Systemic Inflammation with Sarcopenia Predict Survival in Patients with Gastric

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Abstract

Objective: The levels of platelet-related inflammation indicators and sarcopenia have been reported to affect the survival of patients with cancer. To evaluate the prognostic influence of platelet count (PLT), platelet–lymphocyte ratio (PLR), and systemic immune inflammation index (SII), and SII combined with sarcopenia on the survival of patients with gastric cancer (GC).

Methods: A total of 1131 patients with GC (811 men and 320 women, average age: 59.45 years) were evaluated. Receiver operating characteristic curves were used to determine the best cut-off values of PLT, PLR, and SII, and univariate and multivariate Cox risk regression models were used to evaluate whether SII is an independent predictor of overall survival (OS). The prognostic SS (SII-sarcopenia) was established based on SII and sarcopenia. Finally, a comprehensive analysis of the prognostic SS was performed.

Results: SII had the strongest prognostic effect. The SII and OS of patients with GC were in an inverted U-shape (adjusted HR = 1.06; 95% CI: 0.95-1.18; adjusted *P* = 0.271). In patients with SII >1800, SII was negatively correlated with OS (adjusted HR = 0.57; 95% CI: 0.29-1.12; adjusted *P* = 0.102), however, there is no statistical difference. Interestingly, a high SS was associated with a poorer prognosis. The higher the SS score, the worse the OS (*P*<0.001).

Conclusion: SII is an independent prognostic indicator of GC, and high SII is related to poor prognosis. A Higher SS score had worse survival. Thus, the prognostic SS is a reliable predictor of OS in patients with GC.

1. Introduction

Gastric cancer (GC) is the fifth most common malignancy and the fourth leading cause of cancer-related mortality worldwide, with more than 1 million incident cases and 769,000 deaths recorded in 2020. The incidence of GC varies by region and is the highest in East Asia and Eastern Europe and lower in North America and Northern Europe(Sung et al., 2021). Most GC patients are diagnosed with advanced disease owing to lack of suitable biomarkers. Chronic inflammation plays an important role in the occurrence of GC. The European Prospective Survey of Cancer and Nutrition study investigated the association between the inflammatory potential of diet and the risk of GC in 476,160 subjects from 10 European countries. After 14 years of follow-up, the results showed that the inflammatory potential of the diet is associated with an increased risk of GC(Agudo et al., 2018).

Systemic inflammation plays a key role in the pathogenesis and progression of cancer. As such, the role of the tumor microenvironment in tumorigenesis has also attracted increasing attention. However, the interaction between tumors and inflammation is complicated. Preoperative hematological inflammation biomarkers including blood neutrophil, lymphocyte, monocyte, and platelet count (PLT); albumin levels; and their combinations have received increasing attention in recent years. Particularly, studies have reported that PLT plays an important role in inflammatory diseases. In addition, PLTs are involved in the occurrence and metastasis of cancer(Bambace & Holmes, 2011). Another study showed that the cancer type-specific combination of PLT characteristics can be used to diagnose early-stage cancer(Sabrkhany et al., 2017). PLT-related inflammation biomarkers have also been identified to have a predictive value in various cancers(De Giorgi et al., 2019; Zhang, Zheng, Quan, & Du, 2021), including for the prognosis of GC. Among inflammatory biomarkers of inflammation, two PLT-related indicators are widely studied, namely, the platelet–lymphocyte ratio (PLR) and systemic immune inflammation index (SII)(Feliciano et al., 2017; Jomrich et al., 2021; Templeton et al., 2014). PLR independently predicts survival of patients with mucinous gastric cancer(Zhu, Gao, Liu, Li, & Xue, 2021), and SII may serve as a convenient marker of survival after radical surgery in GC patients(Q. Wang & Zhu, 2019).

Sarcopenia is a syndrome that represents degeneration and systemic loss of skeletal muscle mass. According to recent surveys, the prevalence of sarcopenia is relatively high, ranging from 15% at the age of 65 to 50% at the age of 80. Patients with sarcopenia often have a higher incidence of infectious diseases, metabolic syndrome, insulin resistance, and cardiovascular disease. In patients with cancer cachexia, anorexia, malnutrition, and systemic inflammation, the catalytic effect of the metabolic state is enhanced, leading to sarcopenia. Therefore, sarcopenia is considered to be a manifestation of cancer cachexia(Fukushima, Takemura, Suzuki, & Koga, 2018). Recent studies have shown that sarcopenia has an impact on the prognosis of various cancers. The survival rate of patients with sarcopenia is significantly lower than that of patients with esophageal cancer(Jin et al., 2021), colorectal cancer(Xie et al., 2021), pancreatic cancer(Cho et al., 2021), lung cancer(Kawaguchi et al., 2021) without sarcopenia. In general, sarcopenia plays an important role in the prognosis of cancer patients.

Although platelet-related inflammation indicators or sarcopenia have a certain role in predicting the survival of cancer patients, the prediction effect needs to be improved. Hence, we explored the relationship between the combination of the two and the survival of patients with GC.

2. Methods

2.1 Study Design and Population

This observational cohort study analyzed the data of patients with GC who visited one of more than 40 clinical centers in China between 2012 and 2018. The exclusion criteria were missing or abnormal preoperative data (data=0) on neutrophil count, PLT, sarcopenia, tumor stage, and lymphocyte counts (Figure 1). In total, 1131 GC patients were evaluated.

This study was approved by the Institutional Review Board of each hospital (Registration number: ChiCTR1800020329) and was conducted in accordance with the Declaration of Helsinki. All participants signed a written informed consent.

