

Prognostic value of systemic immune-inflammation index (SII) in cancers: a systematic review and meta-analysis

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Background: Systemic immune-inflammation index (SII) is calculated by the value which is based on peripheral lymphocyte, neutrophil, and platelet counts, has been recently investigated as a valuable prognostic marker in several types of tumors. However, the combined prognostic value of SII for these tumors remains unclear. Here, we quantify the prognostic impact of this index and assess its consistency in a motley of cancers.

Methods: We conducted a systematic review of PubMed/Medline, Cochrane Library, American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) with a final date of April 20, 2017. Data from relevant studies reporting a hazard ratio (HR) and 95% confidence interval (CI) were pooled in a meta-analysis. The meta-analysis was conducted by using RevMan 5.3 and STATA software.

Results: Thirteen studies comprising 4,104 patients were included in the final analysis. The median cutoff for SII was 575. The aggregate results indicated that elevated SII was associated with poor overall survival (OS) (HR =1.80; 95% CI: 1.43–2.28), poor cancer-specific survival (CSS) (HR =1.44; 95% CI: 1.04–1.99), time to recurrence (TTR) (HR =1.91; 95% CI: 1.53–2.43) and poor progression-free survival (PFS) (HR =1.18; 95% CI: 0.55–2.52). Further analysis found similar results in various subgroups stratified by cancer type, sample size, and ethnicity.

Conclusions: Our meta-analysis shows that SII may be a potentially useful prognostic biomarker in patients with cancer. We suggest the need for further investigations to delineate the utility of SII for clinical decision making in this population.

Keywords: Systemic immune-inflammation index (SII); biomarker; cancer; prognostic marker; meta-analysis

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Introduction

The inflammatory response in tumor microenvironment plays an essential role in cancer development and progression (1,2). Various measurable blood parameters can mirror the systemic inflammatory response which includes but not limited to C-reactive protein, red blood cell distribution width, hypoalbuminemia, cytokines

such as interleukin-6 and tumor necrosis factor- α , and leucocyte and their subtype counts (3-5). Cancer-associated inflammation is regarded as a hallmark characteristic of tumor development. Therefore, inflammatory biochemical markers have been incorporated in the prognostic scoring systems of several types of cancer (6,7).

It has increasingly been acknowledged that these

inflammatory cells are involved in the production of inflammatory mediators and cytokines that can affect angiogenesis, growth, invasion, and metastasis of the cancers (8). Correspondingly, serum neutrophils, lymphocytes and platelets have been known to predict prognosis and response to the treatment in different malignancies (9). In 2014, Hu *et al.* reported a novel inflammatory index, named as the systemic immune-inflammation index (SII) based on counts of lymphocyte (L), neutrophil (N), and platelet (P), and it was calculated as follows: $SII = P \times N/L$ (10). SII was proven to be a strong independent predictive factor for recurrence and prognosis in patients with hepatocellular carcinoma (HCC). It was concluded that the high recurrence rate in patients with high SII scores might be related to increased release of circulating tumor cells (CTCs) from tumor sites.

Recently, SII was recently explored as a prognostic marker in several other malignancies including renal cell carcinoma and small cell lung cancer (SCLC) (10-12). However, the prognostic value of SII for survival in cancer patients remains conflicting. Therefore, our study focuses on obtaining a combined and unified result based on the several past independent studies which assessed the prognostic value of SII in clinical outcomes in various solid tumors. We hypothesized that SII can be a readily available, objective and inexpensive prognostic index which could be used in the stratification of cancer patients in daily oncological practice.

Methods

Literature source and search

The full search strategy and method are described and attached in the supplementary material (available online). We searched PubMed, Cochrane Library, American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) databases on or up to April 20, 2017. All references incorporated into the literature were manually retrieved. The following terms were used: (I) “systemic immune-inflammation index” in conjunction with (II) “cancer, or tumor, or neoplasm, or carcinoma” and (III) “prognosis, or outcome, or survival, or mortality, or recurrence, or progression, or metastasis.”

Study selection and data extraction

Titles and abstracts were screened and assessed to meet the following inclusion criteria: (I) studies reporting the

prognostic impact of the peripheral blood SII in patients with solid tumors; and (II) reporting of a hazard ratio (HR) and 95% confidence interval (CI) for overall survival (OS). For secondary analysis, studies providing a HR for cancer-specific survival (CSS), progression-free survival (PFS), time to recurrence (TTR) were included as well.

