

Prognostic value of the systemic inflammation response index in human malignancy

A meta-analysis

Lishuang Wei, MS^a, Hailun Xie, MS^b, Ping Yan, MD^{a,*}

Abstract

Background: This meta-analysis aimed to evaluate the prognostic value of the systemic inflammation response index (SIRI) in malignancy based on existing evidence.

Methods: We searched for relevant literature published in the electronic databases PubMed, Web of Science, Cochrane Library, and Embase before April 10, 2020. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated and pooled to evaluate the relationship between SIRI and malignancy outcomes.

Results: We included 14 articles, describing 6,035 patients. Our findings revealed that patients with high SIRI had worse overall survival (OS) (HR = 2.20, 95% CI: 1.85–2.62, $P < .001$), disease-free survival (DFS) (HR: 1.92, 95% CI: 1.49–2.48, $P < .001$), time-to-progression (TTP) (HR: 2.00, 95% CI: 1.55–2.58, $P < .001$), progression-free survival (PFS) (HR: 1.73, 95% CI: 1.38–2.16, $P < .001$), cancer-specific survival (CSS) (HR: 3.57, 95% CI: 2.25–5.68, $P < 0.001$), disease-specific survival (DSS) (HR: 1.99, 95% CI: 1.46–2.72, $P < .001$), and metastasis-free survival (MFS) (HR: 2.26, 95% CI: 1.28–3.99, $P = .005$) than patients with low SIRI. The correlation between SIRI and OS did not change in a subgroup analysis. Meta-regression indicated that heterogeneity may be related to differences in primary therapy strategies. Sensitivity analysis suggested that our results were reliable.

Conclusions: SIRI could be used as a useful predictor of poor prognosis during malignancy treatment.

Abbreviations: CI = confidence interval, CRC = colorectal cancer, CSS = cancer-specific survival, DFS = disease-free survival, DSS = disease-free survival, GPS = Glasgow prognostic score, HR = hazard ratio, MFS = disease-specific survival, MLR = monocyte-to-lymphocyte ratio, NLR = neutrophil-to-lymphocyte ratio, NOS = Newcastle Ottawa Scale, OS = overall survival, PFS = progression-free survival, SIRI = systemic inflammation response index, TTP = time-to-progression.

Keywords: human malignancy, meta-analysis, prognosis, systemic inflammation response index

1. Introduction

According to the world health organization (WHO), in 2015, malignancy remains one of the leading causes of death worldwide. Approximately 9.6 million people die from malignancies globally each year, accounting for one-sixth of total

deaths.^[1] Despite the continuous development of technologies such as improved surgical techniques, adjuvant radiochemotherapy, and targeted therapy, recurrences and metastases are still the main reasons for the poor prognosis of these patients. Therefore, it is critical to find useful biomarkers to predict prognosis and help choose the optimal treatment strategy.

Substantial evidence has suggested that cancer-related inflammation plays a critical role in the occurrence, development, and therapeutic response to cancer.^[2,3] Virchow et al^[4] initially detected the presence of tumor-infiltrating lymphocytes and speculated that there might be inflammation in the tumor. Further studies by Hanahan et al^[5] found that immune cells and inflammation are important components of the tumor microenvironment. Immune cells in the tumor microenvironment influence tumor growth by producing cytokines and chemokines in a both autocrine and paracrine fashion. Inflammation is also considered as the seventh hallmark of cancer, involved in the development, proliferation, metastasis, aging, and apoptosis of tumors. Ostan et al^[6] argued that inflammation triggers initial genetic mutations or epigenetic mechanisms that promote cancer development, metastasis, and progression.

In recent years, many prognostic indicators have been developed based on cancer-related systemic inflammation, including the Glasgow Prognostic Score (GPS),^[7] neutrophil-to-lymphocyte ratio (NLR),^[8] and monocyte-to-lymphocyte ratio (MLR).^[9] These indicators have been reported as risk factors for poor prognosis in cancer. Based on the count of neutrophils, monocytes, and lymphocytes, Qi et al^[10] established a novel

Editor: Peeyush Goel.

LW and HX contributed equally to this work.

The authors report no conflicts of interest.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

^a Geriatric Respiratory Disease Ward, The First Affiliated Hospital of Guangxi Medical University, ^b Department of Colorectal and Anal Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, PR China.

* Correspondence: Ping Yan, Geriatric Respiratory Disease Ward, The First Affiliated Hospital of Guangxi Medical University, 6 Shuangyong Road, Nanning 530021, Guangxi, China (e-mail: yp2000cn@gxmu.edu.cn).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Wei L, Xie H, Yan P. Prognostic value of the systemic inflammation response index in human malignancy: A meta-analysis. *Medicine* 2020;99:50(e23486).