2.2 Assessments

Sarcopenia was diagnosed using a combination of low appendicular skeletal muscle index (ASMI) and low handgrip strength (HGS), based on the Asian Sarcopenia Working Group updated consensus in 2020. The calculation method of ASM has been reported previously in detail(Wen, Wang, Jiang, & Zhang, 2011). Briefly, we used the following equation: ASM = 0.193 × body weight (kg) + 0.107 × height (cm) -4.157 × sex (male: 1; female: 2) -0.037 × age (years)−2.631. ASMI was defined as ASM (kg)/height^2 (m^2)(Choi et al., 2021). Low muscle mass was defined as ASMI <7 kg/m^2 for males and <5.4 kg/m^2 for females. HGS was measured in the dominant hand using a Jamar dynamometer. HGS <28 kg (male) or <18 kg (female) was defined as insufficient muscle strength(L. K. Chen et al., 2020).

Laboratory measurements included albumin levels, neutrophil counts, lymphocyte counts, and PLT counts. All blood tests were performed after fasting for at least 9 h before anti-tumor treatment within 48 h of the first hospitalization. Body mass index (BMI) was calculated as BMI (kg/m^2) = weight (kg) / height^2 (m^2). PLR was calculated as PLR = PLT/lymphocyte counts, while SII was calculated as SII= neutrophil counts × PLT/lymphocyte counts. The SII-Sarcopenia Score (SS) is established based on SII and sarcopenia. Information on smoking status and alcohol and tea consumption was obtained using lifestyle questionnaires. All research results were reviewed and determined by an independent endpoint determination committee, whose members were blinded to the specific tasks of the research team. Pathological staging was according to the TNM staging system of the American Joint Committee on Cancer (8th edition)(Amin et al., 2017).

2.3 Statistical Analysis

The main endpoint was overall survival (OS), including death from any cause. Evidence of death was obtained from follow-up records. Predictive models were compared with the ROC curves and C-index. The chi-square test was used to compare the differences between the categorical variables in the baseline characteristics of the patients, and the t-test was used to compare continuous variables. The risk factors were modeled as continuous variables, and the optimal cut-off point was calculated using the Wilcoxon rank test. The chi-square test was used to model dichotomous and quartile SII and calculate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the OS of patients with GC.

Adjusted variables included age, sex, tumor stage, drinking status, albumin level, neutrophil count, BMI, surgery, chemotherapy, and radiotherapy. The heterogeneity between subgroups was evaluated using Cox regression, and the interaction between SII and the subgroups was checked using the probability ratio. Kaplan-Meier curves of survival according to PLT, PLR, and SII levels were generated. All statistical analyses were performed using R software version 4.0.5 (Lucent Technologies).

3. Results

3.1 Patient Characteristics

In total, 811 and 320 of the patients were male and female, respectively. The average age was 59.45 years. The optimal cut-off values predictive of survival were 270.50 for PLT, 149.57 for PLR, and 712.58 for SII, respectively (Supplemental Figure 1). Accordingly, low and high PLT, PLR, and SII were defined as ≤270.50 and >270.50, ≤149.57 and >149.57, and ≤712.58 and >712.58, respectively. In total, 798 and 333 patients had low and high PLT, 640 and 491 patients had low PLR and high PLR, and 498 and 633 patients had low SII and high SII, respectively. The clinicopathological characteristics of the patients are shown in Table 1.

Table 1
Baseline patient characteristics

	Total (n=1131)	PLT ≤270.50 (n=798)	PLT >270.50 (n=333)	*P* value	PLR ≤149.57 (n=640)	PLR>149.57 (n=491)	*P* value	SII ≤712.58 (n=498)	SII >712.58 (n=633)	*P* value
Sex (%)				<0.001			0.649			0.099
Male	811 (71.71)	598 (74.94)	213 (63.96)		455 (71.09)	356 (72.51)		370 (74.30)	441 (69.67)	
Female	320 (28.29)	200 (25.06)	120 (36.04)		185 (28.91)	135 (27.49)		128 (25.70)	192 (30.33)	
Smoking (%)				0.034			0.135			0.542
No	585 (51.72)	396 (49.62)	189 (56.76)		344 (53.75)	241 (49.08)		252 (50.60)	333 (52.61)	
Yes	546 (48.28)	402 (50.38)	144 (43.24)		296 (46.25)	250 (50.92)		246 (49.40)	300 (47.39)	
Drinking (%)				0.058			<0.001			0.342
No	881 (77.90)	616 (77.19)	265 (79.58)		524 (81.88)	357 (72.71)		395 (79.32)	486 (76.78)	
Yes	250 (22.10)	182 (22.81)	68 (20.42)		116 (18.12)	134 (27.29)		103 (20.68)	147 (23.22)	
Tea consumption (%)				0.015			0.282			0.589
No	837 (74.01)	589 (73.81)	248 (74.47)		482 (75.31)	355 (72.30)		373 (74.90)	464 (73.30)	
Yes	294 (25.99)	209 (26.19)	85 (25.53)		158 (24.69)	136 (27.70)		125 (25.10)	169 (26.70)	
Tumor stage (%)				0.216			0.031			0.136
□	143 (12.64)	112 (14.04)	31 (9.31)		85 (13.28)	58 (11.81)		71 (14.26)	72 (11.37)	
□	260 (22.99)	192 (24.06)	68 (20.42)		149 (23.28)	111 (22.61)		120 (24.10)	140 (22.12)	
□	389 (34.39)	274 (34.34)	115 (34.53)		236 (36.88)	153 (31.16)		174 (34.94)	215 (33.97)	
□	339 (29.97)	220 (27.57)	119 (35.74)		170 (26.56)	169 (34.42)		133 (26.71)	206 (32.54)	
Sarcopenia (%)				0.146			0.448			0.164
No	902 (79.75)	623 (78.07)	279 (83.78)		516 (80.62)	386 (78.62)		407 (81.73)	495 (78.20)	
Yes	229 (20.25)	175 (21.93)	54 (16.22)		124 (19.38)	105 (21.38)		91 (18.27)	138 (21.80)	
Surgery (%)				0.004			<0.001			0.006
No	542 (47.92)	382 (47.87)	160 (48.05)		348 (54.37)	194 (39.51)		262 (52.61)	280 (44.23)	

