | 115 (40.6)             | 60 (37.3)              |                |           |
| 4                              | 92 (32.5)              | 83 (51.6)              |                |           |
| pN                             |                        |                        | 12.925         | 0.005     |
| 0                              | 114 (40.3)             | 38 (23.6)              |                |           |
| 1                              | 109 (38.5)             | 76 (47.2)              |                |           |
| 2                              | 43 (15.2)              | 34 (21.1)              |                |           |
| 3                              | 17 (6.0)               | 13 (8.1)               |                |           |
| pM                             |                        |                        | 36.571         | <0.001    |
| 0                              | 241 (85.2)             | 96 (59.6)              |                |           |
| 1                              | 42 (14.8)              | 65 (40.4)              |                |           |
| TNM stage                      |                        |                        | 40.848         | <0.001    |
| I                              | 62 (21.9)              | 15 (9.3)               |                |           |
| II                             | 47 (16.6)              | 17 (10.6)              |                |           |
| III                            | 132 (46.6)             | 64 (39.7)              |                |           |
| IV                             | 42 (14.8)              | 65 (40.4)              |                |           |
| CEA (μg/L)                     |                        |                        | 4.778          | 0.029     |
| <5                             | 261 (92.2)             | 138 (85.7)             |                |           |
| ≥5                             | 22 (7.8)               | 23 (14.3)              |                |           |
| NLR                            |                        |                        | 52.974         | <0.001    |
| <2.10                          | 197 (69.6)             | 8 (5.0)                |                |           |
| ≥2.10                          | 86 (30.4)              | 153 (95.0)             |                |           |
Comparison between inflammation indexes

We evaluated the prognostic values of these systemic inflammation indexes. Area under the ROC curve (AUC) of SII, NLR, and PLR were 0.612 \((P = 0.003)\), 0.556 \((P = 0.040)\), and 0.572 \((P = 0.009)\), respectively (Fig. 3). These results indicated that SII was superior to NLR and PLR for predicting OS in patients with gastric cancer.

Discussion

In the present study, we found that high SII was an independent predictor of poor prognosis in patients with stage I–III gastric cancer, and SII was a superior prognostic index compared with NLR and PLR.

We found that, in patients with gastric cancer, high SII was associated with old age, large tumor size, poor Borrmann classification, advanced tumor invasion, lymph node metastasis, distant metastasis, advanced TNM stage, and high CEA level. It has recently been shown that systemic inflammatory responses induce malignant tumor behavior and are associated with short survival in patients with various malignant solid tumors and that systemic inflammation indexes can predict cancer prognosis \([19–23]\). Hu et al. \([12]\) showed that high SII was associated with liver cirrhosis, low tumor differentiation, large tumor size, early recurrence, and high circulating tumor cell levels in patients with hepatocellular carcinoma. Moreover, Hong et al. \([13]\) found that high SII was associated with sex and hemoglobin level in patients with small cell lung cancer.

Preoperative inflammation indexes were associated with OS in many cancers. Peng et al. \([23]\) found that high PLR was strongly associated with poor outcome in patients with metastatic colorectal cancer. Ji et al. \([11]\) found that preoperative NLR and PLR were significant predictors of OS in patients with esophageal squamous cell carcinoma and that PLR was superior to NLR as a prognostic index. We also found SII was an independent prognostic index in patients with gastric cancer. In addition, we found that SII was a better predictor than NLR and PLR.

TNM stage is the gold standard for predicting the OS of patients with gastric cancer. However, TNM stage is determined postoperatively. Therefore, preoperative prognostic prediction can be difficult. SII is a convenient, easily obtained, low-cost, and non-invasive biomarker that is a complement to TNM stage as a prognostic predictor for patients with gastric cancer. Moreover, we found that SII was a strong prognostic index for patients with stage I–III gastric cancer. As for patients with stage IV gastric cancer, OS was shorter in patients with high SII level. However, the difference was not significant, and maybe the cutoff value needs to be optimized.

Our study had several limitations. First, it was a single-center, retrospective study with a relatively small sample size. Thus, conclusions from the present study may have a bias. Second, although SII was an independent predictor of gastric cancer prognosis and was superior to NLR and PLR, the sensitivity and specificity of SII was not very high, indicating that perspective studies to find a proper cutoff value are needed.
**Table 3** Univariate and multivariate analyses of clinicopathologic factors and SII for OS of patients with gastric cancer

| Variable                  | Univariate analysis | Multivariate analysis |
|---------------------------|---------------------|-----------------------|
|                           | HR (95% CI)         | P value               | HR (95% CI)         | P value               |
| Sex                       | 0.904 (0.707–1.155) | 0.420                 | NI                   |
| Age                       | 1.301 (1.027–1.647) | 0.029                 | 1.356 (1.059–1.735) | 0.026                 |
| Tumor location            | 0.766 (0.672–0.873) | <0.001                | 0.874 (0.762–1.003) | 0.056                 |
| Tumor size                | 2.421 (1.897–3.092) | <0.001                | 1.290 (0.997–1.670) | 0.017                 |
| Pathologic type           | 0.984 (0.886–1.092) | 0.758                 | NI                   |
| Borrmann classification   | 1.790 (1.524–2.103) | <0.001                | 1.521 (1.279–1.810) | <0.001                |
| TNM stage                 | 2.428 (2.087–2.825) | <0.001                | 2.081 (1.772–2.443) | <0.001                |
| CEA                       | 1.844 (1.303–2.609) | 0.001                 | 1.431 (1.006–2.035) | 0.027                 |
| NLR                       | 1.581 (1.250–2.001) | <0.001                | 0.902 (0.637–1.278) | 0.563                 |
| PLR                       | 1.738 (1.332–2.267) | <0.001                | 1.272 (0.902–1.794) | 0.170                 |
| SII                       | 1.848 (1.455–2.348) | <0.001                | 1.551 (1.211–1.987) | 0.015                 |

HR, hazard ratio; NI, not included; OS, overall survival; CI, confidence interval; CEA, carcinoembryonic antigen; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; SII, systemic immune-inflammation index.
Fig. 3 Predictive ability of SII compared with NLR and PLR by receiver operating characteristic (ROC) curve analysis. NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio

Conclusions

We found that preoperative SII was a simple, strong, and independent predictor of OS in patients with gastric cancer. However, additional studies are needed to verify its prognostic value.

Authors’ contributions

SC, HW, and VH designed the study. KW and FD drafted the manuscript. XZ and ZY reviewed medical records and collected data. HR, TL, and EZ analyzed the data. JC supervised the study and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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