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Systemic inflammation score is a prognostic marker after curative resection in gastric cancer

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Abstract

Background: The systemic inflammation score (SIS), as calculated from preoperative serum albumin level and lymphocyte-to-monocyte ratio, has been demonstrated to be a prognostic marker in cancer. The present study intended to investigate the prognostic role of SIS in gastric cancer patients after curative gastrectomy in comparison with other prognostic markers.

Methods: Preoperative SIS was retrospectively calculated in patients who underwent curative gastrectomy between 2007 and 2011 in Fudan University Shanghai Cancer Center. The prognostic accuracy of each score was compared utilizing time-dependent receiver operating characteristics analysis.

Results: The higher SIS score was associated with older age, larger tumour size, a more advanced tumour-nodes-metastasis stage and lymph node status, deeper tumour invasion, the presence of lymphovascular invasion and a poorer overall survival and disease-free survival. In time-dependent receiver operating characteristics analysis, the SIS had a higher area under the curve for the prediction of 5-year overall survival than the neutrophil lymphocyte ratio. The SIS maintained the predictive accuracy superiority throughout the observation period.

Conclusion: The SIS is a useful prognostic marker in gastric cancer patients after curative gastrectomy.

Introduction

Gastric cancer (GC) is the fourth most common cancer and the third leading cause of cancer-related death around the world.[1,2] Despite recent advancements in the diagnosis and management of GC, the prognosis of GC patients remains to be poor, especially for advanced stage GC patients, with recurrence and metastasis being the main causes of cancer-related death.[3] At present, the most-recognized postoperative prognostic model was the American Joint Committee on Cancer (AJCC) tumour-node-metastasis (TNM) staging system.[4] Yet, accurate prediction of individual survival remains to be difficult. Broad survival variations have been reported in patients with the same stage and similar treatment regimens.[5–7]

Reports have established a link between host inflammatory response and oncologic outcomes.[8–10] Furthermore, cancer patients often present with elevated peripheral blood cell numbers, acute-phase proteins and decreased total albumin levels.[11] Several ratios of the circulating blood cell counts, such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR), have been shown to be the prognostic markers in various cancer patients, including GC.[12–15]

The systemic inflammation score (SIS), which is calculated from preoperative serum albumin level and LMR, has been reported to

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be a prognostic marker in clear cell renal cell carcinoma (ccRCC)[16] and colorectal cancer.[8] However, the prognostic impact of the SIS in GC patients and its superiority to the conventional prognostic markers remain elusive.

The purpose of the current study was to evaluate the correlation of the SIS with patient characteristics and its value in predicating prognoses of GC patients with curative gastrectomy. We also compared the predictive accuracy of the SIS to that of the TNM staging system and NLR.

Methods

Patient population

This study was approved by and under the censorship of the local ethics committee at Fudan University Shanghai Cancer Center (FUSCC, Shanghai, China). The study included 496 patients who underwent gastrectomy with potentially curative intent for gastro-esophageal (GE) junction or gastric adenocarcinoma between April 2007 and July 2011 in FUSCC. The exclusion criteria were as follows: (i) patients who were aged less than 18 years old; (ii) patients who had combined malignancy (n = 2); (iii) patients who had distant metastasis (n = 5); (iv) patients who previously had cancer-related surgery (n = 8); (v) patients had less than 16 lymph nodes retrieved (n = 30); (vi) laboratory tests were not taken within 1 week before surgery (n = 2); (vii) required clinicopathologic characteristics and follow-up data were missing (n = 46); (viii) patients who received anti-inflammatory medicine (including anti-biotics) or immunosuppressive treatment (including steroid) within 3 months before surgery (n = 15); (ix) patients who had chronic inflammatory disease (including autoimmune diseases, n = 6); (x) patients who received neoadjuvant therapy (including chemotherapy and radio-chemotherapy, n = 21); (xi) patients who underwent radical resection under emergent circumstances, including haemorrhage and perforation (n = 1); and (xii) patients who underwent non-curative resection based on histopathologic examination (n = 29).

Follow-up investigation

Follow-up investigation include clinical check-up, laboratory parameters including CA19–9, carcinoembryonic antigen, CA72-4 and CA125, radiological assessment (chest X-ray, magnetic resonance imaging or contrast-enhanced computed tomography scan of the upper abdomen every 3 months during the first 2 years and every 6 months afterwards). The recurrence was diagnosed comprehensively based on the results of radiological and histopathological examinations.