Notes: Continuous variables are presented as the mean ± standard deviation (SD). Meanwhile, BMI, albumin, neutrophil count, lymphocyte count, PLT, PLR, and SII are presented as the median (quartile range). Categorical variables are presented as numbers and percentages. Differences in normally and non-normally distributed baseline characteristics are compared using the chi-square test or t-test and using Wilcoxon rank sum test, respectively.

Abbreviations: BMI, body mass index; PLT, platelet count; PLR, platelet lymphocyte ratio; SII, systemic immune inflammation index; *P*, probability

	Total (n=1131)	PLT ≤270.50 (n=798)	PLT >270.50 (n=333)	*P* value	PLR ≤149.57 (n=640)	PLR>149.57 (n=491)	*P* value	SII ≤712.58 (n=498)	SII >712.58 (n=633)	*P* value
Yes	589 (52.08)	416 (52.13)	173 (51.95)		292 (45.62)	297 (60.49)		236 (47.39)	353 (55.77)	
Chemotherapy (%)				0.029			<0.001			0.003
No	694 (61.36)	493 (61.78)	201 (60.36)		356 (55.62)	338 (68.84)		281 (56.43)	413 (65.24)	
Yes	437 (38.64)	305 (38.22)	132 (39.64)		284 (44.38)	153 (31.16)		217 (43.57)	220 (34.76)	
Radiotherapy (%)				0.107			1.00			0.153
No	1120 (99.03)	793 (99.37)	327 (98.20)		634 (99.06)	486 (98.98)		496 (99.60)	624 (98.58)	
Yes	11 (0.97)	5 (0.63)	6 (1.80)		6 (0.94)	5 (1.02)		2 (0.40)	9 (1.42)	
Age, years (%)	59.45 (11.39)	60.02 (11.24)	58.08 (11.65)	0.170	59.10 (11.41)	59.91 (11.36)	0.235	58.98 (10.85)	59.82 (11.79)	0.218
BMI, kg/m^2	21.58 (3.42)	21.30 (19.00, 23.80)	21.50 (19.40, 24.10)	0.136	21.35 (19.00, 23.92)	21.40 (19.20, 23.90)	0.889	21.60 (19.10, 24.10)	21.30 (19.10, 23.80)	0.227
Albumin, g/L	37.31 (5.63)	37.55 (34.00, 41.77)	36.40 (33.00, 40.00)	0.199	38.70 (35.00, 42.12)	35.40 (32.05, 39.15)	<0.001	38.90 (35.20, 42.40)	35.90 (32.60, 39.80)	<0.001
Neutrophil count, 10^9/L	4.91 (5.43)	3.50 (2.32, 5.27)	4.90 (3.30, 6.77)	0.227	2.90 (2.07, 3.82)	5.79 (4.50, 7.88)	<0.001	3.42 (2.40, 5.17)	4.37 (2.80, 6.47)	<0.001
Lymphocyte count, 10^9/L	1.55 (1.48)	1.40 (1.00, 1.82)	1.50 (1.10, 2.00)	0.081	1.65 (1.24, 2.05)	1.16 (0.85, 1.52)	<0.001	1.85 (1.50, 2.20)	1.12 (0.80, 1.47)	<0.001
PLT, 10^9/L	236.55 (97.86)	196.00 (155.00, 232.00)	330.00 (295.00, 372.00)	2.325	202.50 (153.00, 249.00)	265.00 (211.00, 334.00)	<0.001	187.00 (143.00, 238.00)	259.00 (208.00, 330.00)	<0.001
PLR	234.53 (371.74)	138.60 (97.09, 191.53)	226.52 (164.13, 318.00)	0.327	120.18 (89.71, 162.36)	229.11 (172.03, 314.12)	<0.001	103.47 (80.41, 125.53)	221.33 (175.40, 312.86)	<0.001
SII	1019.24 (1757.98)	491.32 (267.68, 830.85)	1019.96 (657.64, 2000.56)	0.488	365.30 (230.19, 512.88)	1260.29 (889.26, 2065.10)	<0.001	346.38 (213.10, 545.78)	953.00 (603.75, 1807.67)	<0.001

Notes: Continuous variables are presented as the mean ± standard deviation (SD). Meanwhile, BMI, albumin, neutrophil count, lymphocyte count, PLT, PLR, and SII are presented as the median (quartile range). Categorical variables are presented as numbers and percentages. Differences in normally and non-normally distributed baseline characteristics are compared using the chi-square test or t-test and using Wilcoxon rank sum test, respectively.

