Systematic Review and Meta-Analysis

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Systemic immune-inflammation index is a promising noninvasive marker to predict survival of lung cancer

A meta-analysis

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Abstract

Background: The prognostic value of pretreatment systemic immune-inflammation index (SII) in lung cancer has yet to be fully established.

Methods: Relevant articles were obtained by performing a systematic search. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were used to assess the relationship between SII index and overall survival (OS) in lung cancer; the OS was calculated from the time of cancer diagnosis to the date of death due to any cause or to the last date of follow-up.

Results: In total, 2786 patients with lung cancer from 7 studies were included in this meta-analysis. The median thresholds to define high SII was 640 (range 395.4–1600) in the analyzed studies. The pooled HR for OS was 1.77 (95% CI: 1.54–2.00, $P < .001$), suggesting that the patients with a high SII score had a worse OS. In addition, results from subgroup meta-analysis showed the significant prognostic significance of SII in lung cancer. Especially, the predictive value of SII was significant in the multivariable model for NSCLC (HR: 1.97, 95% CI: 1.69–2.25, $P < .001$; 5 studies, 1746 patients), and SCLC (HR: 1.38, 95% CI: 1.02–1.85, $P < .001$; 1 study, 919 patients).

Conclusion: Our data suggest that high SII index indicates poor survival rate in lung cancer. Further researches are warranted to verify the significance of SII index in clinical practice.

Abbreviations: 95% CIs= 95% confidence intervals, CNKI= Chinese National Knowledge Infrastructure, HRs= hazard ratios, LMR= lymphocyte-to-monocyte ratio, MVA= multivariate analysis, NA= not available, NLR= neutrophil-to-lymphocyte ratio, NSCLC= non-small-cell lung cancer, OS= overall survival, PFS= progression-free survival, PLR= platelet-to-lymphocyte ratio, ROC= receiver operating characteristic curve, SCLC= small cell lung cancer, SII= systemic immune-inflammation index.

Keywords: lung cancer, meta-analysis, prognosis, systemic immune-inflammation index

1. Introduction

Lung cancer is an aggressive disease with high mortality and incidence worldwide. Nonsmall-cell lung cancer (NSCLC) and small cell lung cancer (SCLC) were the 2 pathological types.[1,2] Due to the characteristic of rapid growth and metastases, most of the patients with lung cancer had been in an advanced stage when diagnosed, and the median survival rate for such disease is low and unfavorable.[3–5] Predictive indicators that are closely related to cancer survival could assist clinicians to adopt preventive and therapeutic strategies for patients. Therefore, identifying novel prognostic factors that could be conveniently detected and cheaply available is in need of clinical practice.

Systemic immune inflammation (SII) index, as a novel inflammation-related index, is a comprehensive combination based on the peripheral lymphocyte, neutrophil, and platelet counts. It was calculated as follows: SII = platelet count × neutrophil/lymphocyte count.[6]

SII has been investigated as a marker to predict cancer survival in various tumors, such as hepatocellular carcinoma, gastric cancer, germ-cell tumor, and prostate cancer.[6–12] With regard to lung cancer, the prognostic value of SII was reported in several studies, and most of them showed that SII index could be a biological prognostic biomarker for lung cancer[13–18]; however, Chen et al [19] found that there was no significant association between SII index and survival time in lung cancer. Therefore, owing to the inconsistent results and the limited number of individual studies, we aimed to perform a meta-analysis based on all relevant data to assess the relationship between pretreatment SII index in lung cancer and prognosis.

2. Materials and methods

2.1. Search strategy and study selection

Because the present study is a meta-analysis, the ethical approval is not required. We searched the PubMed, Web of Science, Embase, Chinese National Knowledge Infrastructure (CNKI) , and Wanfang databases to identify the relevant articles according to the following terms: "systemic-immune-inflammation index" or "neutrophil × platelets/ lymphocyte" or "SII" or "platelet count × NLR," "lung cancer" or "NSCLC" or "lung tumor" or

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YZ and BC contributed equally to this paper, they are co-first authors.

