

# Prognostic impact of elevated pre-treatment systemic immune-inflammation index (SII) in hepatocellular carcinoma

## A meta-analysis

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### Abstract

**Background:** There is a growing literature on the significance of systemic immune-inflammation index in hepatocellular carcinoma. However, the results were inconsistent due to the small sample size and different study endpoints. Therefore, the purpose of this study was to further systematically and comprehensively verify the prognostic role of the SII in HCC.

**Methods:** Several databases were searched systematically, and relevant papers were selected. The main outcome measure was overall survival (OS); the secondary outcome measure was a composite of time to recurrence (TTR), progression-free survival (PFS), and recurrence-free survival (RFS).

**Results:** Ten published retrospective studies involving 2796 HCC patients were included. The results revealed that elevated pre-treatment SII was related to lower OS (HR:1.54,  $P < .001$ ) and earlier TTR (HR:1.77,  $P < .001$ ).

**Conclusions:** Elevated SII is a poor prognostic factor for patients with hepatocellular carcinoma. The clinical application of SII is encouraged to evaluate the progress of hepatocellular carcinoma.

**Abbreviations:** 95% CIs = 95% confidence intervals, HCC = hepatocellular carcinoma, HRs = hazard ratios, MVA = multivariate analysis, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival, SII = systemic immune-inflammation index, TTR = time to recurrence.

**Keywords:** hepatocellular carcinoma, meta-analysis, prognosis, systemic immune-inflammation index

## 1. Introduction

Hepatocellular carcinoma (HCC), as the main type of liver cancer, is a common malignant tumor, which seriously threatens the health of people around the world.<sup>[1,2]</sup> Approximately 841,000 new cases are identified, and 782,000 deaths are caused by liver cancer each year.<sup>[3]</sup> Currently, various therapies have been used to treat available HCC patients of different stages, such as hepatectomy, liver transplantation (LT), transarterial chemoembolization (TACE), and sorafenib, but the 5-year survival rate is still <12%.<sup>[4,5]</sup> Given this, it is crucial to identify high-risk

HCC patients who tend to tumor recurrence, metastasis, and poor prognosis.

Traditionally, various methods such as the Barcelona-Clinic Liver Cancer (BCLC) staging system, the Tumor, Node, Metastasis (TNM) classification system, the Child-Pugh classification system, have been used by clinicians to develop treatment plans and evaluate patient prognosis. However, these stratification methods are not only unable to reflect the patient's tumor status in real-time, but also invasive and costly. As a new prognostic indicator, the Systemic immune-inflammatory index (SII) is calculated using the formula platelet count  $\times$  neutrophils/lymphocytes, which is non-invasive, low cost, and easy to obtain, is considered as an ideal biomarker candidate. Since Hu<sup>[6]</sup> first proposed in 2014, multiple studies have shown that pretreatment SII can predict the clinical prognosis of various malignancies, including HCC. Due to the differences in the size of experimental samples, the selected treatment regimens, and the end-point indicators of follow-up, the predictive impact of pre-treatment SII in patients with HCC has not been determined.

In this study, we conducted a meta-analysis of relevant published articles to further explore the correlation between pre-treatment SII and prognosis of different endpoint indicators. Also, we compared the prognostic value of pre-treatment SII with other peripheral blood predictors.

## 2. Methods

### 2.1. Search strategy

Relevant literature was extracted by systematic retrieval of PubMed(Medline), EMBASE, Springer, Web of Science, and

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Cochrane Library databases up to date to May 2019. Our search strategy included terms for: “systemic-immune-inflammation index” or “neutrophil × platelets/lymphocyte” or “SII” and “liver cancer” or “HCC” or “liver cancer” or “hepatocellular carcinoma.” At the same time, we manually screened out the relevant potential literature in the references extracted.

## 2.2. Inclusion and exclusion criteria

The inclusion criteria:

1. types of studies: published studies exploring the relationship between pre-therapeutic (including non-operative and operative) SII and HCC prognosis;
2. subjects: pathologically diagnosed HCC patients;
3. exposure factors: patients were divided into high and low subgroups, with one group having SII below the cut-off value and the other having SII above the cut-off value;
4. outcome indicator: The primary endpoint was overall survival (OS) in patients with HCC the secondary endpoint was a composite of TTR, PFS, and RFS.