Literature was screened by following the inclusion criteria, and data was extracted and crosschecked by two independent reviewers. The following details were extracted: first author's name, type of the publication (abstract, full text), year of publication, number of patients included in the analysis, primary cancer site, cancer stage, type of data collection (prospective, retrospective). SII cutoff and HRs were extracted from multivariable analyses where available. Otherwise, HRs from univariate analyses were included in the analysis. The methodology of each study was appraised using a quality score ranged from 0 to 9 based on the Newcastle-Ottawa assessment scale (NOS) (13). The quality score assesses the three major aspects of studies: selection, comparability, and the outcome of study groups. A higher quality score indicated good design with the availability of adequate information in the study.

Statistical analyses

Extracted data were integrated into meta-analysis using Rev Man 5.1 analysis software. Estimation of HRs was weighted and pooled using the generic inverse-variance and random-effect model (14). All studies were included in the analysis, and differences between the subgroups were assessed using methods described (14). The heterogeneity assumption of the model was assessed by Cochrane Q test and inverse-variance method, where a P value <0.10 and $I^2 \geq 50\%$ indicated a significant heterogeneity across studies. Due to the existence of considerable heterogeneity in the studies, a meta-regression analysis was performed to identify heterogeneous factor (STATA 12). We assessed the publication bias of extracted data using the Begg's test and Begg's funnel plots (STATA 12). A sensitivity analysis was performed to examine the robustness of our overall findings to potentially uncertain or influential inputs. All statistical analyses were two-sided, and statistical significance was defined as $P < 0.05$.

Results

Included studies

We identified a total of 170 records from the primary

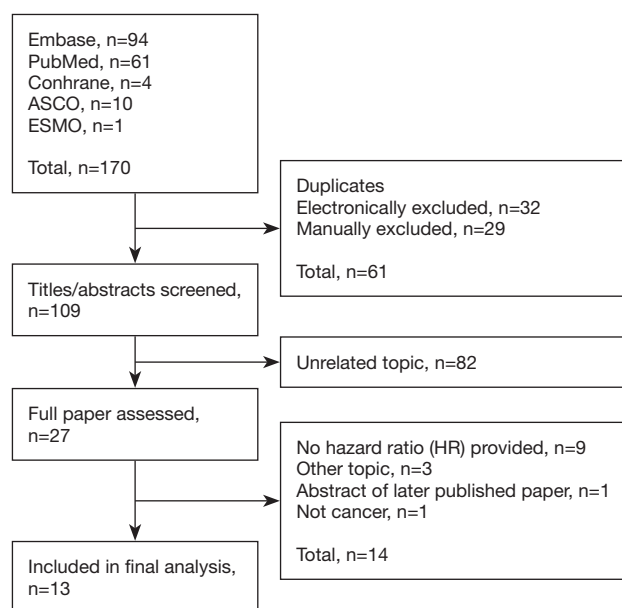


Figure 1 Flowchart presenting literature search and selection steps. ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology.

literature search, of which 13 studies with a total of 4,104 patients from December 2014 to January 2017 met the inclusion criteria (*Figure 1*) (10-12,15-24). Since the Hu *et al.*'s paper included two independent cohorts studies, a total 14 cohorts were included in the final analysis (10). Characteristics of comprised studies are shown in *Table 1*. The utility of SII was reported after multivariate analysis in all but one of the studies. Twelve studies shows the quality score in the range of 6–8 indicating sufficient quality for our meta-analysis, and for Yu *et al.*'s study could not be evaluated because of unavailability of adequate clinical information.

Meta-analysis results

As shown in *Figure 2*, The combined results indicated that elevated SII was associated with poor OS (HR =1.80; 95% CI: 1.43–2.28), poor CSS (HR =1.44; 95% CI: 1.04–1.99), TTR (HR =1.91; 95% CI: 1.53–2.43) and poor PFS (HR =1.18; 95% CI: 0.55–2.52). Except the endpoint of TTR ($I^2=0\%$, $P=0.78$), the rest of meta-analysis demonstrated significant heterogeneity.

