Correlation between preoperative systemic immune-inflammatory indexes and the prognosis of gastric cancer patients

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Abstract. – **OBJECTIVE:** The aim of this study is to explore the potential value of high preoperative systemic immune-inflammation index (SII) expression in the prognosis of patients with gastric cancer (GC) by meta-analysis.

MATERIALS AND METHODS: The major databases were searched to screen relevant clinical studies on the prognostic value of SII in gastric cancer (GC) patients, published from the establishment of the database to May 2022. RevMan 5.3 was utilized to perform meta-analysis on relevant data. The differences in age, tumor size, differentiation degree, tumor-node-metastasis (TNM) stage, overall survival (OS), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) between the high SII expression group (H-SII) and the low SII expression group (L-SII) were compared. Heterogeneity was assessed by Cochran's Chi-square test.

RESULTS: A total of 16 studies with 5,995 GC patients were included. Compared with the L-SII group, the proportion of patients older than 60 years in the H-SII group was markedly higher (OR=0.85, 95% CI: 0.75-0.97; Z=2.45, p=0.01); the proportion of patients with tumor size larger than 5 cm increased (OR=2.18, 95% CI: 1.69-2.81; Z=6.03, p<0.00001); the proportion of patients with TNM stage ≥T3 increased (OR=2.41, 95% CI: 1.89-3.08; Z=7.06, p<0.00001); overall survival (OS) decreased (OR=-23.92, 95% CI: -37.57 to -10.26; Z=3.43, p=0.0006); the 5-year survival rate (SR) decreased markedly (OR=0.39, 95% CI: 0.24-0.64; Z=3.81, p=0.0001); the proportion of patients with high NLR expression was increased (OR=22.19, 95% CI: 10.66-46.18; Z=8.29, p<0.00001); and the proportion of patients with high PLR expression was also markedly increased (OR=15.97, 95% CI: 8.57-29.75; Z=8.73, p<0.00001).

CONCLUSIONS: A high preoperative SII was an independent risk factor for poor prognosis in GC patients.

Introduction

Gastric cancer (GC) is a common gastrointestinal malignancy. In 2020, there were more than 1 million newly diagnosed GC patients worldwide, and approximately 769,000 of them died of GC, ranking 5th and 4th among malignant tumors in terms of incidence and mortality, respectively[1]. Moreover, the incidence of GC in East Asia and Eastern Europe is drastically superior to that in North America and Northern Europe[2]. Current research results have shown that GC is related to *Helicobacter pylori* infection, drinking, smoking, eating habits, sex, age, genetics, environment[3], etc. The incidence of GC in China ranks first in the world, accounting for 41.9% of the world's GC patients, and the northwest region is a high-incidence area of GC[4]. With the development of medical technology, the incidence of GC has decreased, but the diagnosis and treatment of GC diseases is still severe due to problems such as population base and aging[5]. There is no typical clinical manifestation in the early stage of GC. In China, more than 80% of patients with advanced and middle and advanced GC are diagnosed, and the early diagnosis rate is still lower than 20%[6], which leads to increased difficulty in treatment, markedly shorter survival time, and poor prognosis of GC patients. The prognosis of GC patients is mainly evaluated according to clinical stage, tumor diameter, and treatment methods, but the outcome is unsatisfactory due to individual differences[7]. Therefore, effective clinical prognostic indicators are of

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great significance in the treatment and follow-up of GC patients.

As early as the 19th century, some researchers[8] proposed a correlation between inflammation and tumors. Tumor-related inflammation promotes the expression of vascular growth proteins through the release of inflammatory factors, leading to cancer genesis, proliferation, invasion, and metastasis[9]. In recent years, studies[10] have noted that there is a correlation between the inflammatory microenvironment and tumors, and tumor-related inflammation is one of the key factors in cancer progression. Current studies have shown that inflammatory factors such as the systemic immune inflammation index (SII), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) are correlated with tumorigenesis[11,12], among which SII is one of the indicators reflecting the inflammatory state of the host. It has been utilized as a prognostic marker for a variety of tumors[13]. Some researchers[14] have noted that the comparison of SII in GC patients undergoing radical gastrectomy showed that the overall survival (OS) of GC patients with SII≥395 was markedly shorter than that of GC patients with SII<395, and the peritoneal recurrence rate was markedly increased. It was pointed out that SII is an independent prognostic factor of GC. Some researchers have noted that an increased SII is a negative prognostic factor in GC15. Schiefer et al[16] noted that the SII was correlated with the OS of GC patients, but it could not be independently utilized as a prognostic indicator of GC patients. Hence, the value of the preoperative SII in the prognosis of GC patients is controversial at present.

In summary, there is still considerable controversy about the clinical meaning of the preoperative SII in the prognosis of GC patients. A meta-analysis was performed to systematically evaluate the role of SII in the prognosis of GC patients and provide a reference for related studies.

Materials and Methods

Data Inclusion Methods

GC patients were recruited. The types of included studies were randomized controlled trials (RCTs), prospective cohort studies, and retrospective controlled studies. The treatment method included in the study was surgical treatment. Information was collected, such as study author, year, number of GC patients, grouping, number of patients in each group, treatment methods, and prognosis.

Inclusion and Exclusion Criteria

Inclusion criteria: i) studies published from the establishment of the database to May 2022 on the relationship between preoperative SII and prognosis assessment of GC; ii) subjects were more than one GC patient who underwent surgical treatment; iii) RCTs, prospective cohort study, and retrospective controlled study; iv) basic data including sex, age, and grouping of patients were recorded in detail and complete, and the prognostic indicators of patients were recorded and counted in detail.

Exclusion criteria: i) publicity literature such as individual case reports, literature reviews, expert reviews, editorial opinions, news reports, and product descriptions; ii) literature without prognostic index data; iii) no original data were provided; iv) repeated publications, etc.; v) those not related to the prognostic value of SII in GC; vi) GC patients who were not treated by surgery for various reasons; and vii) animal tests, in vitro cell tests, and other basic research.

Retrieval Strategy

The system retrieved the relevant data included in each online database. The duration was from the establishment of the database to May 2022. "Preoperative", "systemic immune index", SII", "Inflammatory index", "Gastric cancer", "GC", "Correlation analysis", and "surgery" were searched in PubMed, Nature, Web of Science, Spring, China National Knowledge Infrastructure (CNKI), Science Direct, and other online databases. The keywords "or" and "and" were utilized for the joint search. Clinical studies on the prognostic role of SII in GC published from the self-established database to May 2022 were searched. All search keywords were freely combined and searched. The search did not restrict the language.

Literature Selection and Quality Evaluation

Regarding the Cochrane Reviewer's handbook system, the quality of the literature was assessed and extracted by two reviewers separately to exclude the literature that did not meet the requirements and was of low quality. If the audit results were inconsistent, two reviewers discussed whether to include the document or consulted a third reviewer for final evaluation. Information on all available variables of the included articles was extracted and entered into a Microsoft Excel database.