The exclusion criteria:

1. non-primary liver cancer, such as metastatic cancer or recurrent tumor;
2. The types of articles are abstract, comment, case, review, systematic evaluation, etc.;
3. insufficient information was provided;
4. unable to obtain full text or quality assessment of the literature;
5. only the research with higher methodological quality is maintained for the analysis with repeated publication or data overlap.

## 2.3. Data extraction

Two researchers (Wang and Lin) independently conducted literature screening, data extraction, and literature quality evaluation, and any differences could be resolved through discussion or a third reviewer (Huang). Information extracted from the included literature included: first author's surname, year of publication, country of the population, sample size, tumor stage, treatment plan, SII cut-off value, outcome index and corresponding HR value, 95%CI, etc.

The Newcastle-Ottawa scale (NOS)<sup>[7]</sup> was adopted to evaluate the process in terms of queue selection, comparability of queues, and evaluation of results. NOS scores of at least six were considered high-quality literature. Higher NOS scores showed higher literature quality.

## 2.4. Statistical analysis

All data analysis was performed using Stata12.0 software. The included HR and 95%CI were treated with the combined effect size. After that, the heterogeneity test was conducted. When  $P \geq .05$  or  $I^2 < 50\%$  was performed, it indicated that there was no obvious heterogeneity, and the fixed-effect model should be applied for a merger. When  $P < .05$  or  $I^2 \geq 50\%$  indicated high heterogeneity, the random-effect model was applied. Combined effect size, if  $HR > 1$  indicates that increased SII is an unfavorable factor for HCC, indicating a poorer prognosis. If  $HR < 1$  is the

opposite. Begg's funnel plot was used to research publication bias detection. If  $P < .05$  indicates obvious publication bias.

## 2.5. Ethics

Ethical committee or medical institutional board approval was not required for systematic reviews and meta-analysis.

## 3. Results

### 3.1. Process of study selection and description of qualified studies

The systematic search yielded 295 potential studies from PubMed, PMC, EMBASE, Web of Science, and Cochrane Library databases. After exclusion of duplicate references, 90 articles were considered for the meta-analysis. After careful review of the full texts, 11 studies were included. One study was excluded,<sup>[8]</sup> as no data were provided for formal meta-analysis. Ten articles published between 2014 and May 2019 met the inclusion criteria<sup>[6,9–17]</sup> (Fig. 1).

The data of 2796 HCC patients from 10 retrospective studies were selected in this meta-analysis.<sup>[6,9–17]</sup> Seven studies were performed in China, and the other three were from Hong Kong,<sup>[17]</sup> Italy,<sup>[10]</sup> and France.<sup>[13]</sup> There were nine studies that evaluated the prognostic impact of pre-treatment SII for OS in HCC patients.<sup>[6,9–11,13–17]</sup> Additionally, three studies reported TTR,<sup>[6,11,12]</sup> two covered RFS,<sup>[14,16]</sup> and one researched PFS.<sup>[10]</sup> All studies used multivariate analysis results to pool HR and 95% CI. All articles are of high quality because of NOS score no  $< 6$ . The main characteristics of the selected articles are detailed in Table 1.

### 3.2. Relationship between SII and survival outcomes in HCC

There were nine studies that reported the relationship between SII and OS.<sup>[6,9–11,13–17]</sup> No significant heterogeneity ( $I^2 = 0\%$ ,  $P = .536$ ) was present, and thus a fixed-effects model was adopted. A pooled HR indicated that Patients with higher SII values were significantly associated with worse OS (HR:1.54, 95%CI:1.36–1.73,  $P < .001$ ) (Fig. 2). Three studies reported the relationship between SII and TTR.<sup>[6,11,12]</sup> As no obvious heterogeneity was observed, the fixed-effect model was used ( $I^2 = 0\%$ ,  $P = .689$ ). The pooled analysis suggested that SII was the independent predictor for TTR in HCC (HR:1.77, 95% CI:1.25–2.30,  $P < .001$ ) (Fig. 3). The relationship between SII and RFS was studied in two studies, but only one provided data.<sup>[16]</sup> Also, one paper studied the correlation between SII and PFS in HCC.<sup>[15]</sup> Therefore, we did not perform a combined analysis of RFS and PFS in this report (Table 2).