Table 1 The characteristics of included studies

Study	Study type	Country	Ethnicity	Cancer type	Sample size	outcome	Cut off value ($\times 10^9$)	NOS
Hu <i>et al.</i> , 2014	SRCS	China	Asian	Hepatocellular carcinoma	133	OS,TTR	330	6
Hu <i>et al.</i> , 2014	SPCS	China	Asian	Hepatocellular carcinoma	123	OS,TTR	330	7
Hong <i>et al.</i> , 2015	SRCS	China	Asian	Small cell lung cancer	919	OS	1,600	6
Yang <i>et al.</i> , 2015	SRCS	China	Asian	Hepatocellular carcinoma	189	OS	300	6
Gardini <i>et al.</i> , 2016	SRCS	Italy	Caucasian	Hepatocellular carcinoma	56	OS	360	6
Geng <i>et al.</i> , 2016	SRCS	China	Asian	ESCC	916	OS	307	6
Huang <i>et al.</i> , 2016	SRCS	China	Asian	Gastric cancer	455	OS	572	6
Lollis <i>et al.</i> , 2016	SRCS	Italy	Caucasian	Renal cell cancer	335	PFS,OS	730	6
Lollis <i>et al.</i> , 2016	SRCS	Italy	Caucasian	Prostate cancer	230	OS	535	6
Passardi <i>et al.</i> , 2016	MPRS	Italy	Caucasian	Colorectal cancer	289	PFS,OS	730	8
Wang <i>et al.</i> , 2016	SRCS	China	Asian	Hepatocellular carcinoma	163	TTR	330	6
Yu <i>et al.</i> , 2016*	SRCS	China	Asian	Acral melanoma	113	OS,TTR	615	NA
Feng <i>et al.</i> , 2017	SRCS	China	Asian	ESCC	298	CSS	410	6
Gao <i>et al.</i> , 2017	SRCS	China	Asian	Hepatocellular carcinoma	183	OS TTR	330	6

*, the type of publication is conference abstract. SRCS, single center retrospective cohort study; SPCS, single center prospective cohort study; MPRS, multicenter prospective randomized study; ESCC, esophageal squamous cell carcinoma; OS, overall survival; PFS, progression-free survival; TTR, time to recurrence; CSS, cancer-specific survival; NA, not available; NOS, Newcastle-Ottawa scale.