Data extraction

The patient demographic variables (age, gender), clinical characteristics and pathological features (tumour location, tumour size, type of resection, tumour gross type, depth of tumour invasion, tumour histology type, number of positive lymph nodes, number of retrieved lymph nodes, lymphovascular invasion, perineural invasion, results of preoperative blood tests and related follow-up data) were collected. All patients were staged based on the 8th edition of the AJCC-TNM staging system. The overall survival (OS) was defined as the period from the date of surgery to the date of death or censored at the date of the last follow-up. The disease-free survival (DFS) was defined as the period from the date of surgery to the date of the diagnosis of tumour recurrence or the last time of tumour observation. Serum samples were drawn and assayed within 1 week before surgery. The laboratory parameters included serum albumin level, total peripheral neutrophils, lymphocyte and monocyte count. The SIS was calculated from the results of the preoperative blood test (serum albumin level and LMR) as described previously.[16] Patients with both hypoalbuminemia (<40 gL^{-1}) and decreased LMR (<4.44) were assigned a score of 2; patients with either a decreased serum albumin level (<40 gL^{-1}) or decreased LMR level (<4.44) were allocated a score of 1; patients with a serum level >40 gL^{-1} and LMR level >4.44 were assigned a score of 0.

Statistical analysis

The statistical analysis was performed with SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Correlation between categorical variables were analysed with chi-squared tests or Fisher's exact test and continuous variables with Wilcoxon rank-sum test or Kruskal–Wallis test. Survival curves were plotted by the Kaplan–Meier method, and significance was determined by the log-rank test. Univariate and multivariate analysis were performed with the Cox proportional hazards regression model to identify factors that are related to GC prognosis. The prognostic or predictive accuracy of each variable was investigated using time-dependent receiver operating characteristic (ROC) analysis in the survivalROC package, and the bootstrap method was applied to test the significance of differences between the ROC curves. A two-sided P-value less than 0.05 was considered to be statistically significant. We utilized the R packages 'survivalROC' and 'timeROC' for time-dependent ROC analysis of the SIS, pStage and NLR.

Results

Association between the SIS and clinicopathological characteristics

Three hundred and thirty-one patients were included in this study. The clinicopathological characteristics of the patients were shown in Table S1. Two hundred and twenty-eight (68.9%) were male and 103 (31.1%) were female, and the mean age at the time of surgery was 55.3 (range 20–82 years). 39.3% of patients was in stage I, 20.8% in stage II and 39.9% in stage III based on the TNM staging system. The median follow-up time of patients was 61.2 months. According to the classification of the SIS, 68 (20.6%) patients were allocated a score of 2, 153 patients (46.2%) were allocated a score of 1 and 110 patients (33.2%) a score of 0. According to the time-dependent ROC curve to predict 5-year OS, a SIS score of 1 was defined as the optimal cut-off value (Fig. S1). Therefore, we divided the patients into two groups: SIS-low group, patients with a SIS score of 1 or 0 (n = 263); SIS-high group, patients with a SIS score of 2 (n = 68). Table S1 demonstrates the correlation between the SIS and clinicopathological factors. The higher SIS score was associated with older age, larger tumour size, a more

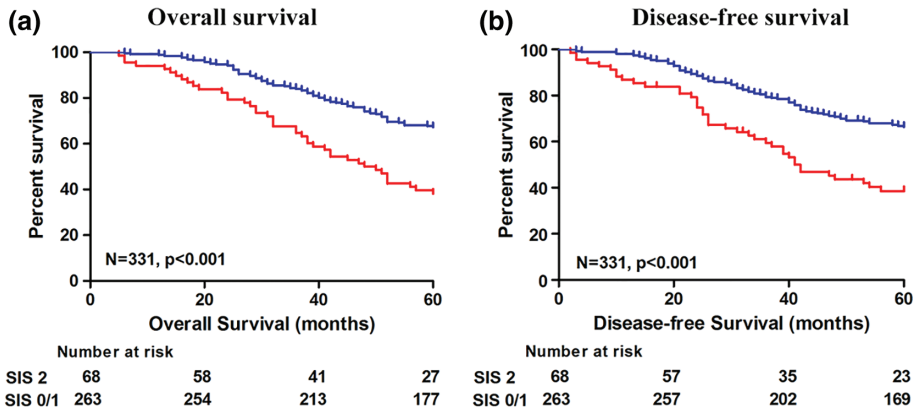

Fig. 1. Kaplan–Meier curves for overall survival (a) and disease-free survival (b) in the systemic inflammation score (SIS)-high (2) or SIS-low (0/1) groups. (a, b) ——, SIS 2 (n = 68); ——, SIS 0/1 (n = 263).

advanced TNM stage and lymph node status, deeper tumour invasion and the presence of lymphovascular invasion.