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"SCLC." The literature search was conducted up to June 1, 2018, and the published language was limited to English or Chinese.

2.2. Inclusion and exclusion criteria

The studies were considered eligible if they met the following criteria:

(1) Studies reported the association between SII index and prognosis in patient with lung cancer.
(2) A definite cutoff-value of pretreatment SII was given.
(3) The hazard ratios (HRs) with 95% confidence intervals (95% CIs) for cancer survival were available.

Articles were excluded if they were reviews or meta-analysis, or not for lung cancer, or involved animal experiments.

2.3. Data extraction and quality assessment

In this meta-analysis, all included studies reported HRs and 95% CIs for OS; among them, 6 studies [13–18] reported the HRs and 95% CIs in multivariate survival analysis for OS, so the HRs and 95% CIs were extracted directly from the studies. And 1 study provided the Kaplan–Meier curve for OS[19]; thus, the Engauge Digitizer version 4.1 (http://digitizer.source forge.net/) was applied to retrieve the HRs and 95% CIs. For progression-free survival (PFS), we did not perform combined analysis in this report for only 1 study reported the relationship between SII and PFS in lung cancer. The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the study, and a study with cumulative scores ≥ 6 was assigned as high-quality.

2.4. Statistical analysis

All the synthesis analyses were carried out using the STATA statistics software (Version 12.0, College Station, Texas, USA). The HRs with its 95% CIs were used to evaluate the prognostic value of SII in lung cancer. Cochran Q test and Higgins I^2 statistic were performed for evaluating heterogeneity among studies. Studies with a $P_{het} > .1$ and/or $I^2 < 50\%$ were considered to have low heterogeneity and then the fixed-effects model was applied.

Egger and Begg tests were conducted to assess the publication bias, and the robustness of the results was assessed by sensitivity analysis. Differences were considered statistically significant when $P < .05$.

3. Results

The detailed selection procedure is listed in Fig. 1. After excluding duplication and reading the texts for further examination, finally, a total of 7 studies [13–19] were proved to be within the scope of the study and all followed an observational design.

A total of 2786 cases were included in this meta-analysis. With respect to prognostic outcomes, 7 studies reported overall survival (OS) and 1 covered PFS. For the relationship between SII index and OS, 5 studies focused on NSCLC,[13–16,18] and 1 study focused on SCLC,[17] and another one focused on both NSCLC and SCLC.[19] All included studies were from Asian countries (China and Japan). The cut-off value of high SII varies in those studies, ranging from