Abbreviations: BMI, body mass index; PLT, platelet count; PLR, platelet lymphocyte ratio; SII, systemic immune inflammation index; *P*, probability

3.2 Predictive capabilities of PLT, PLR, and SII

The C-index of each prognostic model is shown in Table 2. Among the three, SII had the highest C-index at 0.561, followed by PLR at 0.544. PLT had the lowest C-index at 0.533. Similarly, the ROC curve showed that SII had the best predictive capability, and PLT had the least. SII and the OS of patients with GC tended to have a negative correlation, but it was not significant (per SD increment-HR=1.06; 95% CI: 0.95-1.18) (Table 3). The high SII group had poorer OS than did the low SII group (adjusted HR=1.45; 95% CI: 1.19-1.75; adjusted *P*=0.001). When SII was divided into quartiles (Q1, ≤330.2; Q2, >330.2, ≤611.9; Q3, >611.9, ≤1123.2; and Q4, >1123.2), the Q2 group showed a higher risk of death (adjusted HR = 1.43, 95% CI: 1.08-1.89, adjusted *P* = 0.012; Q3 group: adjusted HR = 1.67, 95% CI: 1.27-2.19, adjusted *P* <0.001; Q4 group: adjusted HR = 1.84; 95% CI: 1.39-2.44; adjusted *P* <0.001). The curves before and after adjustment showed an inverted U-shaped trend (Figure 2).

Table 2
C-indexes of PLT, PLR and SII for overall survival

Variables	PLT	PLR	SII
C-index	0.533	0.544	0.561
P value	0.013	0.749	0.229
Notes: PLT, platelet count; PLR, platelet lymphocyte ratio; SII, systemic immune inflammation index; *P*, probability			

Table 3
Association between SII and OS in patients with gastric cancer according to Cox regression models adjusted for potential confounders

SII	patients	Unadjusted		Adjusted	
		P value	HR (95% CI)	*P* value	HR (95% CI)
Per SD	1131	0.023	1.13 (1.02-1.25)	0.271	1.06 (0.95-1.18)
By cutoff					
≤712.58	640		ref.		ref.
>712.58	491	<0.001	1.50 (1.25-1.79)	<0.001	1.45 (1.19-1.75)
By quartile					
Q1 (≤330.2)	283		ref.		ref.
Q2 (330.2-611.9)	283	0.109	1.25 (0.95-1.64)	0.012	1.43 (1.08-1.89)
Q3 (611.9-1123.2)	282	0.003	1.50 (1.15-1.95)	<0.001	1.67 (1.27-2.19)
Q4 (>1123.2)	283	<0.001	1.65 (1.27-2.14)	<0.001	1.84 (1.39-2.44)
P for trend	1131	<0.001	1.18 (1.09-1.28)	<0.001	1.21 (1.11-1.32)
Notes: Data are presented as hazard ratios (95% confidence intervals). The analyses are adjusted for age, sex, tumor stage, drinking status, albumin level, BMI, surgery, chemotherapy, and radiotherapy.					
SII, systemic immune inflammation index; HR, hazard ratio; CI, confidence interval; *P*, probability; BMI, body mass index; Q, quarter					

Table 3
SS prognostic score construction

SS	Score	Patients (n)
SII≤712.58 and No-sarcopenia	0	516
SII>712.58 and No-sarcopenia	1	386
SII≤712.58 and Sarcopenia	1	124
SII>712.58 and Sarcopenia	2	105

Notes: SII, systemic immune inflammation index; SS, SII-Sarcopenia.

To exclude the influence of radiotherapy and chemotherapy on SII, we conducted a sensitivity analysis, and consistent results were obtained (Supplemental Table 1). In addition, we also performed COX regression analysis on patients undergoing surgery, radiotherapy and chemotherapy, and the results showed the same trend (Supplemental Table 2, Supplemental Table 3). High SII is related to poor prognosis. Using SII as a continuous variable for Cox regression analysis, low SII (≤1800) was significantly associated with poor prognosis (adjusted HR=1.16; 95% CI: 1.06-1.28; adjusted *P*=0.002). High SII (>1800) was also negatively correlated with poor prognosis, but there is no significant difference in this negative correlation (adjusted HR = 0.57; 95% CI: 0.29-1.12; adjusted *P* =0.102) (Supplemental Table 4).

3.3 Subgroup Analyses

The relationship between SII and OS among the different subgroups was evaluated using stratified analysis (Figure 4), including age, gender, drinking status, BMI, tumor stage, and sarcopenia. We found significant interactions between SII and tumor stage (*P*<0.001). GC patients with stage III-IV tumors (adjusted HR=1.77, 95% CI: 1.45-2.18, adjusted *P*<0.001) had significantly worse survival than did patients with stage I-II tumors (adjusted HR = 1.29, 95% CI: 0.75-2.22, adjusted *P*=0.353). Combined analysis of SII and tumor stage showed that patients with high SII and high tumor stage had the worst survival (Supplemental Figure 2).

3.4 Overall Survival

Kaplan-Meier curves of OS according to SII, sarcopenia, and SS are shown in Figure 5. High SII and sarcopenia were significantly related to the difference in OS in the univariate Cox proportional hazard regression (*P*<0.001). In addition, in the model comprising SII and sarcopenia showed that patients with high SII and sarcopenia had worse OS. Similarly, patients with a higher SS score also had worse OS (*P*<0.001).

Discussion

This multicenter cohort study found that among the PLT-related inflammation indicators PLT, PLR, and SII, SII has the best prognostic indication. Further analysis showed that patients with high SII is associated with poor OS in GC patients (Figure 3), and the HR gradually declined as SII increased to >1800. However, Cox regression analysis of SII showed that as the SII increased, survival worsened. A statistically significant positive correlation was found in the subgroup analysis with SII <1800 as the cut-off. Whereas in subgroup of SII >1800, HR=0.57, the statistically significant results were not shown. This might be due to the small number of patients with SII >1800. In addition, high SII combined with sarcopenia was associated with poor OS in patients with GC. The higher the SS score, the worse was the patient's OS (Figure 5). These results have also been supported by a number of studies.