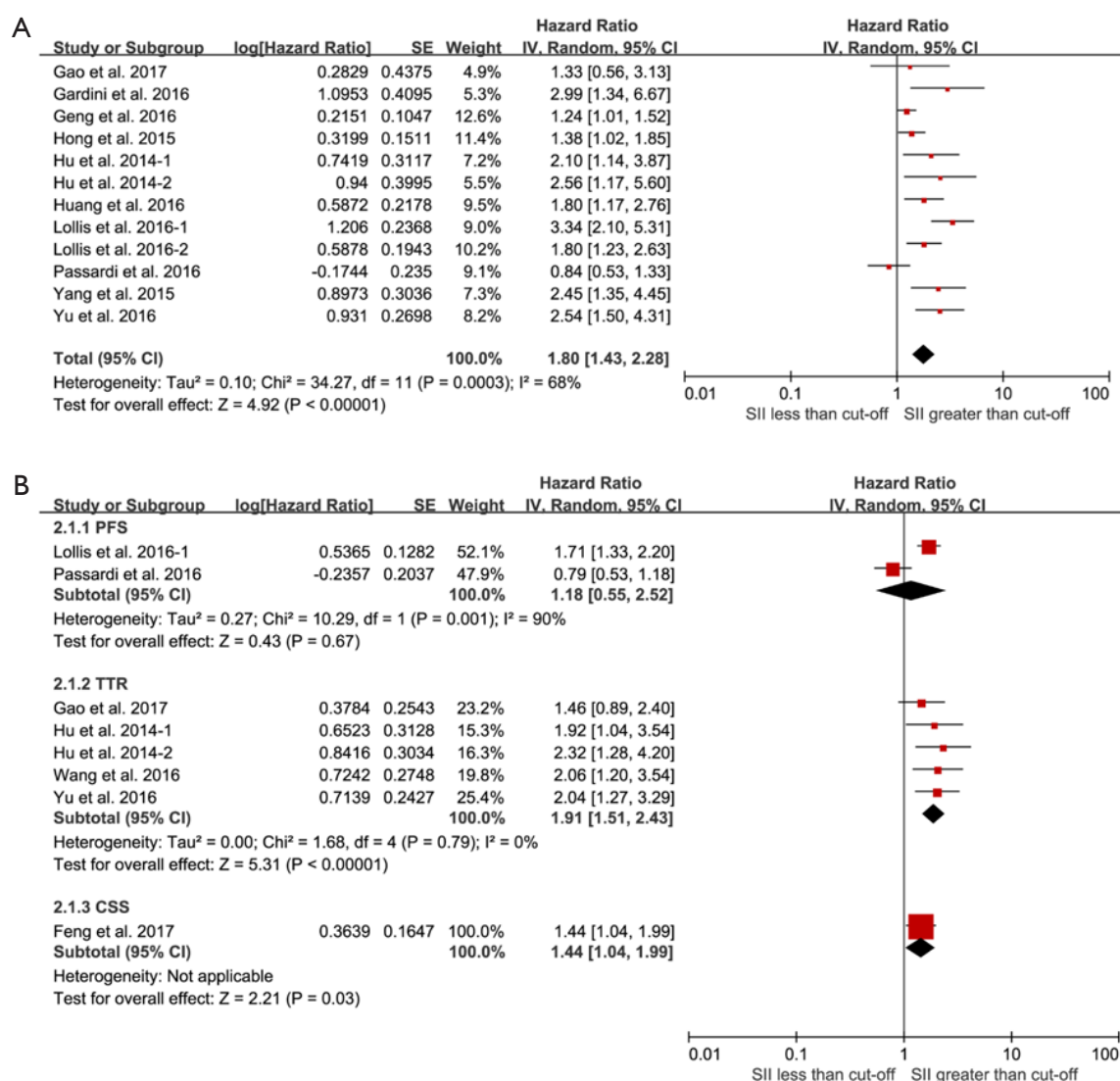


Figure 2 Forest plots with hazard ratios for overall survival (A) and other endpoints (B) for the systemic immune-inflammation index (SII) are greater than or less than the cutoff. PFS, progression-free survival; TTR, time to recurrence; CSS, cancer-specific survival.

Because of the presence of significant heterogeneity, a comprehensive subgroup analysis was conducted. The combined effect of SII on OS among cancer types is shown in *Figure 3A*. The significant prognostic effect of SII was highest in renal cell cancer (HR = 3.34; 95% CI: 2.10–5.31), followed by acral melanoma (HR = 2.54; 95% CI: 1.50–4.31), HCC (HR = 2.25; 95% CI: 1.64–3.09), prostate cancer (HR = 1.80; 95% CI: 1.23–2.63), gastric cancer (HR = 1.80; 95% CI: 1.17–2.76), SCLC (HR = 1.38; 95% CI: 1.02–1.85), esophageal squamous cell carcinoma (ESCC) (HR = 1.24; 95% CI: 1.01–1.52), but was not shown in colorectal cancer (HR = 0.84; 95% CI: 0.53–1.33). Moreover, a subgroup

analysis (stratified by sample size, cutoff value, ethnicity, and study type) for OS, demonstrated statistically significant HR in all defined subgroups (*Figure 3B,C,D*). However, in the prospective analysis cut-off $<330 \times 10^9$, and cut-off $>615 \times 10^9$ subgroups, the negative association was found between the SII and OS (*Figure 3C, Figure 4*).

Sensitivity analyses

Sensitivity analyses were conducted for the meta-analysis of OS by excluding one study at a time, and statistical results were compared. We found that heterogeneity