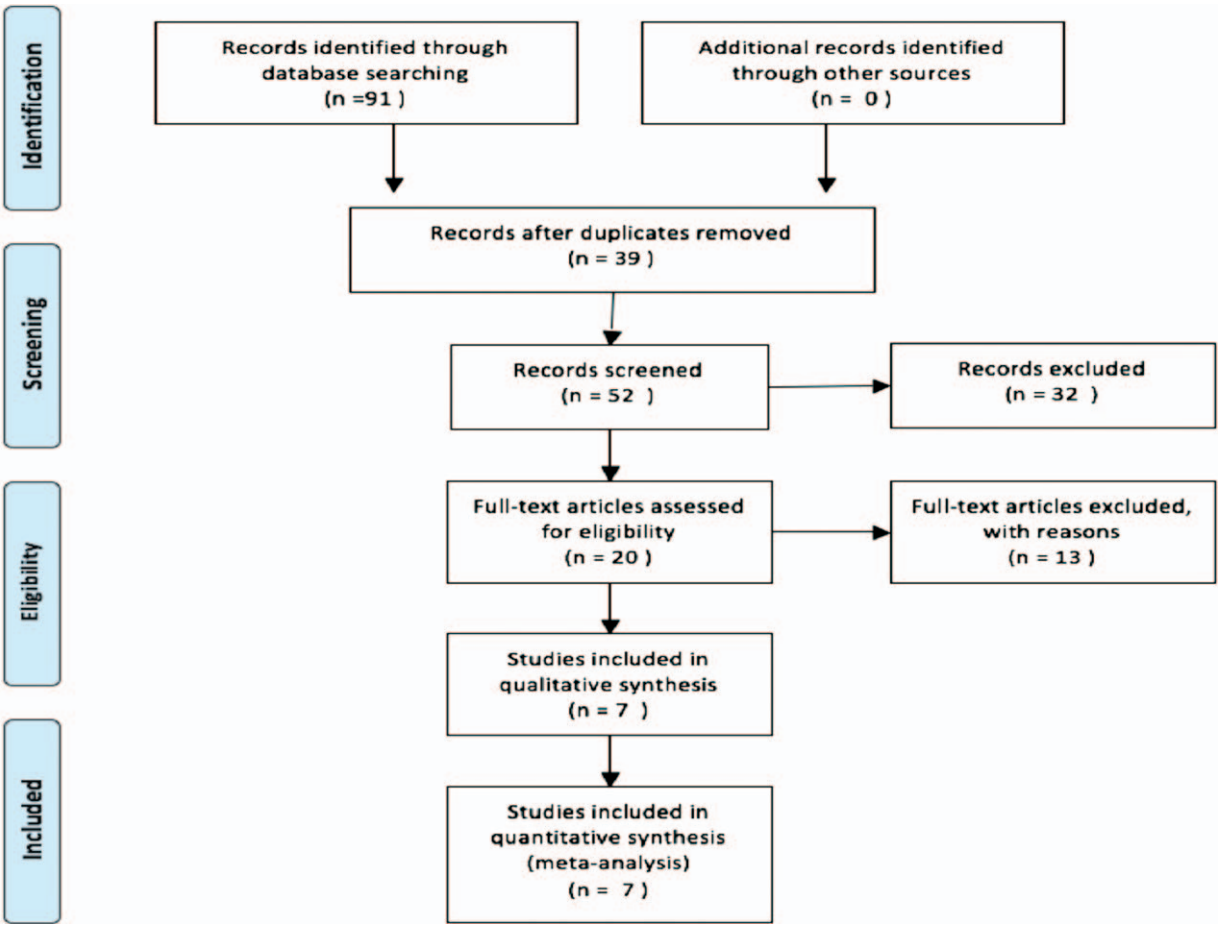

Figure 1. Flow diagram of included studies for this meta-analysis.

Table 1

Main characteristics of all included studies.

Study/ Year	Pathological type	Country	Included period	No. of cases	No. of Male	Age, y	Survival type	Cutoff value (10^9)	Cut-off selection	Treatment methods	Stage	MVA	Adjusted for covariates	N O S
Gao et al[18]	NSCLC	P.R. China	2009–2011	410	267 (65.1%)	NA	OS	395.4	ROC curve analysis	Curative resection	Non metastatic	Yes	Gender, age, smoking history, histological type, tumor location, lesion type, T stage, lymph node metastasis	8
Guo et al[13]	NSCLC	P.R. China	2013–2016	140	95 (67.9%)	Median age: 62 y	OS, PFS	521	ROC curve analysis	Chemoradiotherapy/ chemotherapy or targeted therapy	Mixed	Yes	Sex, age, ECOG score, smoking status, differentiation, histology, tumor stage, EGFR mutations, treatment regimen, albumin, CEA, inflammatory and PET/CT parameters	6
Tomita et al[14]	NSCLC	Japan	2008–2012	341	173 (50.7%)	Median age: 69 y	OS	471.2	Cutoff Finder	Curative resection	Non metastatic	Yes	Gender, smoking status, histology, pT status, pN status, serum CEA level, serum CYFRA21–1 level, serum CRP level	8
Dan et al[15]	NSCLC	P.R. China	NA	523	NA	NA	OS	640	NA	NA	Mixed	Yes	Gender, age, tumor status, smoking status, chemotherapy	6
Tong et al[16]	NSCLC	P.R. China	2006–2012	332	206 (62%)	Median age: 61 y	OS	660	ROC curve analysis	Surgical resection followed by chemotherapy or chemoradiotherapy/ concurrent CRT	Non metastatic	Yes	ECOG PS, T stage, node stage, clinical stage	7
Chen et al[19]	NSCLC, SCLC	P.R. China	2012–2016	121	92 (76.0%)	Range (28–78)	OS	660	According to cut-off value	Resection/chemotherapy and/or radiotherapy	Mixed	No	NA	7
Hong et al[17]	SCLC	P.R. China	2000–2012	919	635 (69.1%)	Median age: 56 y	OS	1600	According to cut-off value	Chemotherapy and/or radiotherapy	Mixed	Yes	Gender, age, smoking history, PS, stage, BMI, response to treatment, platelet count	8