Correlation of the SIS score with patient survival

From the Kaplan–Meier survival curve, a correlation between the high SIS score and a poorer 5-year OS ($P < 0.001$, $P < 0.05$, Fig. 1a) and DFS ($P < 0.001$, $P < 0.05$, Fig. 1b) was observed. After adjusted for pStage, a higher SIS score was found to be associated with a poorer 5-year OS and DFS in pStage I, pStage II patients and pStage III GC patients (Fig. 2a–f).

Moreover, in the univariate analysis, SIS-high, older age, depth of tumour invasion, presence of lymph node metastasis and lymphovascular invasion were associated with a poor OS (Table S2). The multivariate analysis showed that SIS was an independent prognostic indicator for OS.

Comparison of the SIS with its components (serum albumin and LMR) with respect to the prognostic ability

We compared the predictive accuracies of the SIS and each of the components (serum albumin and LMR) utilizing the

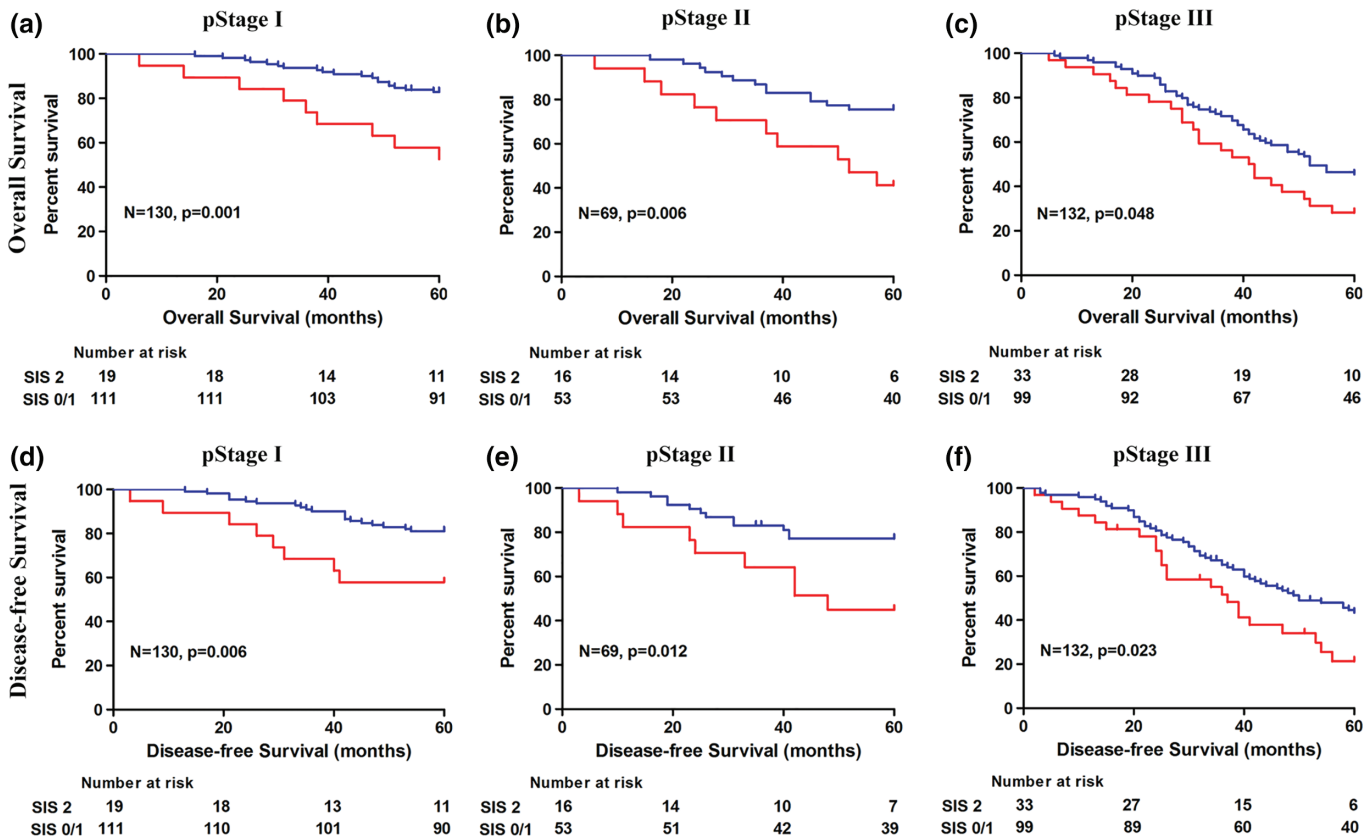

Fig. 2. Kaplan–Meier curves for overall survival (a–c) and disease-free survival (d–f) for each pStage in the systemic inflammation score (SIS)-high (2) or SIS-low (0/1) groups. (a, d) ——, SIS 2 (n = 19); ——, SIS 0/1 (n = 111); (b, e) ——, SIS 2 (n = 16); ——, SIS 0/1 (n = 53); (c, f) ——, SIS 2 (n = 33); ——, SIS 0/1 (n = 99).