Received: 2 July 2020 / Received in final form: 1 October 2020 / Accepted: 3 November 2020

<http://dx.doi.org/10.1097/MD.00000000000023486>

inflammation-related index, called systemic inflammatory response index (SIRI). The SIRI is an independent predictor of prognosis of various malignancies. However, no systematic reviews of the relationship between SIRI and the prognosis of overall malignancy have been performed. Therefore, our meta-analysis aimed to evaluate the prognostic value of SIRI in malignancies based on existing evidence.

2. Materials and methods

2.1. Search strategy

We performed a systematic review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.^[11] We searched the literature on the prognostic significance of SIRI in patients with cancer, published in the electronic databases PubMed, Web of Science, Cochrane Library, and Embase before April 10, 2020. We used a combination of subject words and free words to search the databases. The search terms were as follows: (“systemic inflammation response index” OR “neutrophil × monocytes / lymphocyte” OR “monocytes count × NLR” OR “SIRI”) AND (“neoplasms” OR “carcinoma” OR “leukemia” OR “lymphoma”). To avoid duplication of studies, we examined all authors and organizations and assessed the recruitment period and number of patients in each study. In addition, we also screened the references of the retrieved literature to identify more potential studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were:

- (1) Cancer types objectively confirmed based on pathological evidence;
- (2) Studies investigating the prognostic effect of SIRI in human malignancy, including overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), progression-free survival (PFS), time-to-progression (TTP), disease-specific survival (DSS), metastasis-free survival (MFS);
- (3) A SIRI cutoff value is provided;
- (4) Hazard ratio (HR) and 95% prognostic confidence interval (CI) are provided;
- (5) publications in English.

The exclusion criteria for this meta-analysis were:

- (1) HR and 95% CI were not available;
- (2) abstracts, letters, editorials, reviews, expert opinions or case reports;
- (3) unrelated publications.

2.3. Data extraction and quality assessment of included studies

Two reviewers independently extracted survival outcome data from the included studies. Data on survival outcomes mainly included hazard ratios (HRs) and 95% confidence intervals (CIs). If only the Kaplan-Meier curve provided prognostic results, we used Engauge Digitizer 4.1 software to obtain the estimated HR through the method designed by Tierney.^[12] We performed a quality assessment of included studies using the Newcastle Ottawa Scale (NOS) criteria.^[13] A maximum total score of 9

could be obtained, and each study with scores ≥ 6 was considered a high-quality study.

2.4. Statistical analysis

The HR and 95% CI extracted from each study were used to assess SIRI's prognostic value in patients with malignancies. The combination of the Cochran's Q test and Higgins I^2 statistical measures was used to assess the heterogeneity of the studies. If $I^2 > 50\%$, and $P_h < .1$, then a random-effects model was selected to generate the pooled HR; if not, a fixed-effects model was selected. Publication bias was assessed by visible images and the Begg test. In addition, a sensitivity analysis was used to evaluate the stability of the results. In the meta-analysis, a P value $< .05$ was defined as statistically significant. All statistical analyses were performed using Stata 12.0 software (Stata Corp, College Station, TX).

2.5. Ethics

No ethical or board review approval was required for this study.

3. Results

3.1. Study characteristics

The flow chart of document retrieval is illustrated in Figure 1. We included 14 published articles through systematic search, including 21 cohort studies, and a total of 6,035 cases (Table 1).^[10,14–26] One article included three cohort studies, five articles included two cohort studies, and the remaining eight articles included one cohort study. This meta-analysis involved various malignancies, including pancreatic cancer,^[10] gastric adenocarcinoma,^[14] hepatocellular carcinoma,^[15] esophageal squamous cell carcinoma,^[16] nasopharyngeal carcinoma,^[17] adenocarcinoma of the esophagogastric junction,^[18] clear cell renal cell carcinoma,^[19] pancreatic ductal adenocarcinoma,^[20] non-small-cell lung cancer,^[21] upper tract urothelial carcinoma,^[22] metastatic pancreatic cancer,^[23,25] breast cancer,^[24] and resectable gastric cancer.^[26] The publication years were between 2016 and 2020, the sample capacity ranged from 76 to 542, and the cutoff of SIRI ranged from 0.54×10^9 to 2.3×10^9 . As for the quality assessment of included studies, the NOS score of 17 cohort studies was 8, one cohort study had score 7, and three studies had score 6.

