Systemic immune inflammation index and gastric cancer prognosis: A systematic review and meta-analysis

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Abstract. The present study aimed to pool the available data on the associations between the systemic immune inflammation index (SII) and overall survival (OS) or recurrence-free survival (RFS) in patients with gastric cancer (GC). A systematic search was conducted in the PubMed, EMBASE and Scopus databases for observational studies, and a random effects model was used to conduct the statistical analysis. Pooled effect sizes were reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CI). Data from 30 studies (24 conducted in China) with follow-ups ranging between 15.5 and 65.6 months were analyzed. Patients with GC and high SII levels had poor OS (HR, 1.53; 95% CI, 1.34-1.75) and recurrence free survival (HR, 1.41; 95% CI, 1.17-1.70). These increased risks were present irrespective of the treatment strategy (surgical or non-surgical management), the sample size (<500 and ≥500) and the cut-off used to define high and low SII (<600 and ≥600 x10^9 cells/l). The results of this meta-analysis suggest that high pretreatment SII levels were associated with poor OS and RFS in patients with GC.

Introduction

Gastric cancer (GC), a significant global public health burden, is among the top-ranked cancers for causing significant levels of mortality and disability (1). Globally, as per the estimated data for the year 2019, GC is the fifth most diagnosed cancer, fourth leading cause of cancer-associated mortalities and contributes to 1.7 million disability-adjusted life years (2-4). GC can be difficult to detect in its initial stages due to mild or absent symptoms, and is usually diagnosed at the advanced disease stage (5). GC requires a multidisciplinary approach to treatment, involving gastroenterologists, surgeons, medical oncologists and radiation oncologists (6,7). Advances in surgical techniques, chemotherapy, targeted therapy and immunotherapy have improved GC treatment outcomes, but early detection and timely treatment remain critical targets to improve the prognosis of the disease (8,9).

Despite advances in the diagnosis and treatment of GC, patients with advanced disease stages face a poor prognosis with a 5-year overall survival (OS) rate of <5% (10,11). This highlights the need for improved prognostic indices to guide clinical decision-making and improve patient outcomes. Systemic inflammatory responses contribute to the tumor microenvironment, promoting angiogenesis, tumor development and metastasis (12,13). Neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio and systemic immune-inflammation index (SII) have shown promise as prognostic markers in patients with specific types of cancer, such as metastatic non-small cell lung cancer, testicular germ cell tumor and rectal cancer (14-16). Moreover, the levels of these markers can be measured from routine blood tests, making them easily accessible and relatively inexpensive.

The SII has demonstrated its prognostic value in various types of tumor, such as urological cancers, including prostate cancer, small cell lung cancer and esophageal cancer (17-21), and is used to assess and quantify the systemic inflammatory response. It is a composite index that takes into account blood-based markers, such as neutrophil count, lymphocyte count and platelet count [SII=(platelet count x neutrophil count)/lymphocyte count]. It can be easily and inexpensively measured using blood samples and, therefore, has the potential to be adopted in everyday clinical practice for personalized treatment planning. It may also be used in combination with other clinical and pathological variables, such as tumour size, differentiation, clinical stage, vascular or lymphatic invasion, distant metastasis or abnormal carcinoembryonic antigen (CEA), to improve prognostic accuracy and guide treatment decisions for patients with GC. To the best of our knowledge, only two meta-analyses have focused on SII: One including eight studies and the other including 11 studies (22,23). The meta-analysis by Qiu *et al* showed that a high pretreatment SII is associated with poorer OS, but not poor disease-free survival (DFS) in patients with GC (22). By contrast, the analysis by Fu *et al* showed that higher SII levels are associated with poorer OS and DFS (23). The present study was designed to update the analysis with the data from new publications and evaluate the association of SII with OS or RFS in patients with GC.