### 3.3. Subgroup analysis

To further explore the prognostic value of SII, subgroup analysis was conducted from three aspects: treatment method, country, and cut-off value. Our results revealed that higher SII value predicted poorer OS in all stratified categories. The predictive power of SII was stronger in non-operative patients and patients with a cut-off value lower than 330, respectively (Table 3).

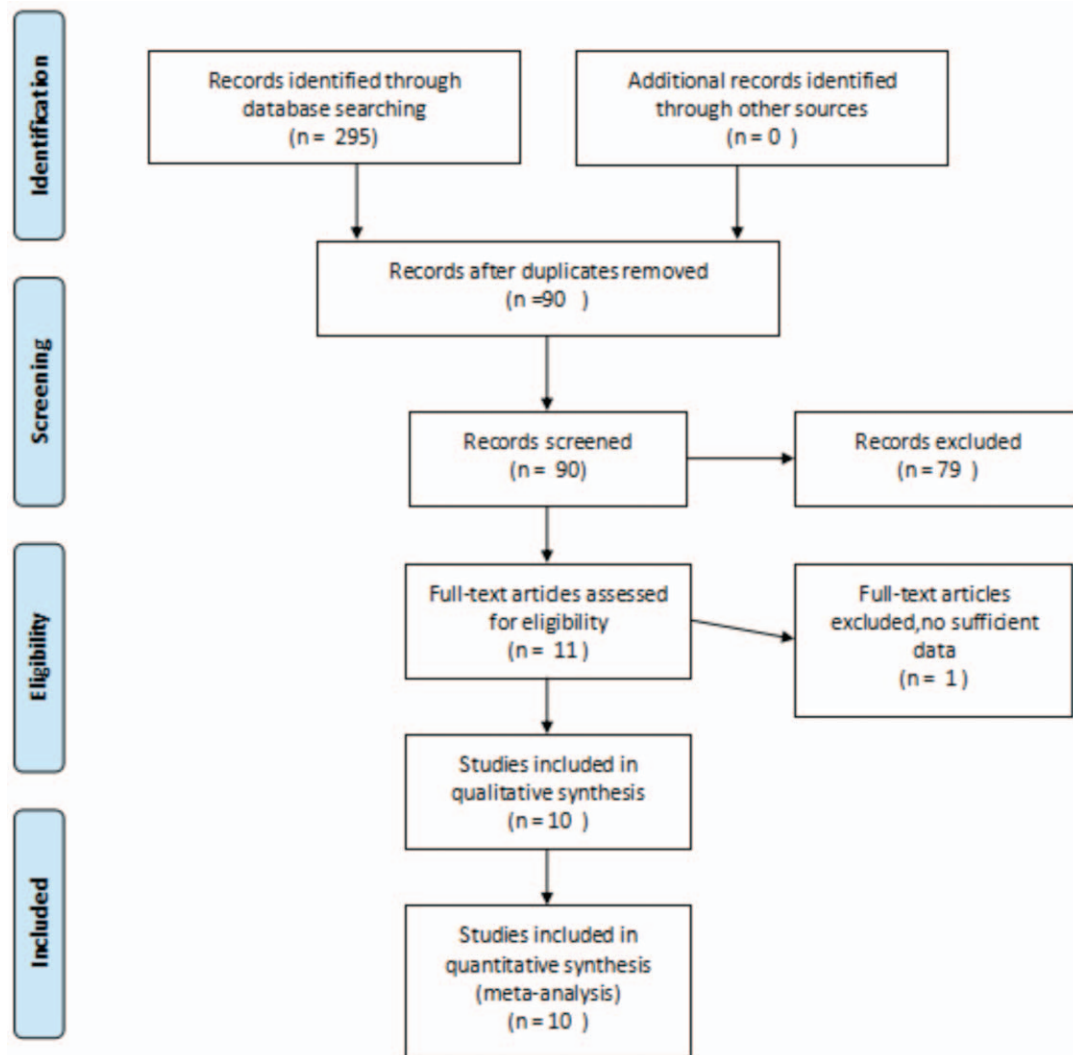


Figure 1. Flow chart of search strategy and study selection.

**Table 1**

Main characteristics of the included studies in our-analysis.