3.2. Meta-analysis for OS

Nineteen cohort studies enrolling 5,253 cases reported the prognostic significance of SIRI for OS. Significant heterogeneity was observed when the HR was pooled ($I^2 = 59.1\%$, $P_h = .001$), and, therefore, a random-effects model was utilized (Fig. 2). High SIRI was a prognostic factor for poor OS in human malignancies (HR = 2.20, 95% CI: 1.85–2.62, $P < .001$). Due to the heterogeneity found, we performed subgroup analyses stratified by publishing time, country, sample capacity, cut-off value, cancer system, primary therapy, and analytical method (Table 2). Although the number of patients varied among subgroups, high SIRI was strongly associated with poor OS in patients with malignancies. In addition, no heterogeneity was found in the subgroups of sample capacity < 240 , cut-off value < 1 , respiratory and urinary cancer system, with-chemotherapy, and univariate analytic method.

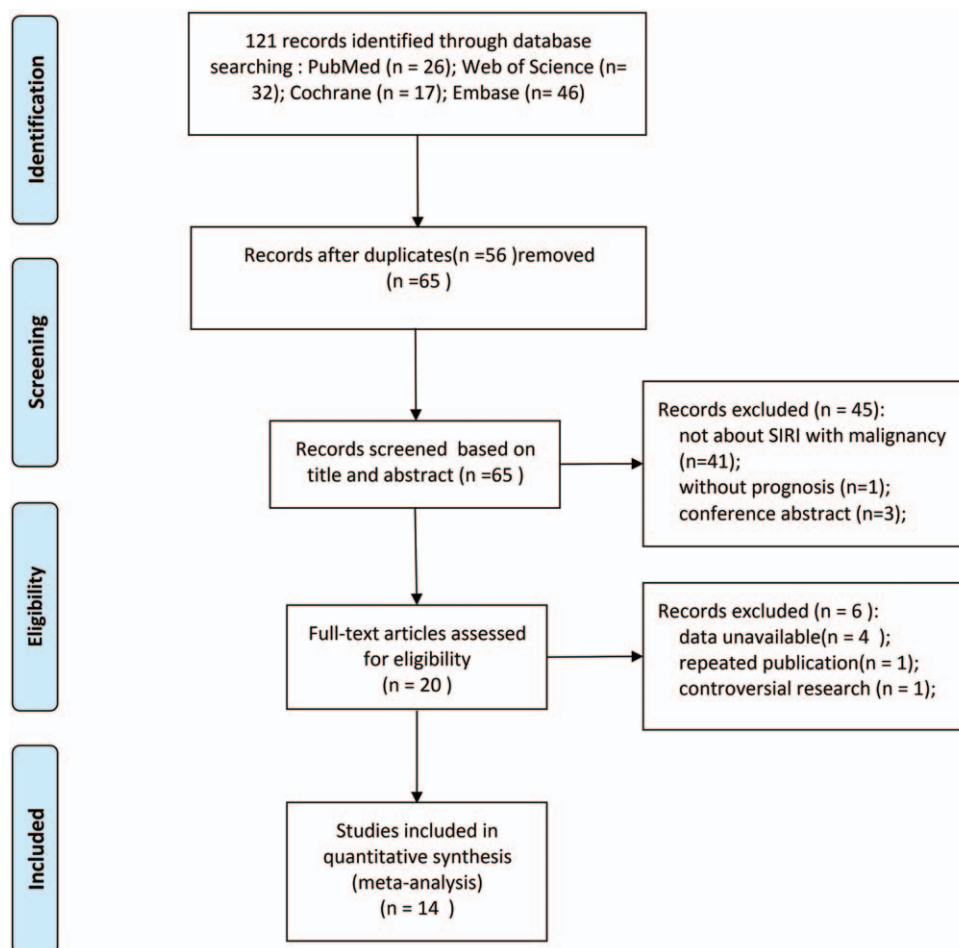


Figure 1. The flow chart of the literature selection.

To further explore the source of heterogeneity, we also used meta-regression to investigate the effects of different subgroups of SIRI on malignancy prognosis. This suggested that the p-value of primary therapy subgroups was below 0.05, which impacted the pooled HR. This could be the source of heterogeneity in this study, while the other subgroups did not show an impact on the pooled HR: $P_{\text{publishingtime}} = 0.144$, $P_{\text{country}} = .826$, $P_{\text{amplecapacity}} = .809$, $P_{\text{cutoffvalue}} = .493$, $P_{\text{cancersystem}} = .052$, $P_{\text{primarytherapy}} = .036$, $P_{\text{analyticmethod}} = .095$.