time-dependent ROC curve for the prediction of 5-year OS. The area under the curves (AUCs) of SIS, serum albumin and LMR were 0.671 (95% confidence interval (CI) 0.628–0.725), 0.562 (95% CI 0.525–0.613) and 0.558 (95% CI 0.516–0.601), respectively (Table S3). The AUC of the SIS was obviously higher than that of serum albumin and LMR.

Comparison of the SIS with other prognostic markers (pStage and NLR) with regard to predictive accuracy

We then determined the prognostic accuracy of NLR and pStage for the prediction of 5-year OS and DFS. The AUCs of NLR and pStage were 0.609 (95% CI 0.549–0.661) and 0.652 (95% CI 0.614–0.695), respectively. The SIS was superior to NLR in the prediction of 5-year OS (Fig. 3a, Table S4). However, the SIS does not have significantly higher accuracy than pStage and NLR in the prediction of 5-year DFS (Fig. 3b). The time-dependent ROC curve of the SIS was continuously superior to NLR in the prediction of 5-year OS postoperatively (Fig. 3c).

Discussion

In the present study, we demonstrated the correlation between systematic inflammation and the survival of patients who underwent curative gastrectomy for GC. Preoperative SIS was significantly correlated with older age, larger tumour size, a more advanced TNM stage and lymph node status, deeper tumour invasion and the presence of lymphovascular invasion. SIS-high was associated with a poorer OS and DFS in all pStages. Even within the same pathological stages, prognosis can be determined with the use of SIS. We also compared the prognostic accuracy of the SIS with other prognostic markers (NLR and pStage) and found that SIS harboured superior prognostic accuracy than that of NLR for the prediction of 5-year OS, but not for 5-year DFS. SIS maintained a high prognostic accuracy at all time points tested. Thus, the SIS is a useful prognostic score for GC patients. Although the most-recognized postoperative prognostic model is TNM staging system for GC, inflammation-based score could provide relatively more accurate prognostic information.

It has been a recognized link between host inflammation and carcinogenesis.[8–10]

The cancer-related inflammation consists of the infiltration of inflammatory cells, including neutrophils, monocytes and leukocytes, and the production of inflammatory mediators.[17] Furthermore, the macrophages have been showed to facilitate cancer development.[18] Several ratios of the circulating blood cell counts, including NLR and LMR have been shown to the prognostic factors in GC.[12,19]

The SIS is an inflammation score calculated on serum albumin and LMR levels, which can be readily available from the routine blood test. The underlying mechanisms for the prognostic value of