Cytokines are key components of the inflammatory process. PLTs play an indispensable role in the development and metastasis of cancer. Once activated, PLTs can bind to tumor cells through P-selectin, which can be found on the surface of PLTs and bind to the CD24 ligand. In addition, PLTs promote tumor growth and metastasis by releasing pro-angiogenesis and growth factors. Therefore, a large number of studies have focused on the prognostic implant of PLT-related inflammation indicators in cancer patients, but the results have been conflicting. Therefore, other indicators that play an important role in predicting cancer survival have been evaluated (Kurtoglu, Kokcu, Celik, Sari, & Tosun, 2015; Peng et al., 2017; Sun, Ju, Han, Sun, & Wang, 2018; J. J. Wang et al., 2019; L. Wang et al., 2017). Notably, PLR and SII both include PLT PLR is considered to be a marker of endogenous residual anti-precancerous inflammation and procoagulant response in malignant tumors (Proctor et al., 2011). It is also considered to be a sensitive marker that could predict certain types of advanced cancer, treatment response, and prognosis (Zhou et al., 2014). In addition, an elevated SII indicates that a highly inflammatory tumor microenvironment. SII can be measured easily at an affordable cost using a reproducible method, making it a promising prognostic indicator in clinical applications(Dong et al., 2020).

Sarcopenia has also been confirmed to be related to poor prognosis in patients with cancer, thus making it a valuable prognostic indicator. A meta-analysis in 2016 showed that most studies on SMI and prognosis of patients with cancer were published after 2012, and more than

half of the studies were published after 2015. This indicates an increasing attention to the prognostic value of SMI in this population (Shachar, Williams, Muss, & Nishijima, 2016). Skeletal muscle loss after surgery has been confirmed to be significantly negatively correlated with adverse postoperative outcomes in patients with non-small cell lung cancer(Takamori et al., 2020). However, sarcopenia was measured using skeletal muscle area, which is different from our research. A retrospective analysis showed that SMI is an independent predictor of OS in patients with breast cancer(Hua et al., 2020). This association between SMI and cancer prognosis could be because certain tumors could induce systemic inflammation, and sarcopenia might be a reflection of more radical tumor metabolism. Cancer patients generally have varying degenerative diseases, causing loss of muscle mass, strength, and dysfunction. The occurrence of these degenerative diseases is influenced by several factors including malnutrition, insufficient physical activity, comorbidities, and other factors directly related to pathophysiology and treatment-related toxicities.

There have been several studies on sarcopenia combined with inflammatory indicators. Chen et al. retrospective analyzed the prognostic significance of preoperative SII in patients with colorectal cancer and concluded that SII has better predictive capability than PLR(J. H. Chen et al., 2017). Consistent findings were found in the current study. A 2021 study on the synergistic effect of sarcopenia and systemic inflammation on the survival of patients with oral cancer found that sarcopenia and systemic inflammation may have a negative synergistic prognostic effect on patients with advanced oral squamous cell carcinoma. (Lee et al., 2021). Despite differences in the assessment method for sarcopenia between this and the current study, it was confirmed that the ASM equation model was in good agreement with the dual X-ray absorbance (DXA) values(Wen et al., 2011). In addition, our study also combined the patients' grip strength. A recent study reported that the combination of skeletal sarcopenia and PLR can help identify the survival risk of patients (Yamahara, Mizukoshi, Lee, & Ikegami, 2021). Based on these findings and of another research(Hirahara et al., 2019), we established the SS score according to the combination of SII and sarcopenia.

In the stratified analysis, there was a significant interaction between tumor stage and SII. High SII patients with stage III-IV tumors showed significantly worse survival. This result was consistent with other studies that patients with stage III and IV tumors had worse 3-year OS rates than those with stage I and II tumors (16% and 9% vs 75% and 52%). The higher the tumor stage, the worse the survival rate (L. J. Chen, Chang, & Chang, 2021). Consistent findings were observed in the current study.

To our best knowledge, this is the first cohort study to explore the relationship between SII combined with sarcopenia and OS in patients with GC. The advantage of this study is that we first screened out the index SII that has the best predictive indication among platelet-related inflammation indexes, and combined with sarcopenia on this basis, we obtained a better predictive model SS. However, the following limitations should be also considered. First, the adopted anthropometric equations that had been validated in Chinese individuals to estimate muscle mass, rather than bioimpedance analysis (BIA) or DXA recommended by the European Working Group on Sarcopenia in Older People(Cruz-Jentoft et al., 2010) and Asian Working Group for Sarcopenia(L. K. Chen et al., 2014). However, DXA is expensive and the patients might have to expose to X-rays. There are very few BIAs in hospitals in mainland China, and the cut-off point for defining low muscle mass on BIA among elderly Chinese individuals has not been established(Zeng et al., 2015). Second, only the PLT was recorded, and thus, PLT-related inflammation indexes did not included the mean PLT volume and PLT distribution width. Third, there was no record of diet and socioeconomic status, which might have affected muscle loss and cancer death. Fourth, this study only included the Chinese population and did not represent other ethnic groups. Future research needs to investigate whether reducing systemic inflammation and increasing muscle mass can prolong patient survival and the underlying mechanisms on their influence in patients with GC.

Conclusion

Systemic inflammation and sarcopenia are relaed to the prognostic significance of GC patients. Among the PLT-related inflammation indicators PLT, PLR, and SII, SII has the best prognostic accuracy. In this study, SII independently predicted survival, thus making it a possible reliable indicator of GC prognosis. In addition, patients with both inflammation and sarcopenia have significantly worse survival than do patients without these impacts.