All studies included were retrospective; the cutoff value for SII was used to define high versus low SII.

MVA = multivariate analysis; NA = not available; NSCLC = nonsmall-cell lung cancer; OS = overall survival; PFS = progression-free survival; ROC = receiver operating characteristic curve; SCLC = small cell lung cancer.

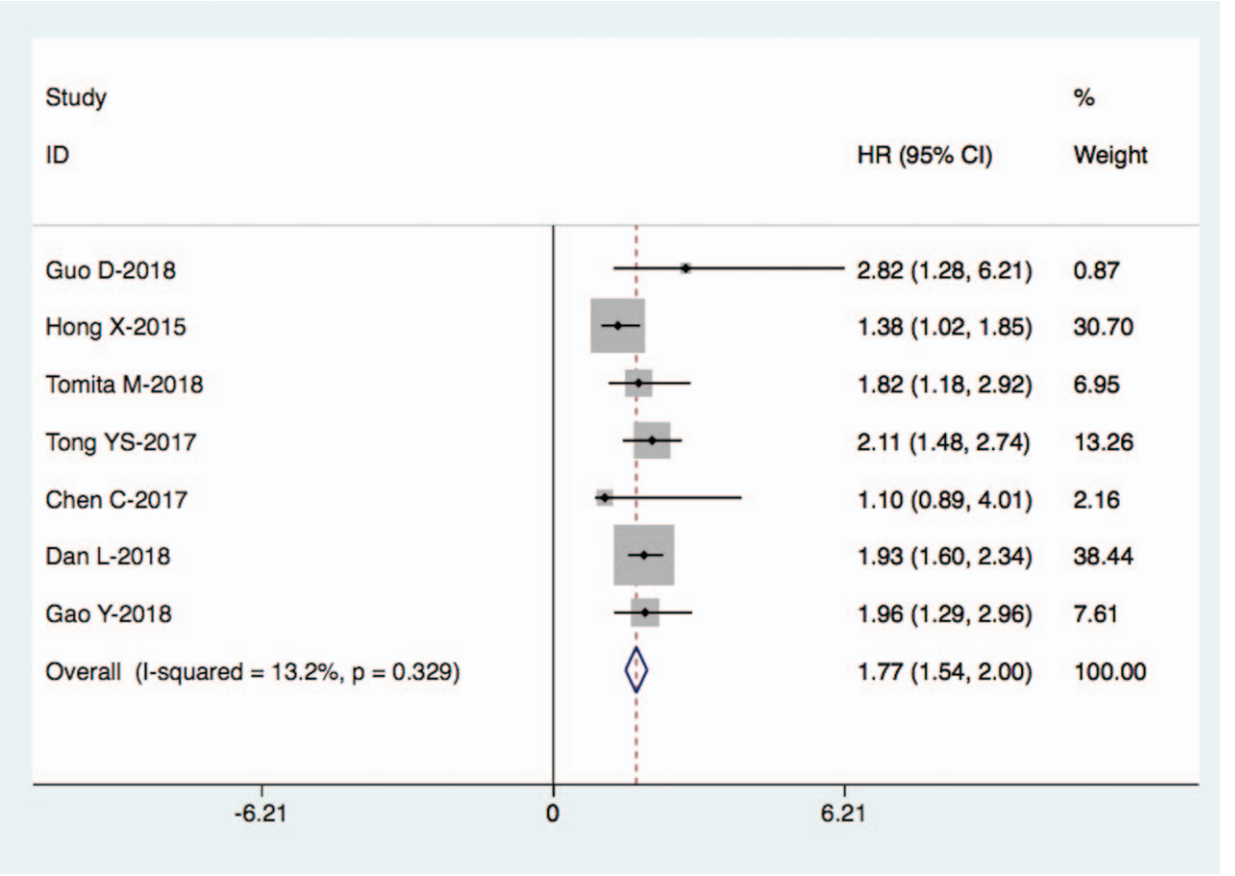

Figure 2. Forest plot for the association between SII and OS in lung cancer.

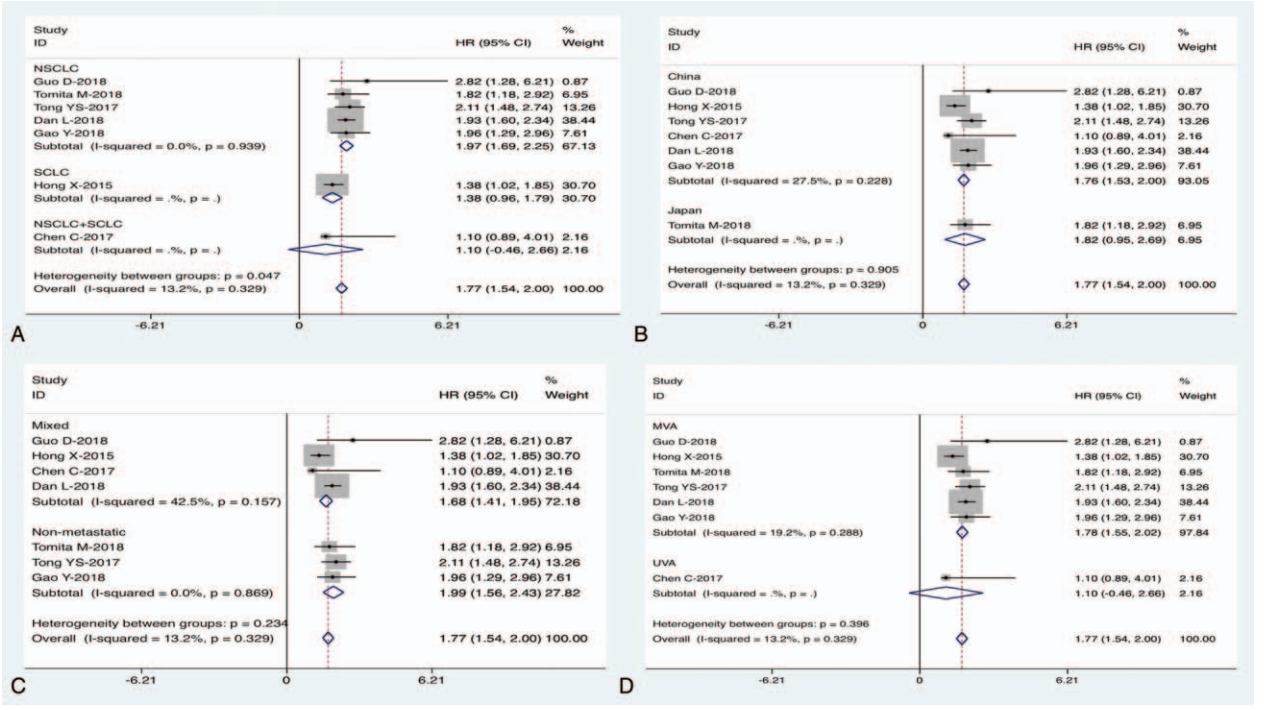

Figure 3. Subgroup meta-analysis of the association between SII and OS in lung cancer.