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Key words: systemic immune inflammation index, gastric cancer, mortality, overall survival, recurrence free survival, systematic review, meta-analysis

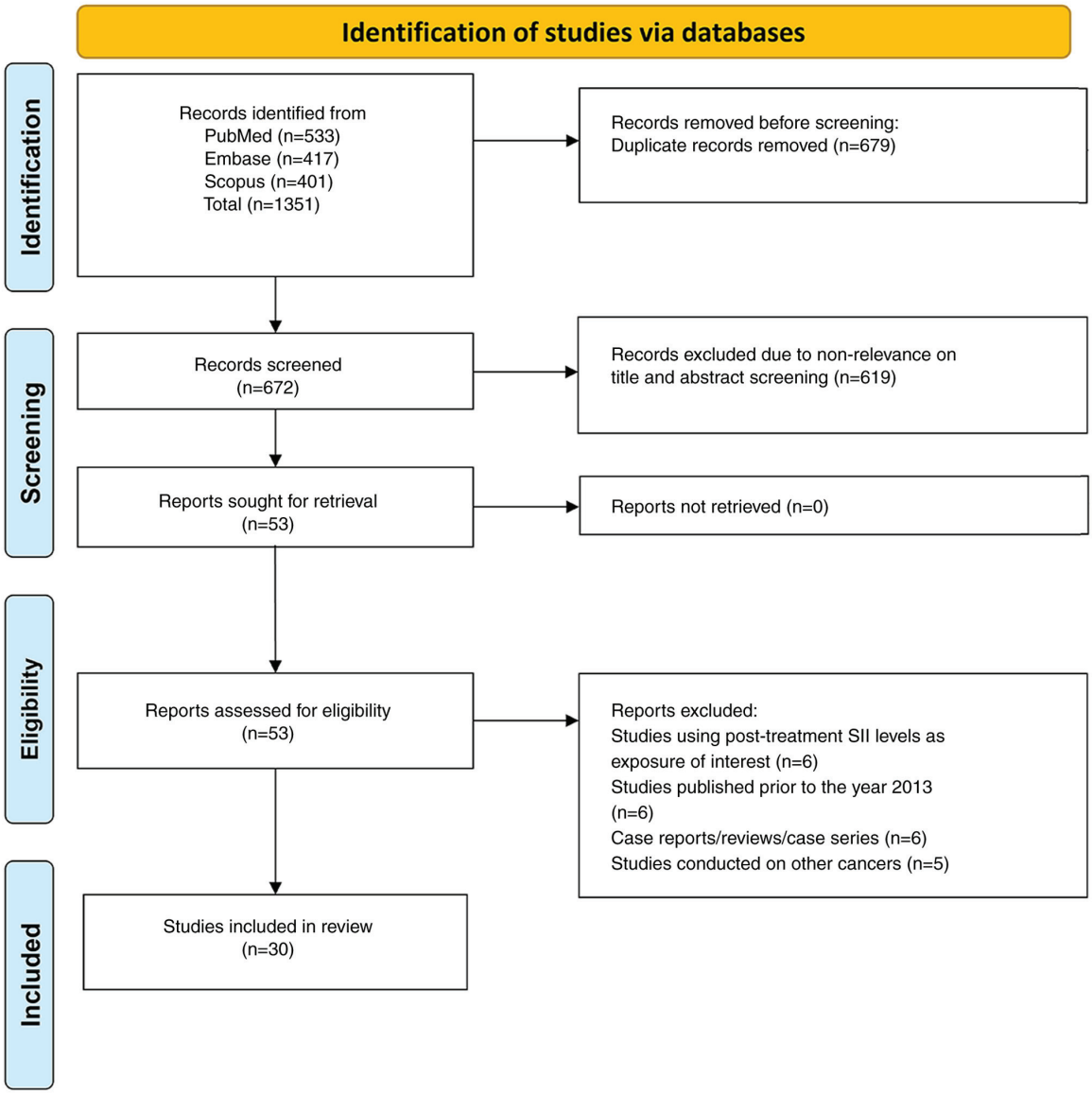

Figure 1. Selection process for studies included in the present review.

Materials and methods

Search for eligible studies. Electronic databases (PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.elsevier.com/products/embase) and Scopus (https://www.scopus.com/home.uri) were searched for relevant studies from the inception of database up to the 15th of April, 2023. The search strategy comprised the following terms: (Systemic immune-inflammation index OR SII OR immunonutritional biomarker OR platelet count OR neutrophil count OR lymphocyte count) AND (stomach tumor OR gastric tumor OR gastric neoplasm OR gastric malignancy OR gastric carcinoma OR gastric adenocarcinoma) AND (clinical outcome OR mortality OR survival OR death OR disease-free survival). The present study also manually reviewed the reference lists of pertinent articles and systematic reviews to identify additional studies that satisfied the inclusion criteria.