3.3. Meta-analysis for other outcomes

We further investigated the prognostic effects of SIRI on other outcomes in patients with malignancies, as shown in Figure 3. Three studies, involving 1,172 patients, reported the prognostic effects of SIRI on DFS. The fixed-effect model was adopted ($I^2 = 0.0\%$, $P_h = .834$) as we did not detect heterogeneity. High SIRI was a prognostic factor for poor DFS in human malignancies (HR: 1.92, 95% CI: 1.49–2.48, $P < .001$). Three studies, involving 574 medical records, reported the prognostic effects of SIRI on TTP. The fixed-effect model was adopted ($I^2 = 26.3\%$, $P_h = .258$) as there was no heterogeneity. High SIRI was a prognostic factor for poor TTP in human malignancies (HR: 2.00, 95% CI: 1.55–2.58, $P < .001$). Three studies, involving 845 medical records, reported the prognostic effects of SIRI on

PFS. The fixed-effect model was adopted ($I^2 = 10.2\%$, $P_h = .328$) since there was no heterogeneity. High SIRI was a prognostic factor for poor PFS in human malignancies (HR: 1.73, 95% CI: 1.38–2.16, $P < .001$). Three studies, involving 841 medical records, reported the prognostic effects of SIRI on CSS. The fixed-effect model was adopted ($I^2 = 40.4\%$, $P_h = .187$) due to no heterogeneity. Higher SIRI was a prognostic factor for poor CSS in human malignancy (HR: 3.57, 95% CI: 2.25–5.68, $P < .001$). Two studies, involving 782 medical records, reported the prognostic effects of SIRI on DSS. The fixed-effect model was adopted ($I^2 = 0\%$, $P_h = .438$) as we did not detect heterogeneity. High SIRI was a prognostic factor for poor DSS in human malignancies (HR: 1.99, 95% CI: 1.46–2.72, $P < .001$). One study, involving 259 medical records, reported the prognostic effects of SIRI on MFS. SIRI was also a prognostic factor for poor MFS in human malignancy (HR: 2.26, 95% CI: 1.28–3.99, $P = .005$).

3.4. Sensitivity analyses for OS

We performed a sensitivity analysis by deleting one of the included studies to check whether any studies affected the pooled HR of the OS (Fig. 4). Removing any of the included studies did not change the effect of SIRI on the comprehensive meta-analysis of OS, providing evidence that our results are robust.

Table 1
The characteristics of included studies.

Study/Year	Country	Cancer type	Sample capacity	Age (years)	Gender ratio	Treatment	Outcome	Follow-up (months)	Cutoff value (10 ⁵)	Analysis	NOS
Qi et al (2016)	China	Pancreatic cancer	177	58.8±10.7	108/69	With-chemotherapy	OS, TTP	Median (8.60)	1.8	M	8
	China		321	61.0±10.1	208/113	With-chemotherapy	OS, TTP	Median (7.73)	1.8	M	8
	China		76	60.9±9.6	46/30	With-chemotherapy	OS, TTP	Median (5.33)	1.8	M	8
Li et al (2017)	China	Gastric adenocarcinoma	455	Median 57.6 (29.0–89.0)	321/134	With-surgery	DFS, DSS	Median 77.53 (3.03–111.73)	0.82	M	8
	China		327	Median 57.6 (29.0–86.0)	235/92	With-surgery	DFS, DSS	Median 56.33 (4.9–76.3)	0.82	M	8
Xu et al (2017)	China	Hepatocellular carcinoma	183	53.7±10.5	155/28	With-chemotherapy	OS	>60	1.05	M	7
Geng et al (2018)	China	Esophageal squamous cell carcinoma	542	Mean 54	416/126	With-surgery	OS	>60	1.2	M	8
	China		374	Mean 51	280/94	With-surgery	OS	>60	1.2	M	8
Chen et al (2018)	China	Nasopharyngeal carcinoma	285	22–80	210/75	With-chemotherapy	OS	>60	0.84	M	8
	China		213	NA	157/56	With-chemotherapy	OS	>60	0.84	M	8
Chen et al (2019)	China	Adenocarcinoma of the esophagogastric junction	302	Median 63 (43–84)	244/58	With-surgery	OS	Median 55 (4–98)	0.68	M	8
Chen et al (2019)	China	Clear cell renal cell carcinoma	414	Median 56.3 (24–80)	257/152	With-surgery	OS, CSS	Median 69.2 (1–151)	1.35	M	8
	China		168	≥60	101/65	With-surgery	OS, CSS	Median 69.2 (1–151)	1.35	U	6
Li et al (2019)	China	Pancreatic ductal adenocarcinoma	371	Median 62 (35–84)	224/147	With-surgery	OS, PFS	>36	0.69	M	8
	China		310	Median 60 (34–82)	164/146	With-surgery	OS, PFS	>36	0.69	M	8
Li et al (2019)	China	Non-small-cell lung cancer	390	NA	147/243	With-surgery	OS, DFS	Median 50 (12–66)	0.99	M	8
	China		259	67.5±10.4	185/74	With-surgery	OS, CSS, MFS	Median 33.3 (15.5–64.2)	1.36	M	8
Zheng et al (2019)	China	Upper tract urothelial carcinoma	259	67.5±10.4	185/74	With-surgery	OS, CSS, MFS	Median 33.3 (15.5–64.2)	1.36	M	8
Yoshitomi et al (2019)	Japan	Metastatic pancreatic cancer	83	Mean 64	52/31	With-chemotherapy	OS	Mean 9 months	1.9	M	6
Hua et al (2020)	China	Breast cancer	390	Median 68 (49–87)	0/390	With-surgery	OS	Median 65.5 (0.9–95.9)	0.54	M	8
Pacheco-Barcia et al (2020)	Spain	Metastatic pancreatic cancer	164	Median 66 (57.5–74)	92/72	With-chemotherapy	OS, PFS	Median 11.8	2.3	M	8
Zhang et al (2020)	China	Resectable gastric cancer	231	Median 62 (26–85)	156/75	With-surgery	OS	Median 43 (3–73)	0.84	U	6