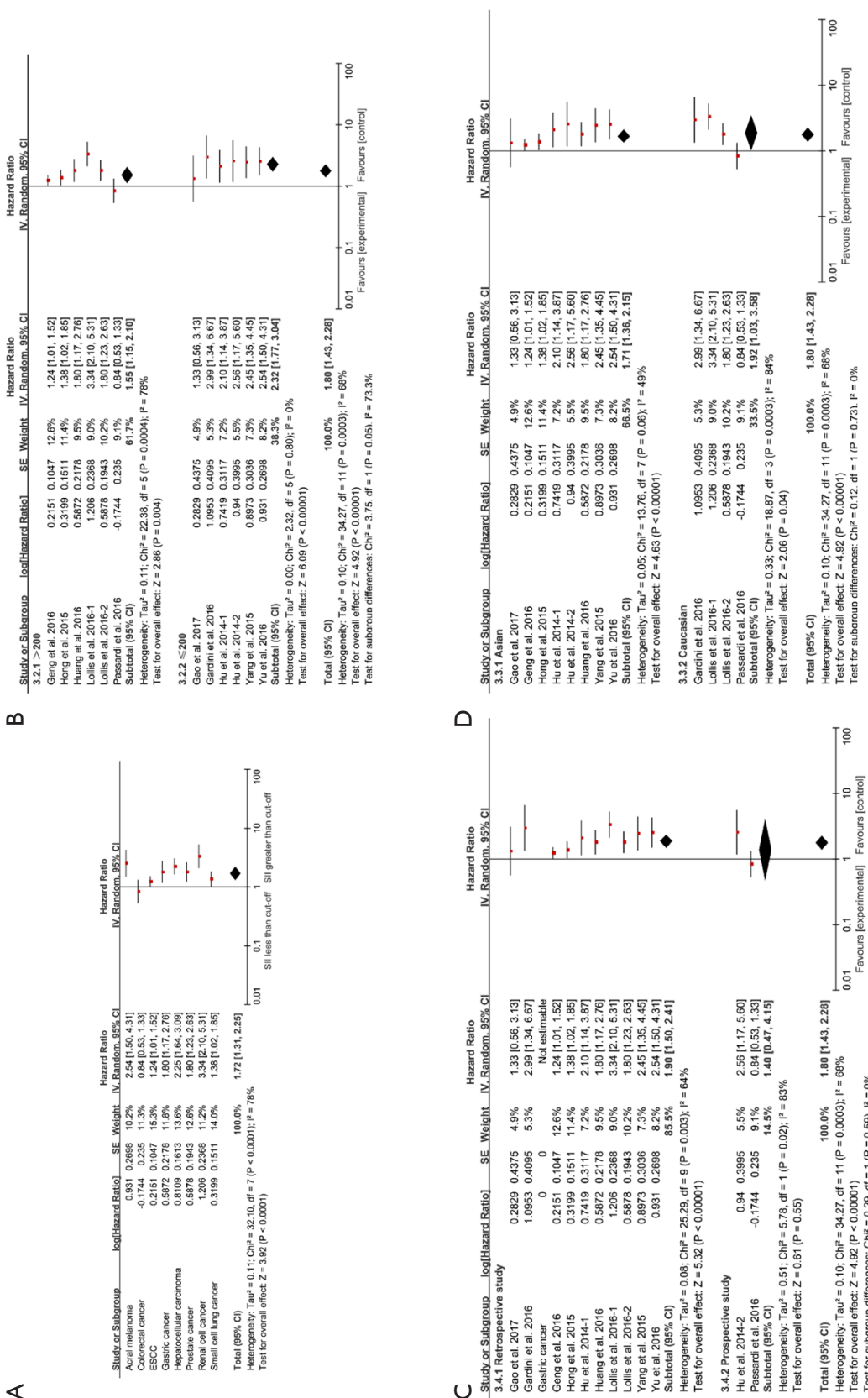


Figure 3 Forest plots showing hazard ratios for overall survival for the systemic immune-inflammation index (SII) greater than or less than the cutoff. (A) Hazard ratios by cancer types; (B) hazard ratios by sample size; (C) hazard ratios by study type; (D) hazard ratios by ethnicity. ESCC, esophageal squamous cell carcinoma.