Screening and selection of studies. Subsequently, two study authors (XY and CW) independently screened all identified studies for inclusion based on pre-established eligibility criteria. The inclusion criteria were: i) Studies examining the association between pre-treatment SII and OS, DFS or recurrence-free survival (RFS) in patients with GC; ii) studies on adult patients with histologically-confirmed GC; iii) studies providing sufficient data on the association between pre-treatment SII and survival outcomes, including odds ratios/relative risks/hazard ratios (HRs) and 95% confidence intervals (CI); iv) studies published in English. The exclusion criteria were: i) Studies published as conference abstracts, case reports or letters to the editor; ii) studies conducted on animal models or cell lines; iii) studies that did not consider pre-treatment SII levels as an exposure of interest; iv) studies that lacked sufficient data or methodological quality (Newcastle Ottawa scale score <5) (24).

The present study specifically focused on observational studies exploring the association between pretreatment SII and survival outcomes in patients with GC. The inclusion criteria were restricted to studies published during the preceding decade, between 2013 and 2023, to ensure that the findings

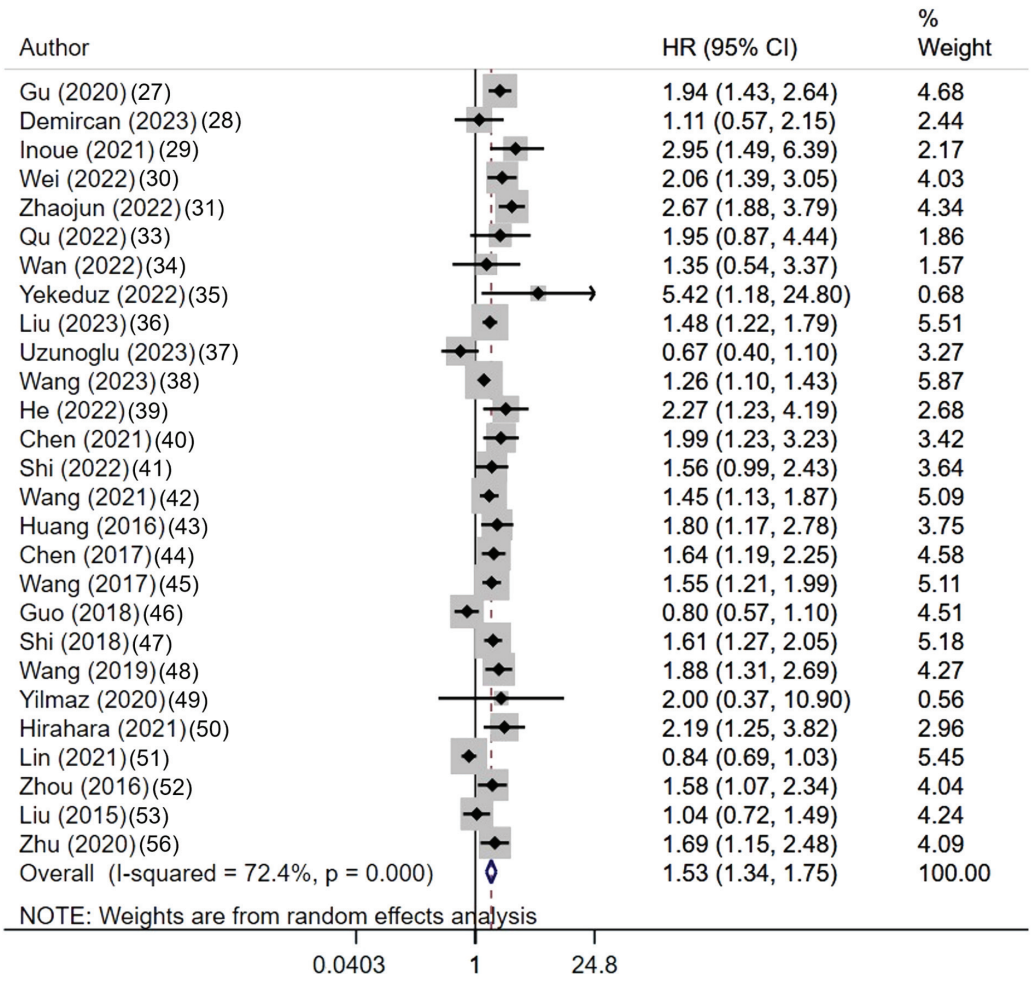

Figure 2. Overall survival in patients with gastric cancer and either high or low pretreatment SII levels. HR, hazard ratio; CI, confidence intervals.

are based on up-to-date literature reflecting contemporary evidence.