Cochrane Reviewer's Handbook 5.1.0 was utilized for quality assessment, which included i) whether the method was correct and clear; ii)

whether the generation method of random sequences was clearly explained; iii) whether the results were clear and definite; iv) whether selective reporting existed in the results; v) whether there was a blinded controlled study of participants and personnel; vi) whether the results were evaluated by a blinded method; and vii) whether the data were complete and whether selective reporting existed. According to the criteria, the included studies were evaluated in 7 aspects, and the total score was 7, with 4 or more being considered high-quality research. The literature was initially screened regarding the title, and the lack of data was supplemented by contacting the original author. After further reading of the abstract and full text, the quality of the included literature was evaluated by combining the Jadad scale. Finally, the literature with Jadad scale scores above three was selected and included in this meta-analysis.

Extraction of Data

Two reviewers were responsible for the extraction of the included literature, which mainly included the following aspects: i) basic information: title of the article, first author, publication year, and publication journal; ii) subjects: number of samples included in the study, number of GC patients in different groups, treatment methods of GC patients, age, sex, etc. ; iii) evaluation method: changes in corresponding clinical indicators under low and high SII; iv) according to the difference in SII, the subjects were divided into a high SII group (H-SII) and a low SII group (L-SII); v) after a review of the relevant literature, the relevant indicators to evaluate the prognostic value of SII in GC included age, sex, tumor size, differentiation degree, tumor-node-metastasis (TNM) stage, OS, NLR, PLR, and carcinoembryonic antigen (CEA).

Statistical Analysis

Excel 2016 was employed to organize the data, and the Cochrane Reviewer's Handbook and Jadad scale was utilized for quality evaluation. RevMan 5.3 (Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark) was utilized for meta-analysis.

In heterogeneity analysis, the Chi-square test was implemented for the preliminary test of literature heterogeneity, and the significance level was set as $\alpha=0.05$ and $p<0.05$. Then, the I^2 test was performed to quantitatively evaluate the heterogeneity results. When I^2 was lower than 25%, the literature had low heterogeneity. When $25\% < I^2 < 50\%$, there was moderate heterogeneity. When $I^2 > 50\%$, there

was substantial heterogeneity. Based on this, when $I^2 < 50\%$, the fixed effects model (FEM) was adopted. When $I^2 > 50\%$, the random effect model (REM) was adopted. Measurement data are represented as the mean (MD) and standard deviation (SD), and point estimates and 95% confidence intervals (CIs) are given for each effect size. The dichotomous variables were denoted by relative risk (RR) and odds ratio (OR). RevMan 5.3 was employed to draw funnel plots to display potential publication bias, and forest plots were output to extract Z values and p-values from the results for judgment of meta-analysis results. Sensitivity analyses were performed by excluding studies with the lowest quality scores. Potential publication bias was observed by a funnel plot showing an inverted funnel plot. When $p<0.05$, the difference was considered significant.

Results

Retrieval Process

"Preoperative", "systemic immune index", SII", "Inflammatory index", "Gastric cancer", "GC", "Correlation analysis", and "surgery" were searched in PubMed, Nature, Web of Science, Spring, CNKI, Science Direct, and other online databases, and 1,052 articles were retrieved. After preliminary screening, 671 duplicate articles were deleted, 165 articles marked as unqualified by automated tools were recorded, 113 articles were deleted for other reasons, and 103 relevant studies were included. After the articles that did not meet the inclusion criteria were excluded according to the title of the article, 52 articles were obtained. Then, by reading the abstract of the article and the content of the study, literature reviews, conference short articles, case analyses, and risk factor assessments were excluded. After preliminary screening, 21 studies met the inclusion criteria. After further intensive reading of the included articles, 5 articles were excluded for which the original data could not be obtained. Finally, 16 articles[17-32] were included for analysis (Figure 1).

Basic Information of the Included Literature

A total of 5,995 GC patients were included in the final 16 references[17-32], including 2,301 in the H-SII group and 3,694 in the L-SII group (Table I).

Quality Evaluation

First, the Cochrane Reviewer's Handbook was utilized to conduct quality assessment of the 16 included articles[17-32], and the evaluation chart was

Table I. Basic information of the included literature.

The first author	Year	The number of cases	H-SII group	L-SII group	Outcome indicators
Chen et al[17]	2017	107	55	52	Age, sex, tumor size, differentiation degree, TNM stage, OS, NLR, PLR, CEA
He et al[18]	2022	358	91	267	Sex, degree of differentiation, NLR, PLR, CEA
Hirahara et al[19]	2021	415	106	309	Sex, differentiation degree, TNM stage, 5-year survival rate (SR)
Hirahara et al[20]	2020	412	105	307	Sex, differentiation degree, TNM stage, 5-year SR
Huang et al[21]	2016	445	110	335	Age, sex, degree of differentiation, TNM stage, OS, 5-year SR
Inoue et al[22]	2021	447	280	167	Sex, 5-year SR
Shi et al[23]	2018	688	332	356	Age, sex, tumor size, differentiation degree, TNM stage, NLR, PLR
Wang et al[24]	2017	444	161	283	Age, sex, tumor size, differentiation degree, TNM stage, OS, NLR, PLR, CEA
Wang et al[25]	2021	608	328	280	Age, sex, tumor size, differentiation degree, TNM stage
Wang et al[26]	2019	182	69	113	Age, sex, tumor size, differentiation degree, OS, NLR, PLR
Yekedüz et al[27]	2021	83	42	41	Sex, degree of differentiation
Yılmaz et al[28]	2020	85	38	47	Age, sex, TNM stage
Yin et al[29]	2021	378	141	237	Age, sex, tumor size, TNM stage, OS, NLR, PLR, CEA
Zhaojun et al[30]	2022	771	240	531	Age, sex, tumor size, differentiation degree, TNM stage, OS, 5-year SR
Zheng et al[31]	2017	60	31	29	Age, sex, differentiation degree, TNM stage
Zhu et al[32]	2020	512	172	340	Age, sex, tumor size, TNM stage, 5-year SR, NLR

Overall survival (OS), neutrophil to lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR).

drawn for the overall evaluation of literature quality (Figures 2-3). The random sequence generation (selection bias), allocation concealment (selection bias), and blinding of participants and personnel (performance bias) of the 16 studies included in the meta-analysis were all "low risk". The blinding of outcome assessment (detection bias) of one study[24] was "high risk", that of one study[21] was "unclear risk", and the others (14 studies)[17-20,22,23,25-32] were "low risk". The incomplete outcome data (attrition bias) of one article[31] was "unclear risk", and the others (15 studies)[17-30,32] were "low risk". One study's[26] selective reporting bias belonged to "unclear risk", two[17,23] were "high risk", and the rest (13 studies)[18-22,24,25,27-32] were "low risk".

Furthermore, the Cochrane Reviewer's Handbook was employed to evaluate the literature quality, and the quality of the included literature was above grade B. Subsequently, the Jadad scale was adopted to evaluate the quality of the included literature. The results showed that the Jadad scale score of the included literature was more than three points, so sensitivity analysis was not needed.

Comparison of the Age of GC Patients

There were 11 studies that statistically analyzed the relationship between SII and whether GC patients were older than 60 years. The correlation between the SII and the age of GC patients was analyzed (Figure 4). No great heterogeneity was indicated between age and SII (I^2=44%, p=0.06). FEM analysis suggested no substantial heterogeneity in the proportion of patients older than 60 years between groups (OR=0.85, 95% CI: 0.75-0.97; Z=2.45, p=0.01).