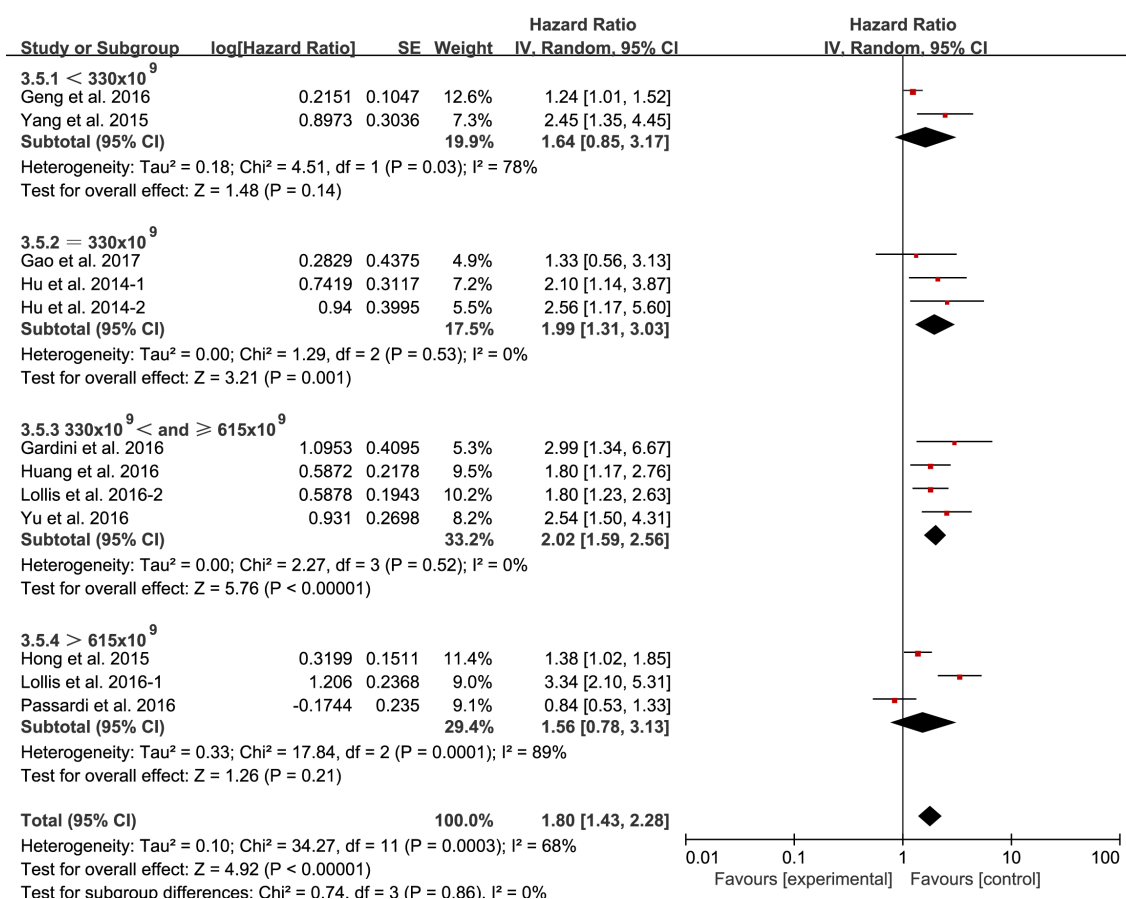


Figure 4 Forest plot for association between systemic immune-inflammation index (SII) and overall survival in the cut-off subgroup.

changed between 58–71% and P value remained stable (all $P < 0.0001$), which suggest that our overall findings were robust without potentially uncertain or influential inputs.

Publication bias and meta-regression

Publication biases were assessed by Begg's test and Begg's funnel plot for meta-analysis of OS (Figure 5). We did not find any publication biases ($P = 0.17$). In order to identify the heterogeneity factor between main available factors (sample size, cut off value, cancer type, ethnicity and study type), meta-regression analysis was conducted. The result showed that any these main factors did not function as heterogeneity factor (data not shown).

Discussion

Recently published studies have suggested that an elevated SII is associated with poor survival in subjects

with cancer. Herein, we undertook a meta-analysis of 13 studies (14 cohorts) comprising 4,012 patients to assess the prognostic utility of pretreatment SII in patients with solid tumors. The combined results indicated that elevated SII significantly predicted poor OS, poor CSS, poor TRR and poor PFS in this patient population. We found a high SII is consistently associated with survival ($HR = 1.80$) among different subgroups.

Inflammation has been reported to be a contributing factor in the development of many cancers and is now considered as a hallmark characteristic in all tumors (25). In recent years, the neutrophil-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratios (PLR) have been suggested as simple indices of systemic inflammatory response and a prognostic indication in different kinds of cancers (26,27). The SII was constructed based on lymphocyte, neutrophil, and platelet counts. Initially, SII was first shown to indicate the host inflammatory and immune status in resected HCC patients. In this study, SII was found to be one of