Full texts of potentially relevant studies were screened to determine their final eligibility. As this research involved analyzing previously published studies through a systematic review and meta-analysis, the need for ethical approval was waived. However, clear and thorough reporting of the methods and findings were ensured in the present study by following the PRISMA guidelines (25). The present study was prospectively registered at PROSPERO, with number CRD42023424804.

Data extraction, quality assessment and analysis. Next, two independent reviewers performed data extraction. The risk of bias of the observational studies was evaluated by calculating the Newcastle-Ottawa Scale values for each study (24). In cases of discrepancies in data extraction and bias assessments, a consensus was reached after discussion. For each outcome of interest, the present study performed a random-effects meta-analysis to calculate the pooled effect sizes along with their corresponding 95% CIs. I^2 statistic was used to assess statistical heterogeneity. Egger's test was used for detecting publication bias (26). Subgroup analysis was also conducted based on the primary treatment modality, sample size, cut-off used for SII and location of conduct of study. P<0.05 was considered to indicate a statistically significant difference.

Results

The present study included data from 30 studies in this analysis (27-56). Fig. 1 presents the process of the study selection. The majority of studies (n=24) were conducted in China (Table I); two studies were conducted in Japan and four in Turkey. Except for one study that had a prospective cohort design, all studies had a retrospective cohort design. In 24 studies, the main GC management strategy was gastrectomy, whereas in the remaining six studies, non-surgical management strategies included immune checkpoint inhibitors, combination of chemotherapy and radiotherapy, anti-programmed death 1 treatment and a combined immune- and chemo-therapy (Table I). The study sample sizes ranged from 45 to 2,257 participants, with 19 studies having <500 participants and 11 studies having ≥500 participants. The follow-up periods varied from 15.5 to 65.6 months. Quality scores on the NOS ranged from 6 to 9, with a mean score of 7.53, indicating overall acceptable study quality (Table I).

OS. Patients with high SII levels had poor OS (HR, 1.53; 95% CI, 1.34-1.75; n=27; I^2=72.4%), compared with patients with low SII levels (Fig. 2). Egger's test (P=0.01) and funnel plots (Fig. S1) indicated the presence of publication bias. Patients with high SII levels had poorer OS, irrespective of

Table I. Characteristics of the studies included in the present meta-analysis.

Author (year)	Study design	Country	Patients characteristics	Sample size	SII cut-off ($x10^9$ cells/l)	Newcastle Ottawa quality score	(Refs.)
Gu (2020)	Prospective cohort	China	With advanced GC; underwent radical resection (distal gastrectomy in majority); mean age, 63 years; men, 68%; T3-T4, 57% and >N0, 59%; follow-up, at least 5 years	598	≥556.0	8	(27)
Demircan (2023)	Retrospective cohort	Turkey	Patients undergoing neoadjuvant chemotherapy; median age, 60 years; men, 68%; poorly differentiated, 36%; median follow-up, 22.5 months	140	≥741.0	8	(28)
Inoue (2021)	Retrospective cohort	Japan	Patients with gastric adenocarcinoma undergoing curative gastrectomy; median age, 67 years; men, 65%; median BMI, 22 kg/m^2; differentiated tumour, 52%; follow-up, at least 5 years	447	≥395.0	8	(29)
Wei (2022)	Retrospective cohort	China	With advanced GC; underwent gastrectomy; median age, 59 years and men, 65%; T4a/T4b, 75%; N3a/N3b, 70%; poorly differentiated, 89%; median follow-up, 15.5 months	218	≥1185.2	8	(30)
Zhaojun (2022)	Retrospective cohort	China	With advanced GC; stage2/3, 82%; underwent gastrectomy; aged ≤60 years, 56%; men, 78%; poorly differentiated, 65%; median follow-up, 46 months	354	≥489.5	7	(31)
Wang (2022)	Retrospective cohort	China	Patients undergoing radical D2 gastrectomy followed by adjuvant chemotherapy; median age, 59 years; men, 77%; pT4, 70%; pN3a/pN3b, 56%; median follow-up, 29.1 months	89	>369.2	8	(32)
Qu (2022)	Retrospective cohort	China	Patients with advanced GC undergoing anti-PD-1 therapy; men, 68%; age >65 years, 27%; poor differentiation, 60%; lymph node metastasis, 72%; median follow-up, 17.5 months	106	>1140.9	9	(33)
Wan (2022)	Retrospective cohort	China	Patients with advanced GC receiving immunotherapy combined with chemotherapy; age <60 years, 76%; men, 78%; stage IV, 80%; poor differentiation, 39%; median follow-up, 27.3 months	45	≥1154.7	7	(34)
Yekeduz (2022)	Retrospective cohort	Turkey	Patients with advanced GC undergoing gastric resection surgery; median age, 53 years; men, 64%; T3/T4, 79%; N2/N3, 48%; median follow-up, 25.5 months	120	>708.0	7	(35)
Liu (2023)	Retrospective cohort	China	Patients with GC undergoing gastric resection surgery, 52% or chemotherapy/ radiotherapy, 40%; mean age, 59 years; men, 72%; T3/T4, 65%	1,133	>712.6	7	(36)
Uzunoglu (2023)	Retrospective cohort	Turkey	Patients undergoing gastrectomy; mean age, 64 years; male, 65%; mean follow-up time, 33.4 months	152	>892.0	6	(37)
Wang (2023)	Retrospective cohort	China	Patients undergoing radical gastrectomy; median age, ~58 years; male, 75%; stage 2/3, 90%; poor differentiation, 40%	542	>489.9	7	(38)