Abbreviations

GC: gastric cancer; PLT: platelet count; PLR: platelet lymphocyte ratio; SII: systemic immune inflammation index; OS: overall survival; HR: hazard ratio; 95% CIs: 95% confidence intervals; *P*: probability; AUC: area under the curve; NLR: neutrophil-to-lymphocyte ratio; ASMI: appendicular skeletal muscle index; HGS: low handgrip strength; ASM: appendix skeletal muscle mass; BMI: body mass index; ROC: receiver operating characteristic; Q: quarter; SD: standard deviation; SMI: skeletal mass index; BIA: Bioimpedance analysis; DXA: dual X-ray absorptance

Declarations

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Competing interests:

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions:

All authors contributed to the study conception and design. R.G.T., L.Y.Y., S.H.P., and W.Z.P. designed research; L.Y. Y and G.Y. Z and L.Q.Q. conducted research; Z.Q., Z.X. and S.M.M. analyzed data; W.M., Y.Q.H. and S.H.P. provided essential materials; L.Y.Y., T.M., Z.X.W., L.X.R., Z.K.P. and Y.M.wrote the paper; H.C.L., L.T., X.H.L., L.X.Y., L.S.Q. verified the results; L.Y. Y. had primary responsibility for final content. All authors read and approved the final manuscript.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate:

This study followed the Helsinki declaration. All participants signed an informed consent form and this study was approved by the Institutional Review Board of each hospital (Registration number: ChiCTR1800020329).

Consent to participate:

Because of the retrospective nature of this study, consent to participate for inclusion was waived.

Consent to publish:

Because of the retrospective nature of this study, consent to publish was waived.

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Figures

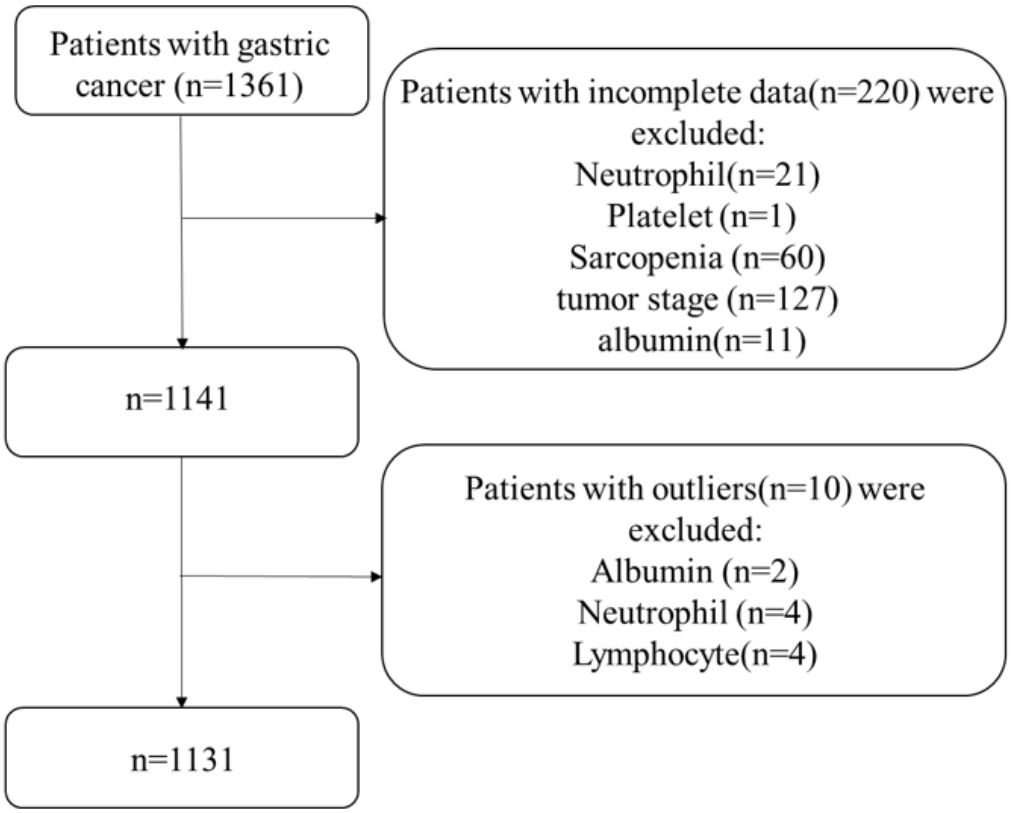

Figure 1

Flow chart

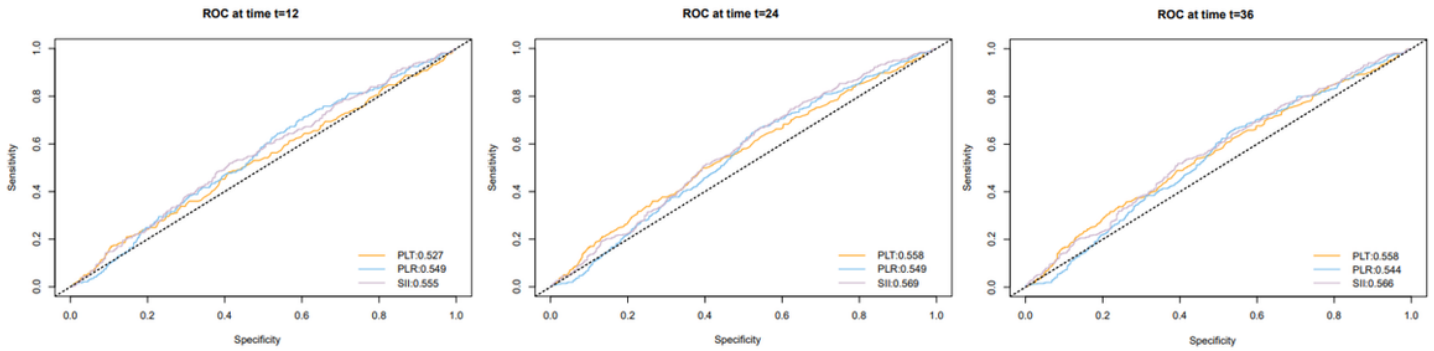

Figure 2

Receiver operating characteristics (ROC) curve for PLT, PLR, SII based on overall survival Notes: PLT,platelet count; PLR, platelet lymphocyte ratio; SII, systemic immune inflammation index; AUC, area under the curve.