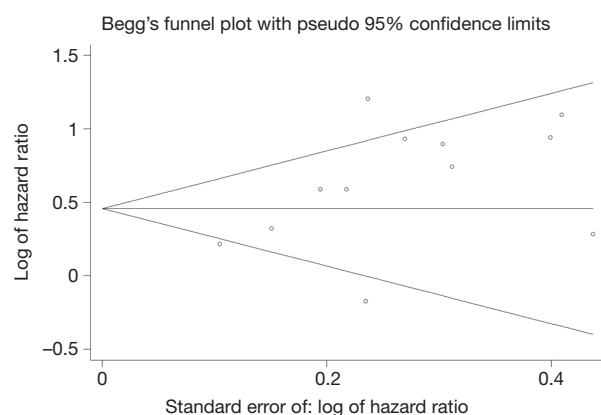


Figure 5 Begg's funnel plot analysis of potential publication bias in the meta-analysis for the association between systemic immune-inflammation index (SII) and overall survival in all studies. Circles indicate the corresponding studies.

the strongest predictive ability among other indices (NLR, PLR, and other parameters in predicting survival and recurrence), and possibly associated with CTCs levels (10). Later, Hong *et al.* and Yang *et al.* demonstrated that SII could also help in the prediction of poor prognosis in SCLC and HBV-related HCC, respectively (12,15). Many other studies were published later which showed the prognostic ability of SII in different kinds of cancers (11,18-21,24). Recently dynamic changes in SII were shown to be useful to predict the prognosis of patients with resected HCC (16). However, the study by Passardi *et al.* showed an insignificant association between SII and OS in metastatic colorectal cancer (17).

In our study, the results of the primary meta-analysis and most of the subgroup analysis showed that SII is indeed a robust predictive index for OS and TRR, which is consistent with previous reports (10,12,18,20). The prognostic values of SII in cancers can be explained by four types of cells (10). The first kind of cells are the CTCs which play a crucial role in the initiation of recurrence and metastases of cancer after surgery (28). The second type of cells are the neutrophils which secretes circulating growth factors promoting cancer cells adhesion and seeding in distant organ sites, as well as assisting cancer cells in evading immune surveillance (25,29). The third type of cells are the lymphocytes which play a vital role in tumor defense by inhibiting tumor cell proliferation and migration and inducing cytotoxic cell death (26). The fourth type of cells are the platelets which have emerged as a vital player in the systemic and local response to the tumor growth (27).

Moreover, recent evidence indicates that platelets could facilitate tumor cell survival and metastasis (29,30).

We also did not find statistical significance between the prognostic value of SII and survival in colorectal cancer subgroup, cut-off $<330 \times 10^9$ subgroup, cut-off of $>615 \times 10^9$ subgroup, and prospective study subgroup. Study by Passardi *et al.* included most of the above insignificant subgroups, except for cut-off of $<330 \times 10^9$ subgroup. Moreover, limited number of other studies had the four subgroup analysis. Thus, the presented insignificant results seem not be reliable, and these results warrant further studies to validate.

Our study has some limitations which are worth to point out. One of the limitation of our meta-analysis is a small number of published studies with the specific subgroup which could affect the interpretation. Furthermore, most of these studies were retrospective, and the cutoff values of SII were not consistent. We also found another meta-analysis on prognostication value of SII, but this meta-analysis did not include the combined value of SII in TTR which is the end point in many studies (31). Our analysis is more comprehensive with four subgroups of SII cutoffs.

In conclusion, we performed a comprehensive meta-analysis revealing that the elevated SII is an unfavorable predictor of prognosis in patients with cancers. SII can be used a potential prognostic indicator, and further large-scale prospective studies are warranted to investigate the efficacy of SII in clinical decision making in patients with cancers.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jlpm.2018.03.04>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Our search strategy

PubMed: [cancer or tumor or neoplasm or carcinoma (MeSH Terms)] AND (Systemic immune-inflammation index or SII) and AND [prognosis or outcome or survival or mortality or recurrence or progression or metastasis (MeSH Terms)] were used to search relevant studies.

Embase: all field [(cancer or tumor or neoplasm or carcinoma) and (prognosis or outcome or survival or mortality or recurrence or progression or metastasis) and (Systemic immune-inflammation index or SII)] were used to search relevant studies in the journal section, and the article

and short communication were chosen as type of journal.

Cochrane Library: SII or Systemic immune-inflammation index in title, abstract, keywords AND cancer or tumor or neoplasm or carcinoma in all text AND prognosis or outcome or survival or mortality or recurrence or progression or metastasis in all text were used to search relevant studies.

ASCO: SII or Systemic immune-inflammation index in all text.

ESMO: SII or Systemic immune-inflammation index in all text.