Table I. Continued.

Author (year)	Study design	Country	Patients characteristics	Sample size	SII cut-off ($x10^9$ cells/l)	Newcastle Ottawa quality score	(Refs.)
He (2022)	Retrospective cohort	China	Patients undergoing radical gastrectomy; median age, ~61 years; male, 79%; stage 1, 65%; negative lympho-vascular invasion, 87%; mean follow-up, 65 months	548	>508.3	8	(39)
Chen (2021)	Retrospective cohort	China	Patients undergoing treatment with immune checkpoint inhibitor; median age, 60 years; male, 75%; stage 3/4, 100%; poor differentiation, 75%; median follow-up, 23.8 months	139	≥665.3	9	(40)
Shi (2022)	Retrospective cohort	China	Patients undergoing radical surgery; age ≤60 years, 68%; male, 67%; stage 2/3, 76%; poor differentiation, 34%; median follow-up, 57 months	496	>315.0	8	(41)
Wang (2021)	Retrospective cohort	China	Patients undergoing radical surgery; median age, 61 years; male, 76%; stage2/3, 80%; median follow-up 56 months	608	≥372.8	8	(42)
Huang (2016)	Prospective cohort	China	Patients undergoing radical surgery; age >50 years, 71%; male, 67%; stage 3, 50%; median follow-up, 655 days	455	≥572.0	7	(43)
Chen (2017)	Retrospective cohort	China	Patients undergoing neoadjuvant chemotherapy or radical surgery; median age, 57 years; male, 71%; stage 2/3, 100%	292	≥600.0	8	(44)
Wang (2017)	Retrospective cohort	China	Patients undergoing radical surgery; age <60 years, 56%; male, 63%; TNM stage 3/4, 68%	444	≥660.0	7	(45)
Guo (2018)	Retrospective cohort	China	Patients undergoing radical surgery; age >65 years, 31%; male, 67%; TNM stage 3, 57%; poor differentiation, 62%; median follow-up, 35 months	1,058	≥521.6	8	(46)
Shi (2018)	Retrospective cohort	China	Patients undergoing radical surgery; age >60 years, 33%; male, 69%; TNM stage 2/3, 73%; poor differentiation, 47%; median follow-up, 36 months	688	>320.0	7	(47)
Wang (2019)	Retrospective cohort	China	Patients undergoing radical surgery; age >60 years, 37%; male, 73%; TNM stage 3, 100%; poor differentiation, 61%	182	≥600.0	8	(48)
Yilmaz (2020)	Retrospective cohort	Turkey	Patients undergoing radical surgery; median age, 59 years; male, 63%; TNM stage 3, 43%; median follow-up of 30 months	85	≥802.0	6	(49)
Hirahara (2021)	Retrospective cohort	Japan	Patients undergoing radical surgery; median age, 73 years; male, 73%; TNM stage 2/3, 58%; follow-up >60 months	212	≥661.9	7	(50)
Lin (2021)	Retrospective cohort	China	Patients undergoing radical surgery; mean age, 70 years; male, 75%; TNM stage 2/3, 70%; median follow-up, 65.6 months	2,257	≥569.9	8	(51)
Zhou (2016)	Retrospective cohort	China	Patients undergoing radical surgery; median age, 63 years; male, 81%; median follow-up, 48 months	192	>543.9	7	(52)
Liu (2015)	Retrospective cohort	China	Patients undergoing radical surgery; age >60 years, 45%; male, 69%; TNM stage 3, 65%; median follow-up, 25 months	455	≥660.0	8	(53)