Study	Year	Country	Time	Sample	Age (years)	Study endpoints	Cutoff value	Treatment methods	Follow-up (months)	Stage	MVA	NOS
Hu	2014	China	2005-2006	133	Median: 64.1	OS,TTR	330	With-surgery	Median: 61.3	0-A-B-C (BCLC)	Yes	7
Hu	2014	China	2010-2011	123	NA	OS,TTR	330	With-surgery	1-42	0-A-B-C (BCLC)	Yes	7
Yang	2015	China	2009-2015	189	NA	OS	300	No-surgery	1-60	A-B-C (BCLC)	Yes	7
Gardini	2016	Italy	2012-2015	56	NA	OS,PFS	360	No-surgery	1-8	B-C (BCLC)	Yes	6
Wang	2016	China	2012-2013	163	Median: 54.16	TTR	330	With-surgery	Median: 25.6	NA	Yes	6
Gao	2017	China	2014-2015	183	NA	OS,TTR	330	With-surgery	>24	0-A-B-C (BCLC)	Yes	7
Conroy	2017	France	2007-2015	161	Mean: 67.2	OS	600	Mixed	>40	A5-6;B7-9; (Chid-Pugh)	Yes	7
Margetts	2018	Hong Kong	2000-2013	1168	Median: 65.0	OS	569	Mixed	1-192	I-II-III-IV	Yes	8
Pang	2018	China	2002-2016	470	Mean: 52.2	OS,RFS	340.66	With-surgery	Median: 29.0	A-B-C (Chid-Pugh)	Yes	8
Fu	2018	China	2003-2016	150	Median: 51.0	OS,RFS	226	With-surgery	Median: 41.0	A-B-C (Chid-Pugh)	Yes	7