Table 2

Subgroup analysis of the relationship between SII and OS in lung cancer.

Subgroup factor	Divided standard	No. of studies	Pooled HR (95% CI)	*P*	Heterogeneity	
					I^2 (%)	P_{het}
Pathological type	NSCLC	5	1.97 (1.69–2.25)	<.001	0.0	.939
	SCLC	1	1.38 (1.02–1.85)	.034	—	—
	Mixed	1	1.10 (0.89–4.01)	NS	—	—
Country	China	6	1.76 (1.53–2.00)	<.001	27.5	.228
	Japan	1	1.82 (1.18–2.92)	<.001	—	—
Clinical stage	Mixed	4	1.68 (1.41–1.95)	<.001	42.5	.157
	Non-metastatic	3	1.99 (1.56–2.43)	<.001	0.0	.869
Analysis type	MVA	6	1.78 (1.55–2.02)	<.001	19.2	.288
	UVA	1	1.10 (0.89–4.01)	NS	—	—

95% CI = 95% confidence interval; ESCC = esophageal squamous cell carcinoma; HR = hazard ratio; NS = not significant.

395.4 to 1600 with the median of 640. The main characteristics of the studies included are summarized in Table 1.

3.1. SII and OS in lung cancer

There were 7 studies with a total of 2786 cases exploring the relationship between SII and OS of lung cancer; the combined findings are shown in Fig. 2. Our meta-analysis revealed that a high SII index was significantly correlated with a poor OS in patients with lung cancer (HR: 1.77, 95% CI: 1.54–2.00, $P < .001$). The result suggested that SII index could predict prognosis of lung cancer. Furthermore, subgroup meta-analysis stratified by the pathological type, country, clinical stage, and analysis type also confirmed the prognostic role of SII in lung cancer (Fig. 3A–D, Table 2).

3.2. Publication bias

The Begg test and Egger test were carried out to assess the potential publication bias; the Begg test ($Pr_{\text{continuitycorrected}} > |z| = 1.000$) and Egger test ($P > |t| = 0.822$) (Fig. 4) all showed that there was no possibility of publication bias among studies.

3.3. Sensitivity analysis

The sensitivity analysis was performed (Fig. 5), which showed that the pooled results did not change after the removal of any one study.

4. Discussion

Numerous researches have reported the link between inflammation and cancer and found that cancer-related inflammation is an indispensable component of the tumor microenvironment.[20,21] Inflammatory cycling cells, such as neutrophils, lymphocytes, and platelets, play important roles in the oncogenesis and cancer development.[22–25] These cells could contribute to tumor cell invasion and distant metastasis.[26,27] In recent years, several inflammation-related biomarkers based on the systemic inflammatory cells, such as the platelet-to-