Table I. Continued.

Author (year)	Study design	Country	Patients characteristics	Sample size	SII cut-off ($x10^9$ cells/l)	Newcastle Ottawa quality score	(Refs.)
Fang (2022)	Retrospective cohort	China	Patients undergoing gastrectomy; age >60 years, 50%; male, 75%; TNM stage 2/3, 65%; poor differentiation, 45%; minimum follow-up, 24 months	755	Change in SII (Δ SII)	7	(54)
Yin (2020)	Retrospective cohort	China	Patients undergoing gastrectomy along with chemotherapy; age >60 years, 30%; male, 74%; TNM stage 2/3, 89%; poor differentiation, 65%; follow-up, 60 months	576	Change in SII (Δ SII)	8	(55)
Zhu (2020)	Retrospective cohort	China	Patients undergoing gastrectomy; age <55 years, 48%; male, 65%; TNM stage 3, 57%	512	≥527.0	7	(56)

GC, gastric cancer; TNM, tumor node metastasis; BMI, body mass index.

Figure 3. Recurrence free survival in patients with gastric cancer and either high or low pretreatment SII levels. HR, hazard ratio; CI, confidence intervals.

whether they had received surgical or non-surgical management, whether they were part of sample sizes <500 or >500, or the cut-offs used to define high and low SII (<600 and ≥600 $x10^9$ cells/l) (Table II). Notably, the elevated risk of poorer OS associated with a high SII level was statistically significant in studies conducted in China (HR, 1.53; 95% CI, 1.34-1.75; n=21; I^2=73.7%), but not in studies conducted in other settings (Table II).

RFS. Patients with high SII levels had poorer RFS (HR, 1.41; 95% CI, 1.17-1.70; n=11; I^2=45.2%) compared with those with low SII levels (Fig. 3). Egger's test (P=0.591) and funnel plot inspection suggested a lack of publication bias (Fig. S2). Subgroup analyses showed that regardless of sample size, type of treatment received or the cut-off used to define high and low levels of SII, individuals with high SII levels had poorer RFS. However, the association between high SII levels and elevated risk of poor RFS was statistically significant in studies conducted in China (HR, 1.43; 95% CI, 1.23-1.66; n=7; I^2=19.9%), but not in studies conducted in other locations (Table II).

Discussion

The present meta-analysis revealed that high SII levels were associated with poor OS and RFS in patients with GC irrespective of the sample size, treatment received or cut-offs used to define high and low SII levels.

A meta-analysis by Qiu *et al* demonstrated a significant correlation between high SII levels and unfavorable OS outcomes (22). However, this study revealed no significant associations with the RFS (22). Another review by Fu *et al* that included 11 studies with ~7,000 patients with GC revealed that a higher SII is associated with an ~53% increase in the risk of death and a 57% increase in the risk of disease recurrence or progression (23). Studies have also shown that a high SII is associated with unfavorable survival outcomes in patients with solid tumors, hepatocellular cancer, urological cancers, small cell lung cancer and esophageal squamous cell cancer (19,57-59). The findings from these meta-analyses indicate that SII may serve as a reliable marker of prognosis in various cancer types and could

Table II. Association between SII and overall survival as well as recurrence free survival, within various subgroups.