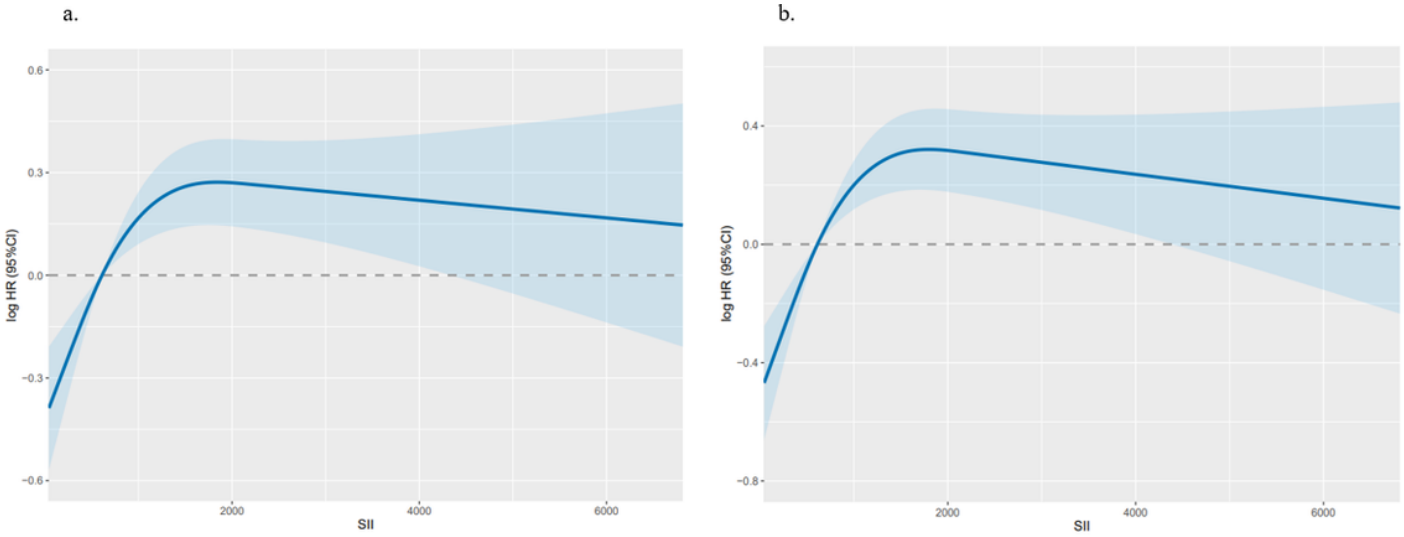

Figure 3

Relationship between SII and OS in patients with gastric cancer Notes: Use cox regression to analyze SII (a: as continuous variable P=0.023; OR=1.13; 95% CI: 1.02,1.25) and adjusted (b: as continuous variable P=0.271; adjusted OR=1.06; 95% CI :0.95,1.18). The analyses are adjusted for age, sex, tumor stage, drinking status, albumin level, BMI, surgery, chemotherapy, and radiotherapy. SII, systemic immune inflammation index; HR, hazard ratio; CI, confidence interval; BMI, body mass index.