Comparison of the Sex Ratio in GC Patients

The relationship between the SII and sex (male proportion) in GC patients was statistically analyzed in 16 included studies[17-32]. The correlation between the SII and the age of GC patients was discussed (Figure 5). No notable heterogeneity was indicated between sex and SII (I^2=21%, p=0.22). Using the FEM, no obvious heterogeneity was found in the proportion of male GC patients between groups (OR=0.97, 95% CI: 0.86-1.09; Z=0.54, p=0.59).

Comparison of Tumor Size

The relationship between SII and tumor size (whether greater than 5 cm) in GC patients was statistically analyzed in 8 studies[17,23-26,29,30,32]. The correlation between the SII and tumor size in GC patients was analyzed (Figure 6). Remarkable heterogeneity between tumor size and SII was found (I^2=66%, p=0.005). REM analysis showed that the proportion of patients with tumor sizes larger than 5 cm in the H-SII group was
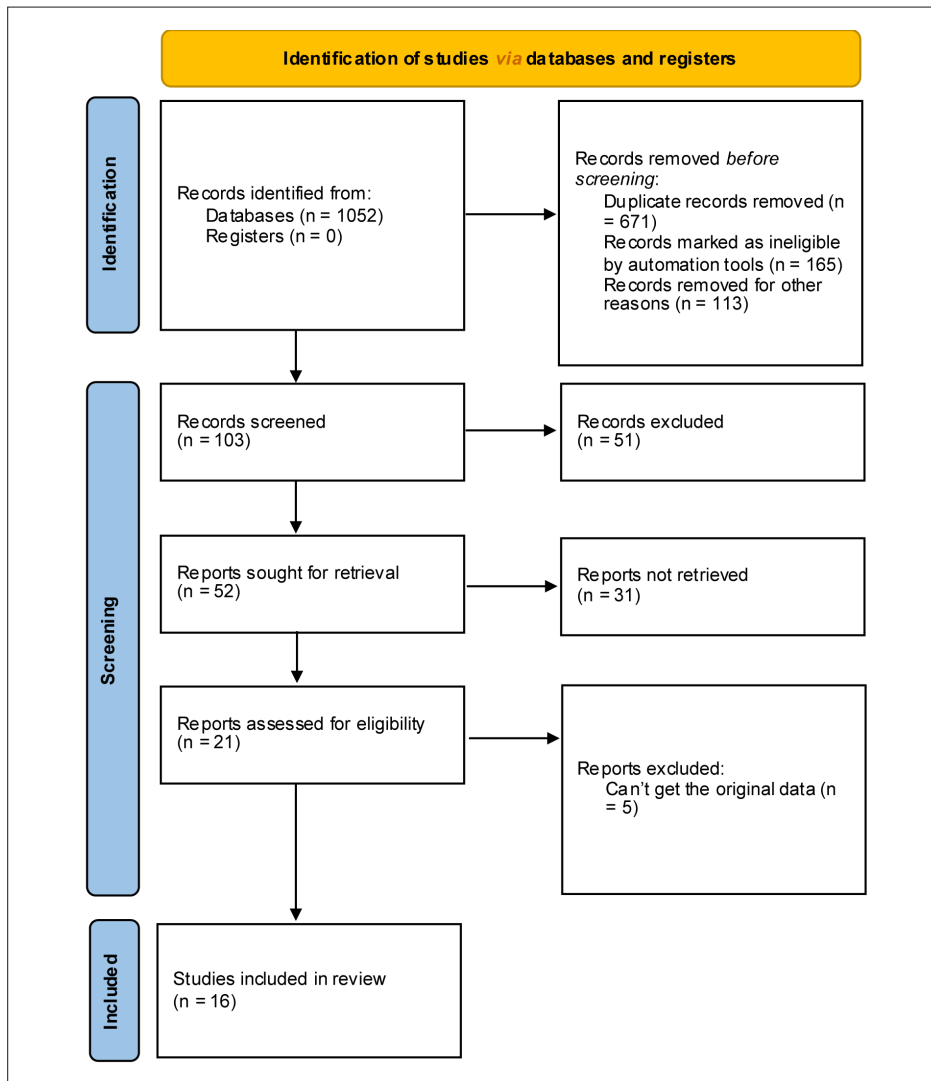
Figure 1. Literature retrieval and screening process.

drastically superior to that in the L-SII group, and considerable heterogeneity was suggested between the proportion of patients with tumor sizes larger than 5 cm in the H-SII and L-SII groups (OR=2.18, 95% CI: 1.69-2.81; Z=6.03, p<0.00001).

Comparison of the Proportion of Tumor Differentiation in GC Patients

The relationship between the SII and the degree of tumor differentiation (undifferentiated) in GC patients was statistically analyzed in 12 studies[17-21,23-27,30,31]. The correlation between SII level and tumor differentiation degree in GC patients was analyzed (Figure 7). The degree of tumor differentiation and SII showed great heterogeneity in GC patients (I^2=72%, p<0.0001). REM analysis showed no great heterogeneity in the proportion of GC patients with undifferentiated tumors between groups (OR=0.89, 95% CI: 0.66-1.19; Z=0.80, p=0.42).

Comparison of the Proportion of Patients with Various TNM Stages

The relationship between SII and tumor TNM stage (greater than or equal to T3 stage) in GC patients was statistically analyzed in 12 studies[17,19-21,23-25,28-32]. The correlation between SII and tumor TNM stage (greater than or equal to T3 stage) in GC patients was analyzed (Figure 8). Heterogeneity was suggested in the proportion of patients with TNM stage ≥T3 between groups
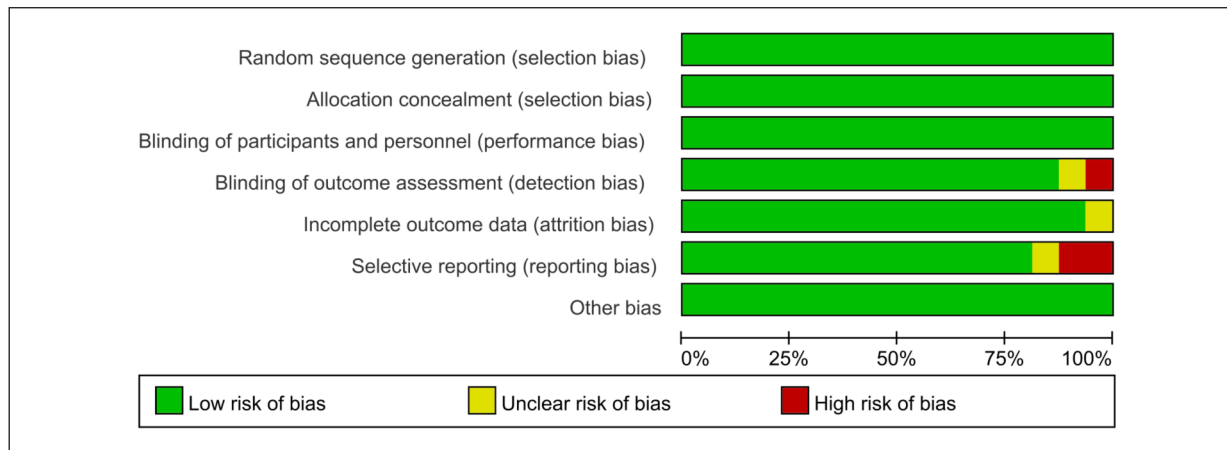
Figure 2. Bar chart of the risk assessment of bias in the included literature.