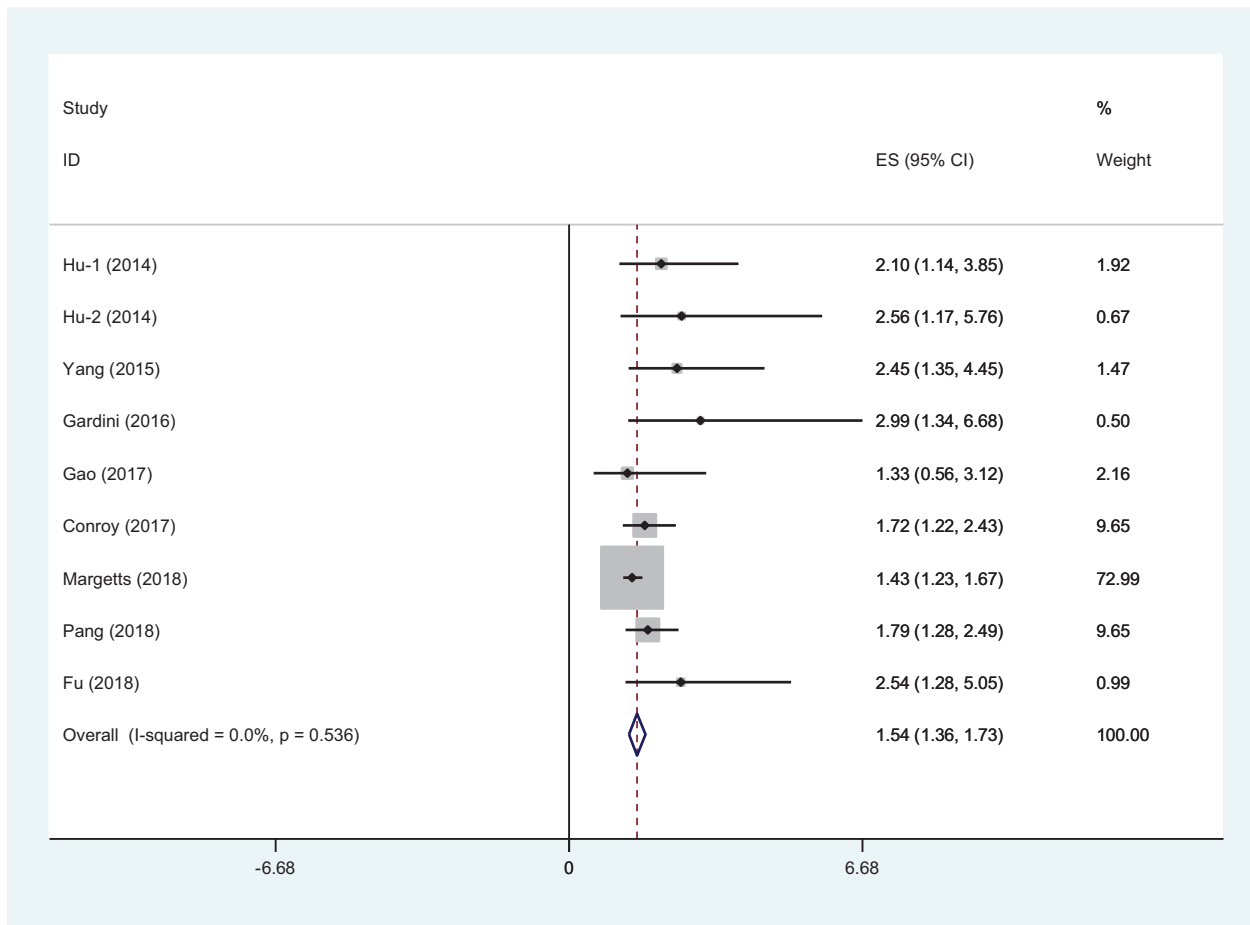


Figure 2. Forest plot for association between SII and OS in HCC.

### 3.4. Publication bias

Figure 4 shows a funnel plot of studies included in this meta-analysis. The Begg's test was used to detect publication bias (Pr continuity corrected  $>|z|=0.251$ ), it showed that there was no possibility of publication bias.

### 3.5. Prognostic value comparison between SII and other peripheral blood predictors

Increased peripheral blood indexes neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) before treatment can predict the prognosis of HCC. Our study shows that the predictive power of SII and NLR is stronger than that of PLR (Table 4).

## 4. Discussion

As far as we know, this is the first meta-analysis of the prognostic value of various endpoint indicators in HCC patients before treatment. We also compared the predictive sensitivity of different prognostic indicators. 2796 patients with HCC were enrolled in 10 studies. The results showed that higher SII before treatment might be an objective risk factor for the prognosis of HCC patients, especially those who received nonsurgical

treatment, and SII has a significantly higher prognostic evaluation value than PLR.

In the early 1960s, the relationship between cancer progression and inflammatory response was first proposed.<sup>[18]</sup> After that, the relationship between cancer and inflammation has been extensively explored through animal models and clinical trials. SII is a new inflammatory index proposed in recent years, which is based on the count of neutrophils, platelets, and lymphocytes in peripheral blood. Previous studies have shown that SII is significantly correlated with the infiltration, recurrence, and metastasis of renal cancer,<sup>[19]</sup> gastric cancer,<sup>[20]</sup> and esophageal cancer.<sup>[21]</sup>

However, the precise mechanism of the prognostic impact of SII in HCC was not clarified. The following may explain the potential relationship between higher SII value and poorer prognosis in patients with HCC. The increase of neutrophils accelerates the release of inflammatory factors (vascular epithelial factor, IL-8, IL-16, etc) and helps to construct a microenvironment for tumors to promote invasion, recurrence, and metastasis.<sup>[22,23]</sup> At the same time, the increase of platelet count leads to the increase of secretion of vascular endothelial growth factor, which stimulates angiogenesis of tumors and protects tumor cells from damage.<sup>[24]</sup> The increase in neutrophil and platelet counts symbolizes the activation of inflammatory pathways. Lymphocytes are immune cells that clear tumor cells through both cellular