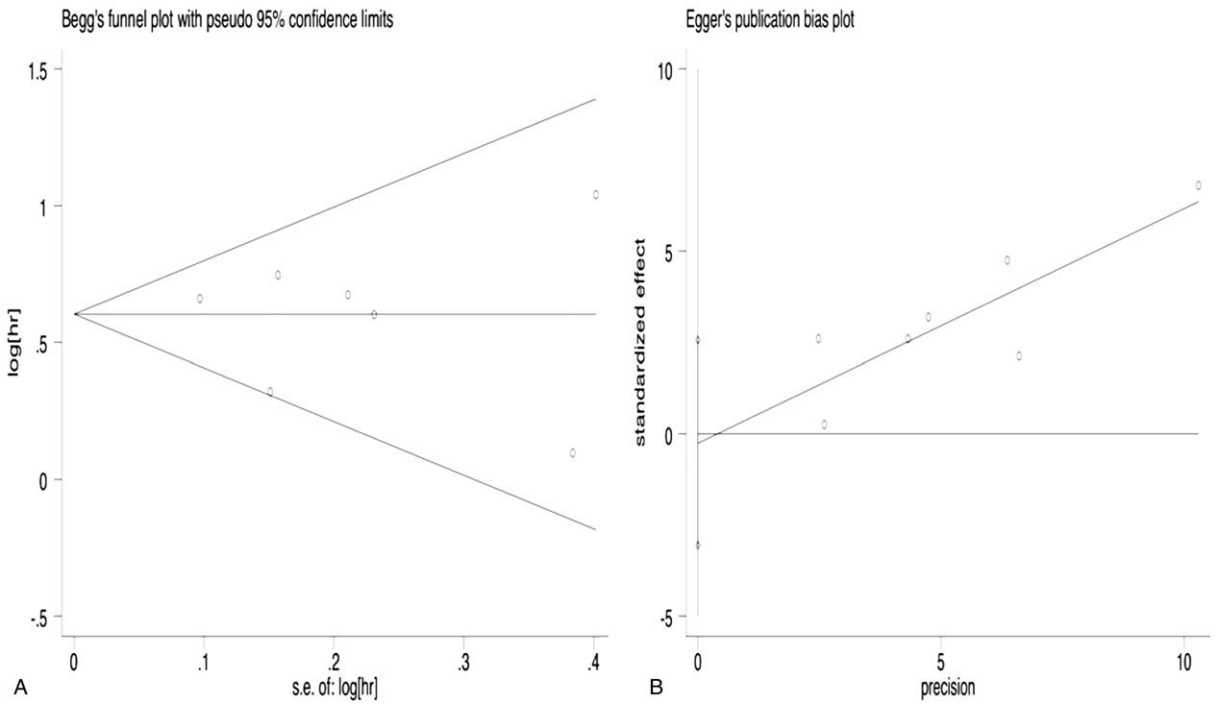

Figure 4. Publication bias assessment. (A) Begg funnel plot. (B) Egger publication bias plot.