(I^2=69%, p=0.0002). REM analysis showed that the proportion of patients with tumor TNM stage ≥T3 in the H-SII group was drastically superior to that in the L-SII group, showing substantial heterogeneity between the proportion of patients with tumor TNM stage ≥T3 in the H-SII and L-SII groups (OR=2.41, 95% CI: 1.89-3.08; Z=7.06, p<0.00001).

Comparison of OS in GC Patients

The relationship between SII and OS in GC patients was statistically analyzed in 7 studies[17,21,24,26,28-30]. Figure 9 shows considerable heterogeneity in OS between groups (I^2=99%, p<0.00001). REM analysis showed that the OS in the H-SII group was greatly inferior to that in the L-SII group, with great heterogeneity in OS between groups (OR=-23.92, 95% CI: -37.57 – 10.26; Z=3.43, p=0.0006).

Comparison of Patients' 5-Year Survival Rate (SR)

The 5-year SR of GC patients with different SII levels was statistically analyzed in 5 studies[19,20,22,30,32]. The 5-year SR of GC patients with different SII levels was compared and analyzed (Figure 10). Substantial heterogeneity was revealed in the 5-year SRs between groups (I^2=83%, p<0.0001). The 5-year SR of GC patients in the H-SII group was greatly inferior to that in the L-SII group, indicating remarkable heterogeneity between groups (OR=0.39, 95% CI: 0.24-0.64; Z=3.81, p=0.0001).

Comparison of the Proportion of Patients with High NLR Gene Expression

Seven studies[17,18,23,24,26,29,32] statistically analyzed the proportion of patients with high NLR

gene expression in GC patients with different SII levels. Figure 11 shows that great heterogeneity was found in the proportion of GC patients with high NLR expression between groups (I^2=87%, p<0.00001). REM analysis showed that the proportion of patients with high NLR expression in the H-SII group was drastically superior to that in the L-SII group, with certain heterogeneity between the proportion of patients with high NLR expression in the H-SII and L-SII groups (OR=22.19, 95% CI: 10.66-46.18; Z=8.29, p<0.00001).

Comparison of the Proportion of Patients with High PLR Gene Expression

Six studies[17,18,23,24,26,29] statistically analyzed the proportion of patients with high PLR gene expression in GC patients with different SII levels. Figure 12 displays that substantial heterogeneity was revealed in the proportion of patients with high PLR expression between groups (I^2=74%, p=0.002). REM analysis showed that the proportion of patients with high PLR expression in the H-SII group was drastically superior to that in the L-SII group, with notable heterogeneity between the proportion of patients with high PLR expression in the H-SII and L-SII groups (OR=15.97, 95% CI: 8.57-29.75; Z=8.73, p<0.00001).

Comparison of the Proportion of Patients with High CEA Gene Expression

Five studies[17,18,22,24,29] statistically analyzed the proportion of GC patients with high CEA gene expression with different SII levels. Figure 13 shows heterogeneity in the proportion of patients with high CEA expression between groups (I^2=64%, p=0.02). REM analysis showed no sub-

stantial heterogeneity in the proportion of patients with high CEA expression between groups (OR=1.29, 95% CI: 0.82-2.05; Z=1.10, *p*=0.27).

Publication Bias

The inverted funnel plots of the included literature on the value of SII in the prognostic assessment of GC were symmetric (Figures 14-15), most of the included studies fell in the inverted funnel plots, and almost all the evaluation indexes were close to the central axis. This indicates that the publication bias of the included literature was low and met the requirements.

Discussion

A chronic persistent inflammatory response increases the risk of malignant diseases. The progression of a variety of malignant tumors is related to inflammation, among which approximately 20% of malignant tumors are related to the inflammatory response caused by pathogen infection and immune system dysregulation. Tumor cell proliferation and other processes are correlated with poor prognosis of various tumors[33]. Cancer associated with inflammation causes malnutrition and cachexia in patients, resulting in increased muscle loss and further markedly increasing the incidence and mortality of cancer[34]. Immune inflammatory factors such as NLR and PLR are related to cancer prognosis[35]. As a new inflammatory index, the SII can reflect the global immune status of tumor patients. At present, studies[36] have noted that the SII is related to various liver cancers and can be utilized as a prognostic predictor for patients with these tumors. Neutrophils can promote tumor growth by secreting inflammatory factors and are an imperative part of tumor metastasis and spread. In addition, tumor cells can activate platelets so that tumor cells are not affected by the host immune system[37]. In addition, the elevated neutrophils and platelets in the above mechanisms of tumorigenesis and development are reflected in SII[38]. This meta-analysis included studies related to the prognostic assessment of SII in GC according to the inclusion and exclusion criteria, which has certain scientific and evidence-based medical value. Through screening, 16 studies[17-32] were finally included.

Wang et al[39] showed that colorectal cancer patients with a high SII had a poor prognosis. Eraslan et al[40] noted that the prognosis of esopha-

Figure 3. Summary of the risk assessment of bias in the included literature.