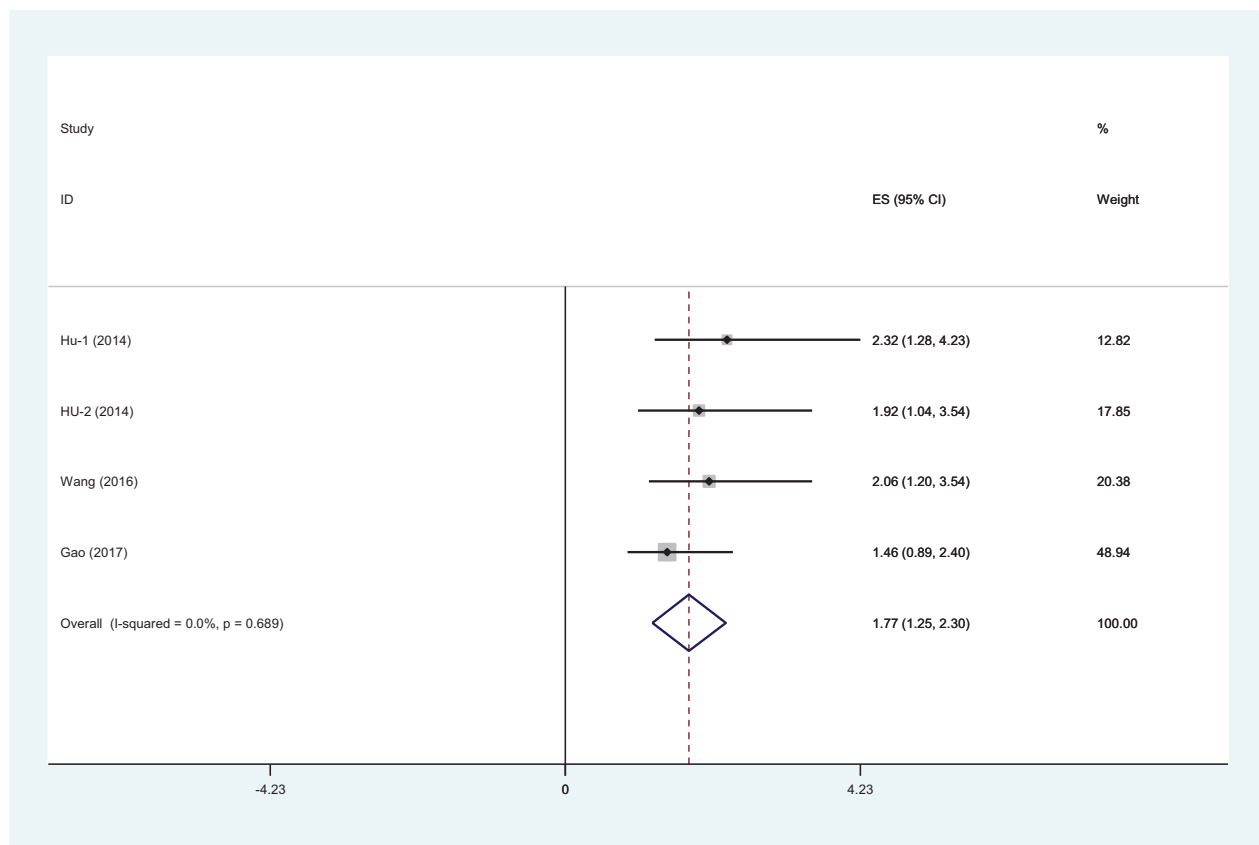


Figure 3. Forest plot for association between SII and TTR in HCC.

Table 2

Analyses of outcomes for SII in HCC.

Outcomes	No. of studies	HR (95%CI)	P	Heterogeneity		Model used
				I <sup>2</sup>	P <sub>h</sub>	
OS	9	1.54 (1.36–1.73)	<.001	0	.536	Fixed
TTR	4	1.77 (1.25–2.30)	<.001	0	.689	Fixed
PFS	1	1.73 (0.91–2.29)	.096	–	–	–
RFS	1	1.77 (1.30–2.41)	<.001	–	–	–

Table 3

Stratified analysis of SII and overall survival in HCC.

Variable	No. of studies	HR (95%CI)	P	Heterogeneity		Model used
				I <sup>2</sup>	P <sub>h</sub>	
Country						
China	6	1.90 (1.44–2.36)	<.001	0	0.818	Fixed
Hong Kong	1	1.43 (1.21–1.65)	<.001	–	–	Fixed
France	1	1.72 (1.12–2.33)	<.001	–	–	Fixed
Italy	1	2.99 (0.32–5.66)	<.001	–	–	Fixed
Cut off value						
≤330	5	2.04 (1.34–2.74)	<.001	0	0.749	Fixed
>330	4	1.51 (1.31–1.70)	<.001	0	0.396	Fixed
Treatment methods						
With-surgery	5	1.85 (1.37–2.33)	<.001	0	0.793	Fixed
No-surgery	2	2.59 (1.25–3.93)	<.001	0	0.732	Fixed
Mixed	2	1.46 (1.26–1.67)	<.001	0	0.377	Fixed