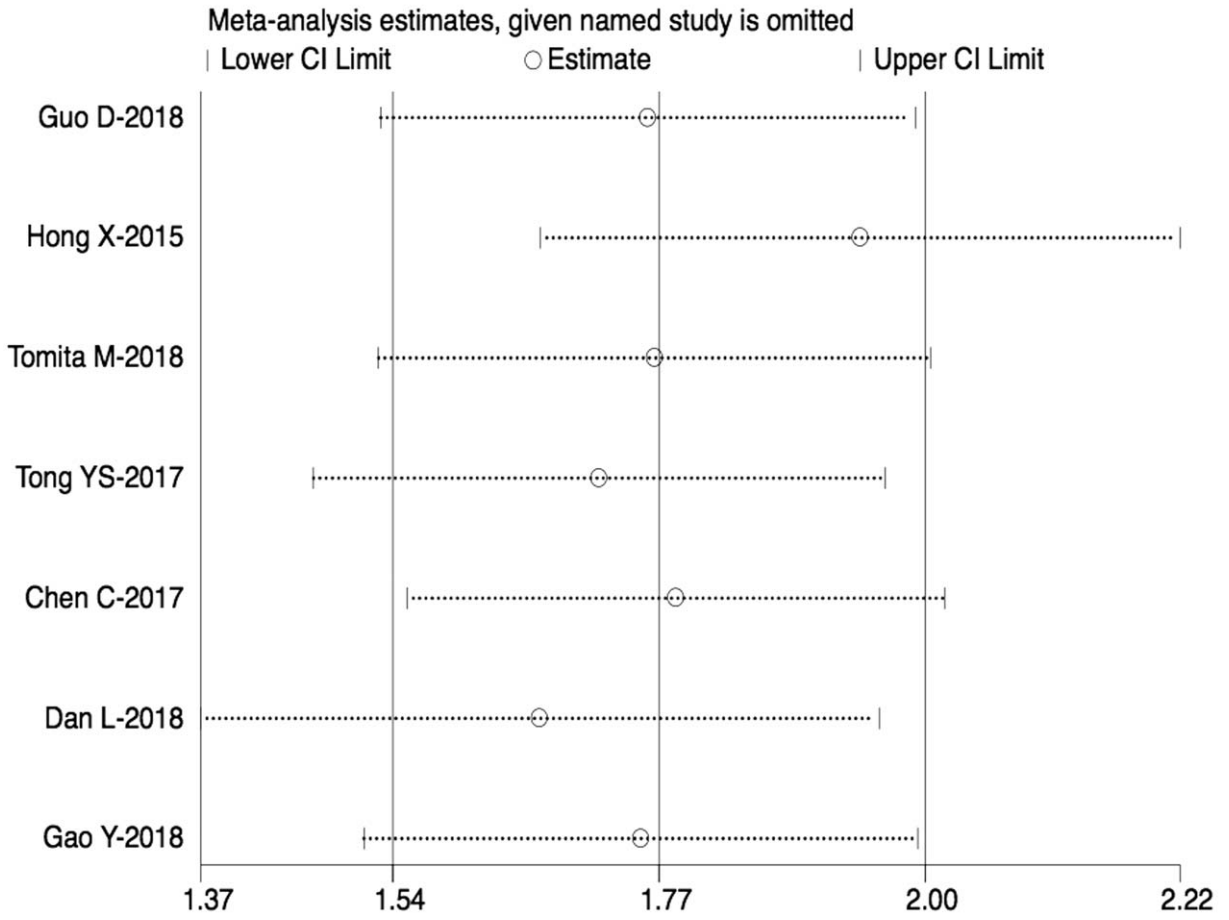

Figure 5. Sensitivity analysis.

lymphocyte ratio (PLR), the lymphocyte-to-monocyte ratio (LMR), and the neutrophil-to-lymphocyte ratio (NLR), have been shown to be of prognostic value in various cancers, including lung cancer.[28–33] However, these predictors are typically based on 2 inflammatory cells, and systemic immune-inflammation index (SII), a novel noninvasive biomarker, which is based on 3 peripheral blood parameters (platelet, neutrophil, and lymphocyte counts), could comprehensively reflect the balance of host immune and inflammatory status and has shown to be a more objective marker with a better predictive reliability for prognosis.[16–18]

To our knowledge, this is the first meta-analysis to investigate the impact of SII index on the survival of patients with lung cancer. On this topic, a total of 7 studies with up to 2786 cases were enrolled after a comprehensive search of literature. From the pooled results, we found that there was a significant association between SII index and prognosis in lung cancer. The patients with high SII index had a shorter OS when compared with the group in low SII index, suggesting that SII index could serve as a promising prognostic factor for patients with lung cancer.

Our meta-analysis has several limitations. First, the studies included were relatively small both in number and overall patients. There was an insufficient number of studies to perform more subgroups analysis for OS. In addition, only 1 study reported the association between SII index and PFS, which showed that SII was an independent factor for PFS in NSCLC; the prognostic value of SII index for PFS still needs to be confirmed by more studies. Third, all included studies were retrospectively designed and all patients from these studies were Asians from China and Japan; more studies conducted in other countries are needed. Fourth, low heterogeneity was observed for OS for the reported HR-adjusted different factors or diverse therapies utilized. In addition, although the SII was significant in the multivariable model for NSCLC and SCLC, the various individual studies were not adjusted for the same outcome-related covariates. At last, the thresholds used by the 7 studies to define high SII were different.

In conclusion, the present meta-analysis identified pretreatment SII index as a prognostic factor for OS in patients with lung cancer. SII index might be a cost-effective and significant biological marker for monitoring of survival in lung cancer. In future, larger multicenter researches should be required to further validate the prognostic value of SII index for lung cancer in clinical practice.

Author contributions

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Methodology: Yi Zhang, Bo Chen, Lijuan Wang, Rong Wang.
Software: Lijuan Wang, Rong Wang.
Supervision: Xianjin Yang.

Writing – original draft: Yi Zhang, Bo Chen.
Writing – review & editing: Xianjin Yang

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