geal cancer patients with a high SII is correlated with OS and DFS, as well as with some clinical indicators of patients. Peng et al[41] analyzed thymidine phosphorylase in GC patients under-
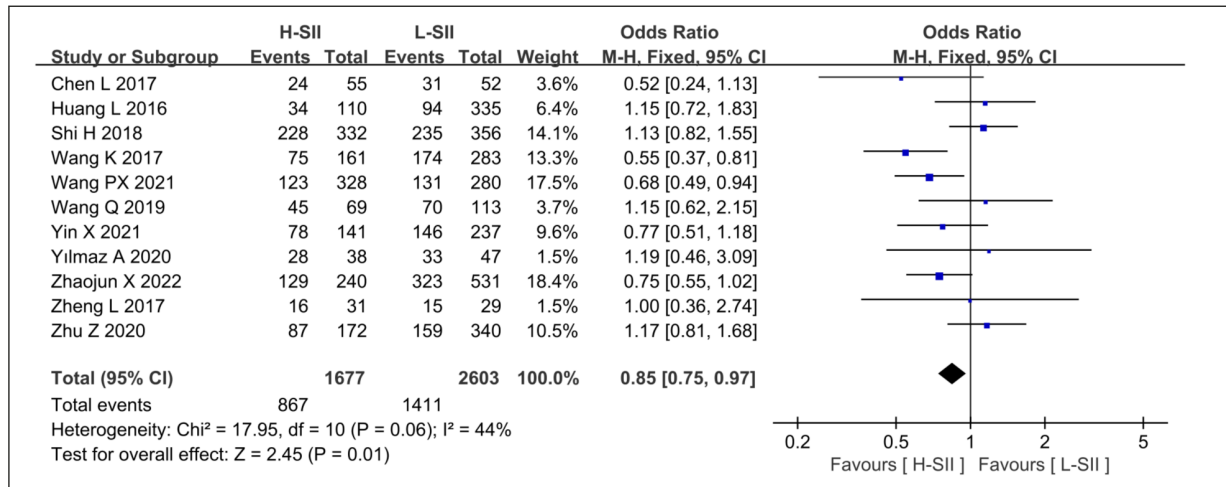
Figure 4. Forest plot for analysis of the relationship between SII level and age of GC patients.
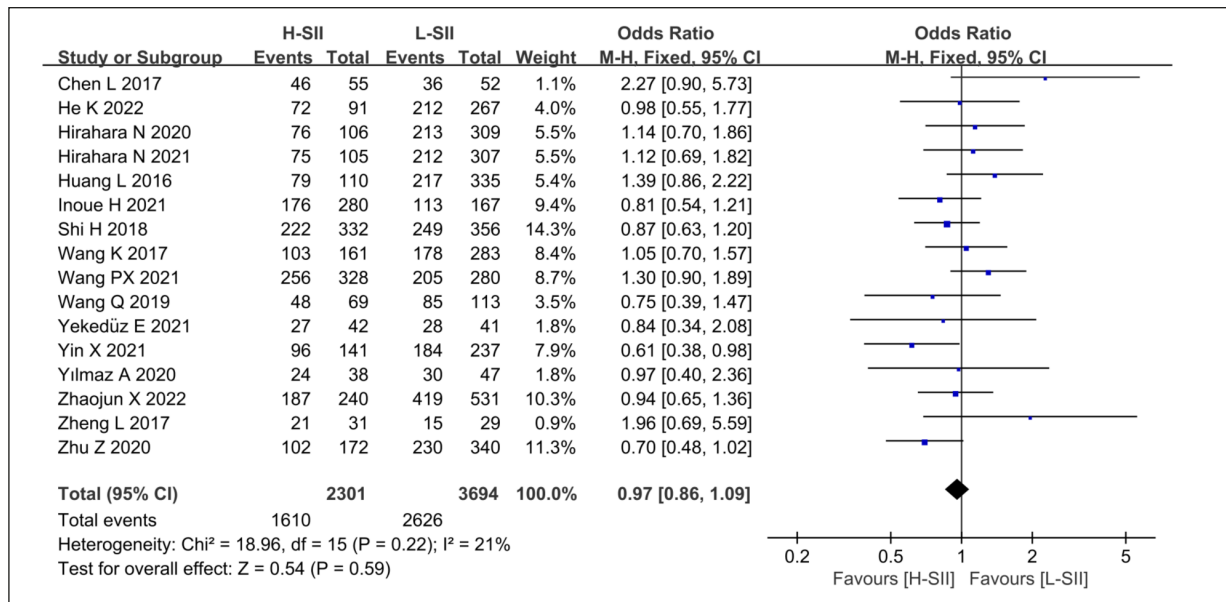
Figure 5. Forest plot for analysis of the relationship between SII and sex of GC patients.

Figure 6. Forest plot of the relationship analysis between SII level and tumor size in GC patients.

Study or Subgroup	H-SII Events	Total	L-SII Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen L 2017	33	55	32	52	7.1%	0.94 [0.43, 2.04]
He K 2022	61	91	192	267	9.7%	0.79 [0.48, 1.33]
Hirahara N 2020	45	106	134	309	10.4%	0.96 [0.62, 1.50]
Hirahara N 2021	45	105	134	307	10.4%	0.97 [0.62, 1.51]
Huang L 2016	4	110	33	335	5.0%	0.35 [0.12, 1.00]
Shi H 2018	118	332	203	356	11.9%	0.42 [0.31, 0.57]
Wang K 2017	4	161	6	283	3.9%	1.18 [0.33, 4.23]
Wang PX 2021	227	328	179	280	11.6%	1.27 [0.90, 1.78]
Wang Q 2019	41	69	70	113	8.6%	0.90 [0.49, 1.66]
Yekedüz E 2021	30	42	28	41	5.8%	1.16 [0.45, 2.97]
Zhaojun X 2022	167	240	329	531	11.7%	1.40 [1.01, 1.95]
Zheng L 2017	6	31	6	29	4.0%	0.92 [0.26, 3.26]
Total (95% CI)		**1670**		**2903**	**100.0%**	**0.89 [0.66, 1.19]**
Total events	781		1346			

Heterogeneity: Tau² = 0.17; Chi² = 39.30, df = 11 (P < 0.0001); I² = 72%
Test for overall effect: Z = 0.80 (P = 0.42)

Figure 7. Forest plot for analysis of the relationship between SII and tumor differentiation degree in GC patients.

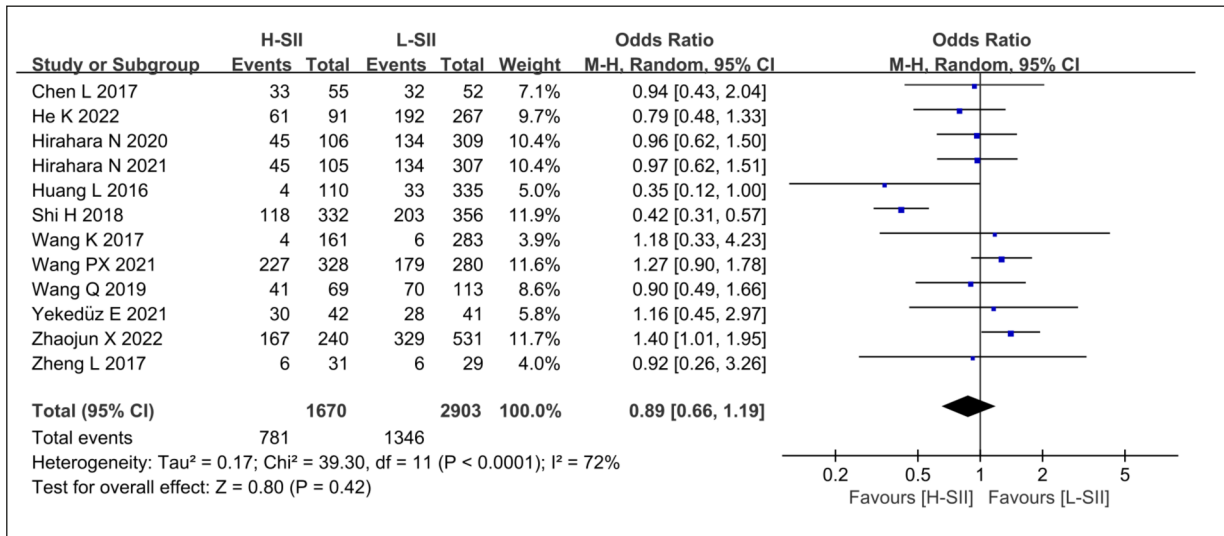| Study or Subgroup	H-SII Events	Total	L-SII Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen L 2017	41	55	43	52	4.5%	0.61 [0.24, 1.57]
Hirahara N 2020	37	106	55	309	8.6%	2.48 [1.51, 4.06]
Hirahara N 2021	37	105	55	307	8.6%	2.49 [1.52, 4.09]
Huang L 2016	73	110	150	335	9.1%	2.43 [1.55, 3.82]
Shi H 2018	199	332	91	356	10.8%	4.36 [3.15, 6.02]
Wang K 2017	129	161	174	283	9.1%	2.53 [1.60, 3.98]
Wang PX 2021	210	328	142	280	10.7%	1.73 [1.25, 2.39]
Yin X 2021	81	141	61	237	9.2%	3.90 [2.50, 6.07]
Yılmaz A 2020	21	38	16	47	4.9%	2.39 [0.99, 5.77]
Zhaojun X 2022	159	240	289	531	10.8%	1.64 [1.20, 2.26]
Zheng L 2017	20	31	11	29	3.8%	2.98 [1.04, 8.51]
Zhu Z 2020	125	172	167	340	9.8%	2.76 [1.85, 4.10]
Total (95% CI)		**1819**		**3106**	**100.0%**	**2.41 [1.89, 3.08]**
Total events	1132		1254			