	Overall survival			Recurrence-free survival		
Subgroups	Pooled HR (95% CI)	n	Heterogeneity I^2 (%)	Pooled HR (95% CI)	n	Heterogeneity I^2 (%)
Primary treatment						
Surgery (gastrectomy)	1.54 (1.31, 1.80)	21	77.7	1.35 (1.06, 1.85)	6	63.0
Non-surgical	1.54 (1.33, 1.79)	6	0.0	1.51 (1.23, 1.86)	5	0.0
Sample size of the included studies						
<500	1.67 (1.42, 1.97)	9	81.8	1.47 (1.17, 1.85)	10	41.9
≥500	1.36 (1.12, 1.65)	18	52.7	1.23 (1.08, 1.40)	1	-
Cut-off for SII used in the included studies						
<600	1.54 (1.26, 1.88)	13	81.8	1.68 (1.02, 2.78)	3	65.4
≥600	1.54 (1.30, 1.82)	14	48.2	1.36 (1.07, 1.73)	8	41.1
Location of study						
China	1.53 (1.34, 1.75)	21	73.7	1.43 (1.23, 1.66)	7	19.9
Other than China	1.70 (0.92, 3.13)	6	72.7	1.18 (0.65, 2.13)	4	69

SII, systemic immune inflammation index; HR, hazard ratio.

provide valuable information for clinical decision-making and patient management.

Systemic inflammatory responses are involved in cancer progression (12,13,60,61). SII is a commonly used systemic inflammation marker. A high SII score has been associated with poor prognosis in different types of cancers, such as hepatocellular, prostate, renal cell and non-small cell lung cancers (19,58). One potential explanation for the observed association may be the involvement of lymphocytes, specifically tumor-infiltrating lymphocytes, which inhibit the increases in the number of cancer cells (62,63). Thus, low lymphocyte counts, contributing to high SII scores, may indicate a weakened immune response favoring cancer cell survival and growth (64,65). Another hypothesis involves the role of neutrophils, which are capable of secreting various growth factors and interleukins that stimulate tumor cell growth. These neutrophils could enhance tumor progression (66,67) by promoting tumor angiogenesis and invasion, and releasing proteases that degrade the extracellular matrix and facilitate cancer cell migration (67). Thus, high neutrophil counts, which contribute to high SII scores, may be indicative of inflammatory environments supporting tumor growth and metastases (68,69). Finally, elevated platelet counts have been shown to increase SII scores and may be indicative of tumor microenvironments that support the survival and spread of cancer cells (70,71). Taken together, increased SII scores may reflect the presence of prevailing pro-tumor microenvironments, which could contribute to poor prognosis for patients with GC.

The findings of the present study may be used for improving clinical practice, since they support the use of SII as a potentially valuable prognostic tool that can lead to more personalized treatment strategies. By modifying prognostic criteria to incorporate SII, clinicians could improve the prediction of outcomes and tailor treatment plans, ultimately leading to improved patient care and timely monitoring. Incorporation of SII in the panel of prognostic indicators for GC may foster multidisciplinary collaboration among healthcare professionals, particularly oncologists, hematologists and immunologists. The present study also provided incentive to conduct further research into the underlying mechanisms connecting high SII levels to adverse outcomes.

The present meta-analysis has some limitations. First, all included studies were conducted in Asian countries, mostly in China, and this may complicate the generalizability of the findings. The significant association of SII with poor OS and RFS in the Chinese studies and the lack thereof in studies conducted outside of China may be attributed to the considerably larger number of studies from China, which could have increased the statistical power of the analysis. Conversely, the limited number of studies from non-Chinese countries may have underpowered the analysis. As a result, statistical significance may have remained undetected, even if it genuinely existed. Second, the selected studies used diverse thresholds to categorize patients into high and low SII groups, leading to discrepancies in the interpretation of SII levels and subsequent outcomes. Third, most of the included studies were retrospective in nature, which may have introduced various selection and misclassification biases. Fourth, the heterogeneity among the included studies was significant, and the specific reasons for this heterogeneity remain unclear. Finally, the present study found evidence of publication bias in the analysis for the overall survival outcome, which may have influenced the results.

In conclusion, high pretreatment SII levels were associated with poor OS and RFS in patients with GC. SII levels, therefore, may serve as a potential prognostic marker. However, the present study has limitations, such as the lack of diversity in patient ethnicity, the variability in cut-off values and the reliability on retrospective studies. Thus,

larger studies with a prospective design are needed to confirm the findings.

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Availability of data and materials

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

Authors' contributions

XY conceived and designed the study. XY and CW collected the data and performed the literature search. XY was involved in the writing of the manuscript. XY and CW confirm the authenticity of all the raw data All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patients consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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