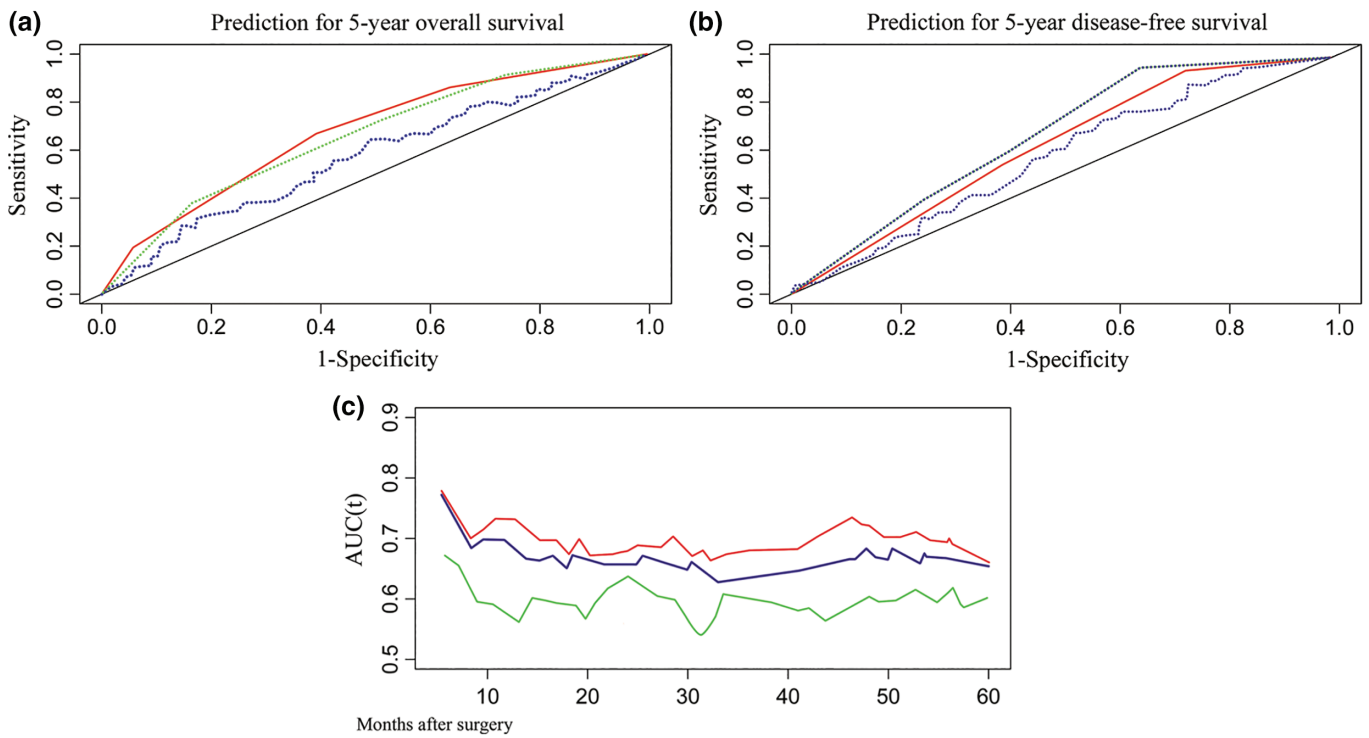

Fig. 3. Time-dependent receiver operating characteristic (ROC) curves of systemic inflammation score (SIS), neutrophil-to-lymphocyte ratio (NLR) and pStage for the prediction of 5-year overall survival (a) and disease-free survival (b). (c) Time-dependent AUC curves for the SIS, NLR and pStage. The horizontal axis represent the years after surgery and the vertical axis of the estimated area under the ROC curve for the overall survival at the time of interest. The time dependence of each AUC for overall survival is shown for the period up to 5 years after surgery. (a, b) ——, SIS; ·····, NLR; ·····, pStage; (c) ——, SIS; ——, pStage; ——, NLR.

the SIS might be attributed to the biological function of lymphocytes, monocytes and albumin. As a protein synthesized in the liver, serum albumin level is an indicator of nutritional status and sustained systematic inflammation response.[20] Low serum albumin level is negatively correlated with prognosis in various kinds of cancer with or without integrated into the prognostic score system.[21,22] Lymphocyte has been demonstrated to promote tumour immune-surveillance and suppresses tumour progression.[23] Thus, total circulating lymphocyte count may be a marker of host immunological status and low lymphocyte count is correlated with a poor prognosis.[24–26] Tumour-associated macrophages, derived from monocytes, have been reported to take part in the tumour invasion, metastasis, metabolic remodelling, immunosuppression and therapeutic resistance in cancer.[18,27] Peripheral monocyte count is a prognostic biomarker in a diversity of cancers.[25,28,29] SIS harboured superior prognostic accuracy than that of NLR for the prediction of 5-year OS possibly due to the reason that SIS took the patient nutritional status and inflammatory status into consideration, which may better reflect the prognosis of GC patients.

There are some limitations to our study. To start with, this study was retrospectively designed and included patients from one institution. Thus, selection bias might be unavoidable. Furthermore, we did not determine the association of SIS with other immunological features, such as ImmunoScore,[30] which has been shown to be associated with prognosis of GC.

In conclusion, we found that SIS is a useful prognostic indicator in GC patients, which might be used clinically in the future. We made an effort to identify a new tool to risk-stratify patients to aid in clinical decision making.

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Conflicts of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Time-dependent receiver operating characteristic (ROC) curve of the systemic inflammation score (SIS) for the prediction of 5-year overall survival. The optimal cut-off score of SIS was determined as 1.

Table S1. Demographic and clinicopathologic variables of patients with gastric cancer.

Table S2. Results of univariate and multivariate analysis of factors associated with overall survival in gastric patients with curative resection (n = 331). **P*-values <0.05 were considered statistically significant.

Table S3. The AUC for prediction of 5-year overall survival of systemic inflammation score (SIS), serum albumin and lymphocyte-to-monocyte ratio (LMR).

Table S4. The AUC for prediction of 5-year overall survival of systemic inflammation score (SIS), neutrophil-to-lymphocyte ratio (NLR) and pStage.