Heterogeneity: Tau² = 0.12; Chi² = 35.66, df = 11 (P = 0.0002); I² = 69%
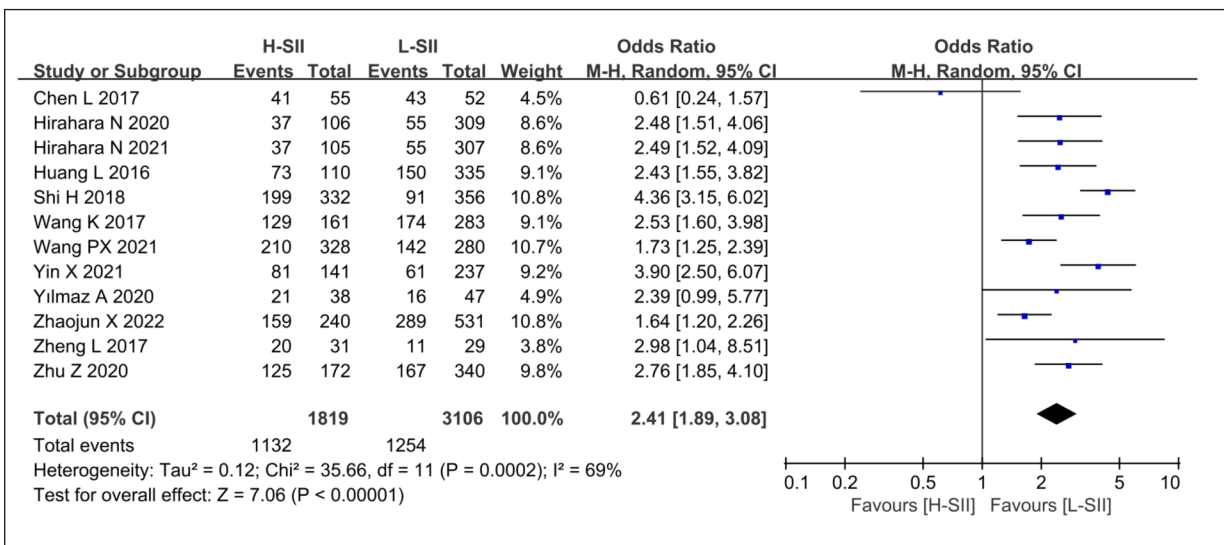Test for overall effect: Z = 7.06 (P < 0.00001)

Figure 8. Forest plot of correlation analysis between SII level and TNM stage of GC patients.

Study or Subgroup	H-SII Mean	SD	Total	L-SII Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chen L 2017	45.6	14.81	55	62.25	18.69	52	14.1%	-16.65 [-23.06, -10.24]
Huang L 2016	52.99	17.94	110	72.35	14.7	335	14.4%	-19.36 [-23.06, -15.66]
Wang K 2017	22	11.85	161	65	37.04	283	14.3%	-43.00 [-47.69, -38.31]
Wang Q 2019	49.27	12.63	69	56.89	13.77	113	14.3%	-7.62 [-11.53, -3.71]
Yin X 2021	20.7	19.74	141	44.33	19.56	237	14.3%	-23.63 [-27.73, -19.53]
Yılmaz A 2020	37.7	14.01	38	49.4	13.87	47	14.1%	-11.70 [-17.66, -5.74]
Zhaojun X 2022	28	4.97	240	73	11.59	531	14.5%	-45.00 [-46.17, -43.83]
Total (95% CI)			**814**			**1598**	**100.0%**	**-23.92 [-37.57, -10.26]**

Heterogeneity: Tau² = 334.27; Chi² = 635.09, df = 6 (P < 0.00001); I² = 99%
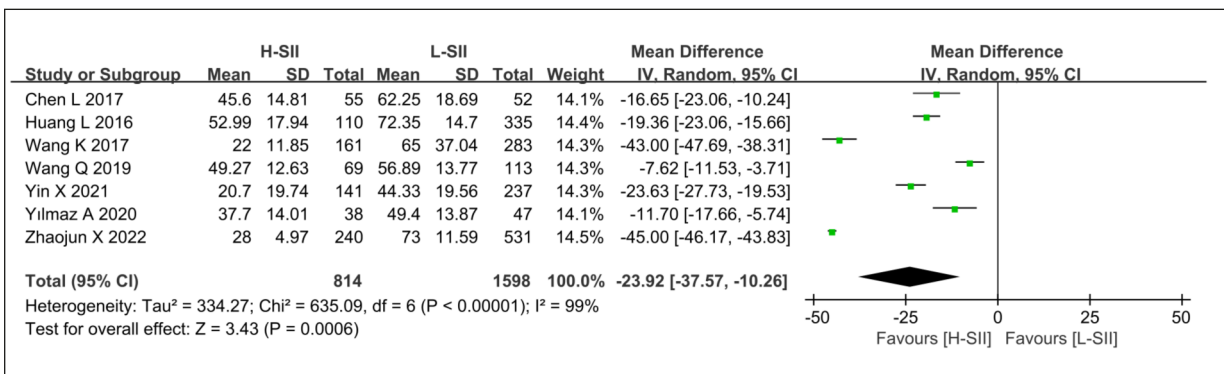Test for overall effect: Z = 3.43 (P = 0.0006)