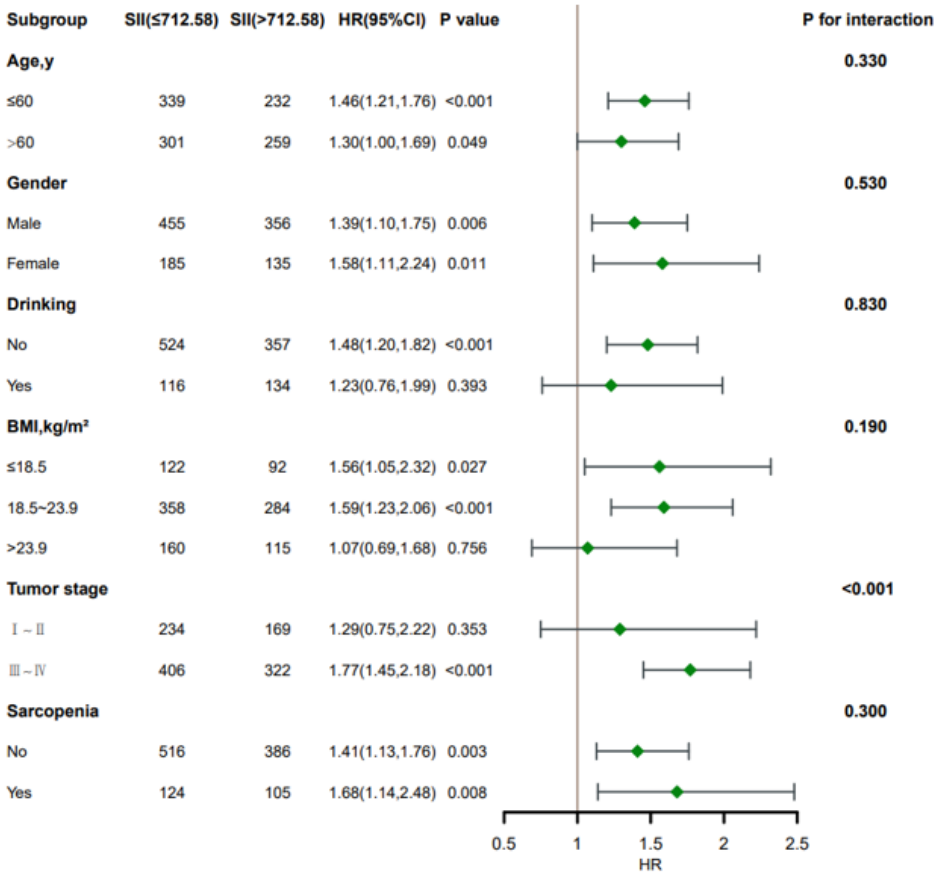

Figure 4

The relationship between SII and the OS of patients with gastric cancer in different subgroups Notes: The cox regression model was used to calculate hazard ratios (HRs) and 95% confidence interval (CI). Each subgroup is adjusted for age, sex, tumor stage, drinking status, albumin level, BMI, surgery, chemotherapy, and radiotherapy. SII, systemic immune inflammation index; HR, hazard ratio; CI, confidence interval; P, probability; BMI, body mass index.

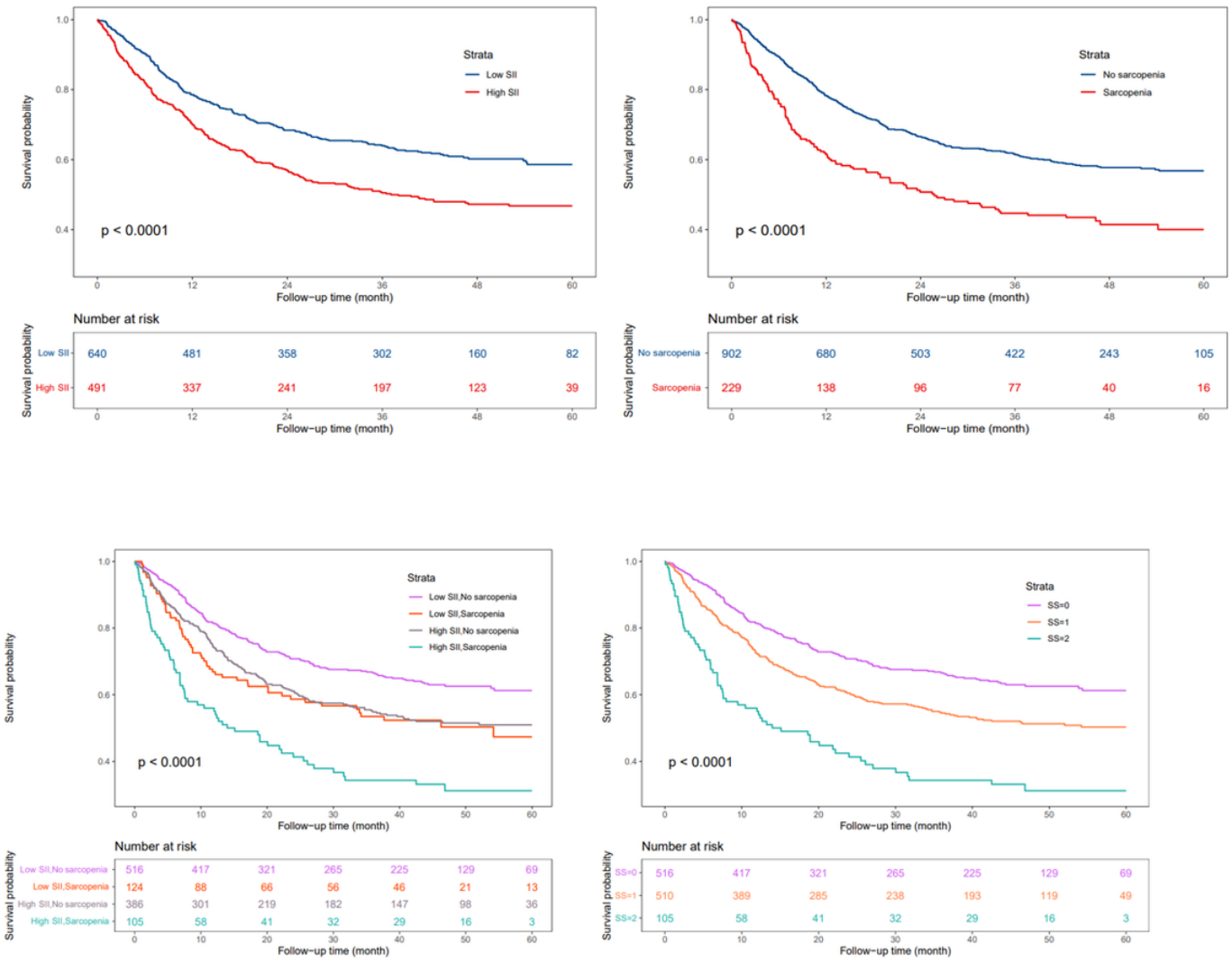

Figure 5

Kaplan-Meier survival curves for overall survival for patients with gastric cancer with high SII(>712.58) and sarcopenia versus low SII(≤712.58), no sarcopenia and SS, respectively. Notes: SII, systemic immune inflammation index; SS, SII-Sarcopenia; P, probability.

Supplementary Files

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