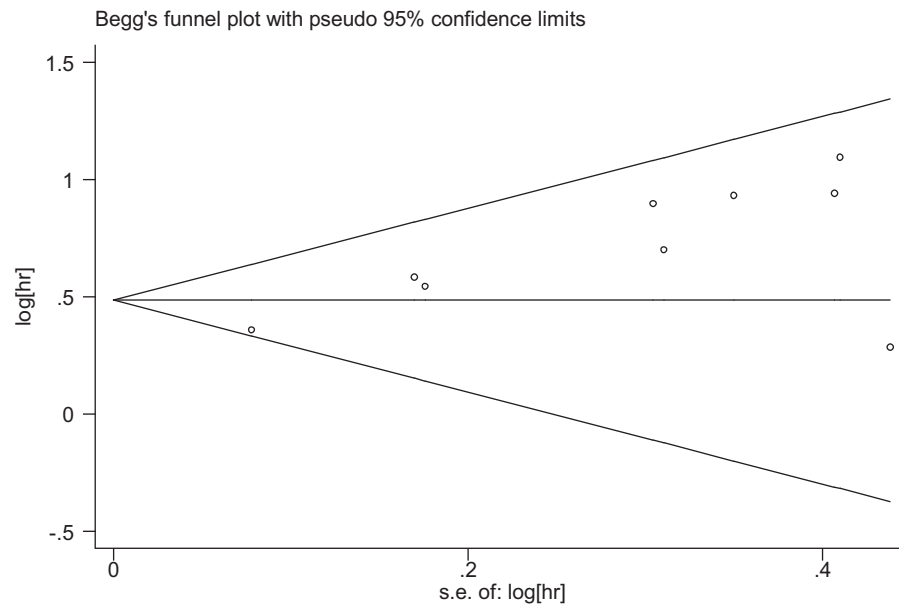


Figure 4. Funnel plot for publication bias.

Table 4

## Prognostic value of SII compared with PLR, NLR, and MLP.

Outcomes	No. of studies	HR (95%CI)	P	Heterogeneity		Model used
				I <sup>2</sup>	P <sub>h</sub>	
OS						
SII	9	1.54 (1.36–1.73)	<.001	0	.536	Fixed
NLR	5	1.57 (1.16–1.98)	<.001	0	.929	Fixed
PLR	3	1.26 (1.30–2.41)	<.001	26.2	.248	Fixed
MLR	1	1.60 (0.71–3.62)	<.001	–	–	–

and humoral immune mechanisms. The increase of lymphocyte symbolizes the activation of the immune pathway.<sup>[25]</sup> Therefore, SII can be regarded as a state indicator reflecting the activation of inflammatory and immune pathways in the body. The increase of SII value indicates that the tumor grows toward infiltration, recurrence, or metastasis, and the prognosis of patients is poor.

The most critical clinical value of this study is not only to help clinicians assess the risk of HCC patients based on the level of SII but also to help develop clinical treatment strategies. Patients with higher SII before treatment may benefit more from neoadjuvant chemoradiotherapy, postoperative adjuvant chemoradiotherapy, and cancer-related therapy than patients with lower SII.

This study also has some deficiencies. First, this study is an observational study, which inevitably limits the limitations of the original data defects and deviations. Second, the number of samples about HCC patient's prognosis is too few. Thirdly, the cut-off values SII have not yet been unified. Finally, publication bias cannot be avoided entirely.

In conclusion, elevated SII before treatment is a marker of poor prognosis in HCC patients. SII, as a non-invasive and low-cost prognostic marker, may be a promising predictor for HCC patients. Given the limitations of this conclusion, a more comprehensive perspective, and multicenter studies are needed to determine the cut-off value of SII, to explore the impact of SII

dynamic changes on treatment, and whether the survival of patients can be prolonged by interfering with the three peripheral blood cells required for SII calculation.

### Author contributions

**Conceptualization:** Bolin Wang.

**Data curation:** Bolin Wang, Tao Lin.

**Formal analysis:** Bolin Wang.

**Investigation:** Bolin Wang.

**Methodology:** Bolin Wang, Tao Lin.

**Project administration:** Bolin Wang.

**Software:** Bolin Wang.

**Writing – original draft:** Bolin Wang.

**Writing – review & editing:** Yan Huang.

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