Figure 9. Forest plot of OS comparison between GC patients in the H-SII and L-SII groups.
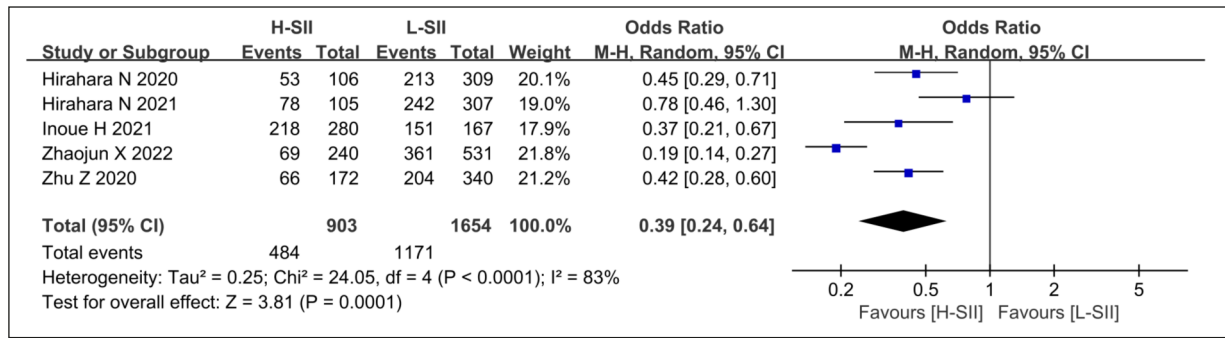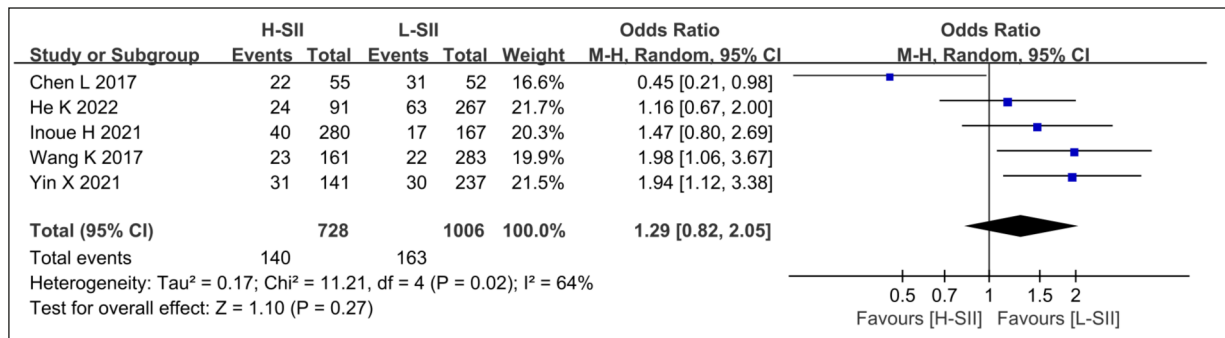
Figure 10. Comparison of the 5-year SR of GC patients in the H-SII and L-SII groups.
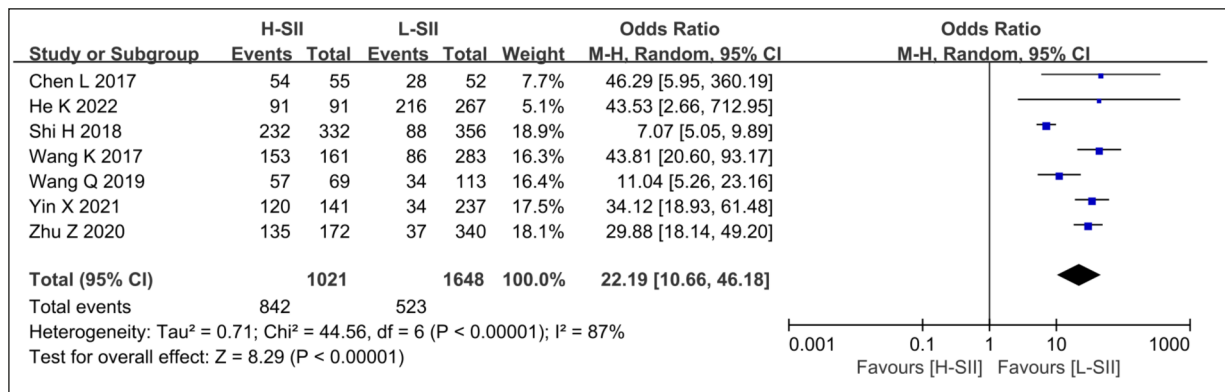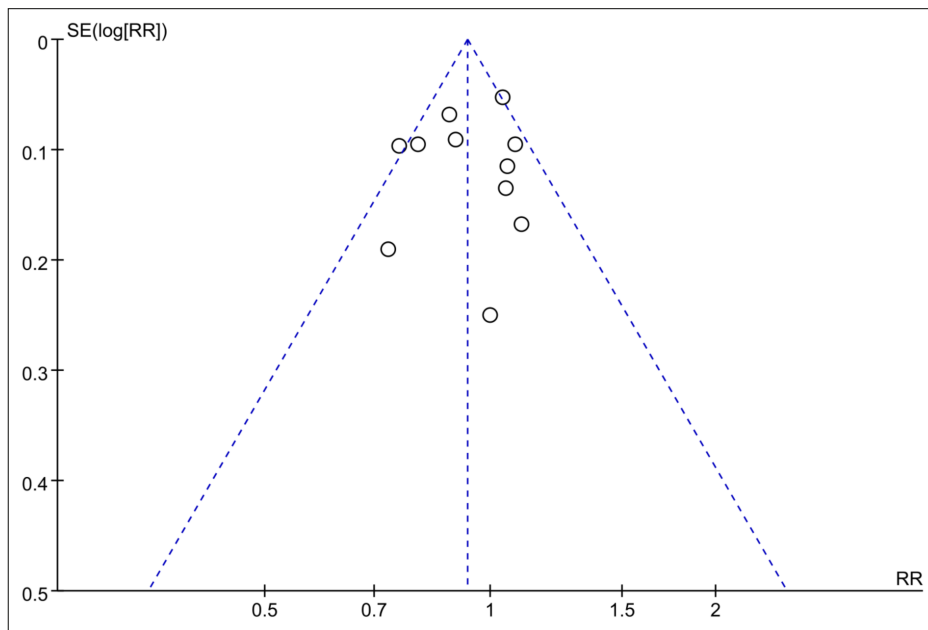

Figure 11. Comparison of the proportion of GC patients with high NLR gene expression.
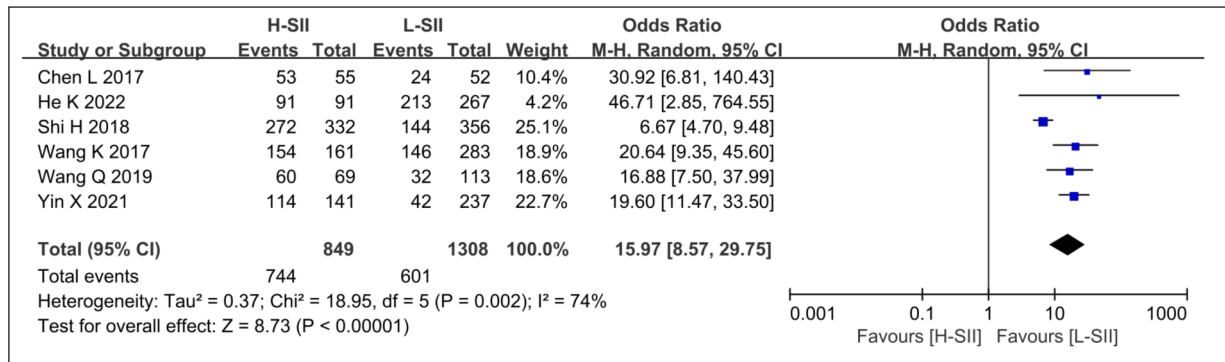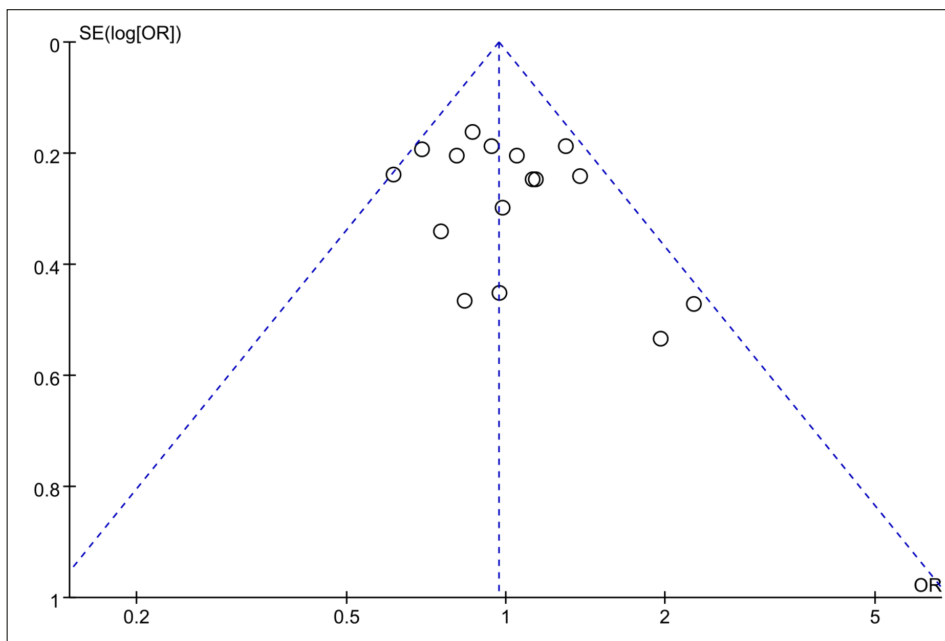

Figure 12. Comparison of the proportion of GC patients with high PLR gene expression.

Figure 13. Comparison of the proportion of GC patients with high CEA gene expression.

Figure 14. Funnel plot of the proportion of GC patients older than 60 years in the H-SII and L-SII groups.

Figure 15. Funnel plot of the proportion of male GC patients in the H-SII and L-SII groups.

going resection and found that GC patients with high preoperative SII had poor prognosis, and SII could be utilized as a prognostic marker for resection. The clinical indicators age, sex, tumor size, and differentiation degree of GC patients with different SII levels in the included literature were analyzed. The results suggested no substantial heterogeneity in the proportion of patients older than 60 years between groups (OR=0.85, 95% CI: 0.75-0.97; Z=2.45, p=0.01). The proportion of patients with tumors larger than 5 cm in the H-SII group was drastically higher than that in the L-SII group (OR=2.18, 95% CI: 1.69-2.81; Z=6.03, p<0.00001). The pro-

portion of patients with TNM stage ≥T3 in the H-SII group was drastically superior to that in the L-SII group (OR=2.41, 95% CI: 1.89-3.08; Z=7.06, *p*<0.00001). Hence, the higher the SII level, the higher the proportion of GC patients older than 60 years. The proportion of patients with a tumor size greater than 5 cm and TNM stage ≥T3 increased markedly, suggesting that the SII level is positively correlated with the age, tumor size and TNM stage of GC patients. Cortellini et al[42] showed that factors such as old age and large tumors were markedly correlated with the SII in GC patients, and the prognosis of GC patients in the SII high expression group was markedly worse. The results of this study are similar.

Furthermore, the OS and 5-year SRs of GC patients in the two groups were compared and analyzed. The results showed that OS in the H-SII group was greatly inferior to that in the L-SII group (OR=-23.92, 95% CI: -37.57 – -10.26; Z=3.43, *p*=0.0006). The 5-year SR of GC patients in the H-SII group was greatly inferior to that in the L-SII group (OR=0.39, 95% CI: 0.24-0.64; Z=3.81, *p*=0.0001). The higher the SII level, the lower the OS and 5-year SRs of GC patients, indicating that there is an inverse ratio between the SII level and the OS and 5-year SRs of GC patients. This is consistent with previous findings[43,44] in other tumors. Shin et al[45] found that GC patients with high SII had shorter OS and recurrence-free survival (RFS), indicating that SII could be utilized as a potential prognostic factor for GC patients. Jomrich et al[46] followed-up GC patients for 45 months, and a remarkable difference was found in OS between patients with high SII and patients with low SII (*p*<0.001), and the risk of death increased with increasing SII. Only 3 studies[17,27,28] included in this study compared and analyzed the RFS of GC patients in the H-SII and L-SII groups, and the RFS of patients in the H-SII group was greatly inferior to that in the L-SII group. Due to space reasons, the relevant results are not shown in the results.

Studies[47,48] have shown that GC patients with increased SII, NLR, PLR, and lymphocyte-monocyte ratio (LMR) have a worse prognosis, and the risk of death in patients with high SII is 1.6 times higher than that in patients with L-SII. These results suggest that OS is an independent prognostic factor for GC patients[49]. The proportion of patients with high NLR expression in the H-SII group was drastically superior to that in the L-SII group (OR=22.19, 95% CI: 10.66-46.18; Z=8.29, *p*<0.00001). The proportion of patients with high PLR expression in the H-SII group was drastically superior to that in the L-SII group (OR=15.97, 95% CI: 8.57-29.75; Z=8.73, *p*<0.00001). Hence, the SII is positively correlated with the NLR and PLR. The NLR can reflect the balance between tumor-promoting factors and tumor-suppressor factors, which may be a risk factor for reduced SR in GC patients after radical resection[50]. Some studies[51,52] have noted that preoperative NLR and PLR can be utilized as potential biomarkers for predicting lymph node metastasis in GC patients.

Conclusions

A meta-analysis was performed to evaluate the prognostic value of the preoperative SII in GC patients. The higher the SII, the lower the OS and 5-year SRs of patients, namely, the worse the prognosis. However, there are still some shortcomings in this study. Some of the included studies were retrospective studies, which may lead to selection bias. In addition, due to the limited number of studies, the potential heterogeneity of SII in GC prognosis assessment was not further analyzed. In the future, clinical trials will be conducted to verify the value of the preoperative SII in the prognosis of GC patients. In conclusion, a high preoperative SII is an independent risk factor for poor prognosis in GC patients, which provides a reference for the prognostic assessment of GC patients undergoing surgical treatment.

Informed Consent
A data secondary analysis was used in this study, in which all the information and data involved were from published literature and did not require direct participation by subjects. Therefore, informed consent from subjects was not required and no human trials were conducted in this study.

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Authors' Contributions

All the authors in this study participated in the whole process of this study, including problem posing, determination of study methods and selection of inclusion/exclusion criteria, formulation of retrieval strategies, screening and evaluation of literature, extraction of raw data, and statistical analysis.

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