CSS=cancer-specific survival, DFS=disease-free survival, DSS=disease-specific survival, MFS=metastatic-free survival, NOS=Newcastle Ottawa Scale, OS=overall survival, PFS=progression-free survival, TTP=time-to-progression.

3.5. Publication bias

We used the Begg test and funnel plots to assess potential publication bias. We observed evidence of publication bias (Fig. 5) (The *P* values for OS < .05). There were fewer than ten cohort studies included in the other outcomes. Therefore, for these publication bias could not be assessed.

4. Discussion

Systemic inflammation plays a critical role in different malignant progression stages, including initiation, malignant transformation, promotion, tissue invasion, and metastasis. Inflammatory responses can destroy cancer cells, but also establish a tumor microenvironment that assists the proliferation and metastasis of cancer cells.^[27] SIRI, which combines counts of neutrophils, monocytes, and lymphocytes, is a promising biomarker for inflammation and is thought to be associated with the prognosis of multiple malignancies.

This is the first meta-analysis based on existing evidence that high SIRI scores are associated with poor prognosis in human malignancies. We found that patients with cancer with a high SIRI tended to have a poor OS. In addition, we performed a subgroup analysis to correct for subgroup effects. This showed that although publishing time, country, sample capacity, cutoff value, cancer system, primary therapy, and analytic method were variable within the different groups, high SIRI still was a powerful predictor of poor prognosis. Due to the heterogeneity of pooled HR of OS, we further performed a meta-regression analysis, which indicated that differences in primary therapy might cause the heterogeneity. From the included studies, eight

adopted chemotherapy, and eleven adopted surgical treatment. This could have led to SIRI differences, as chemotherapy may result in bone marrow suppression and immune system damage, causing changes in neutrophils, monocytes, and lymphocytes levels. This may be the source of heterogeneity in this meta-analysis. We further verified the stability of this meta-analysis by deleting one study at a time for sensitivity analysis. We found that the comprehensive meta-analysis effect did not significantly change due to one study, indicating that our results are reliable. In addition, we explored the relationships between SIRI and other prognostic outcome measures of malignancy. We found that high SIRI was associated with adverse outcomes of DFS, TTP, PFS, CSS, DSS, and MFS. In summary, SIRI may be considered as a predictor of significant clinical utility in human malignancy.

Several possible mechanisms may explain the prognostic value of SIRI. It has been reported that neutrophils secrete cytokines and chemokines to create a tumor microenvironment suitable for tumor proliferation, invasion, and microvascularization, promoting tumor development and progression.^[28] Similarly, monocytes also play a vital role in tumorigenesis and metastasis. Tumor-associated macrophages derived from peripheral monocytes can inhibit the acquired immune response, promote tumor growth and tumor angiogenesis, and cause tumor invasion and migration.^[29] Additionally, monocytes influence cancer stem cells' activity by modifying the factors secreted by neutrophils and tumor-associated macrophages, thereby affecting the sensitivity to chemotherapy resistance.^[30–32] In contrast, lymphocytes play an essential role in cancer immune surveillance, and can lead to cytotoxic cell death, inhibiting the proliferation and growth of tumor cells.^[33] A comprehensive index based on

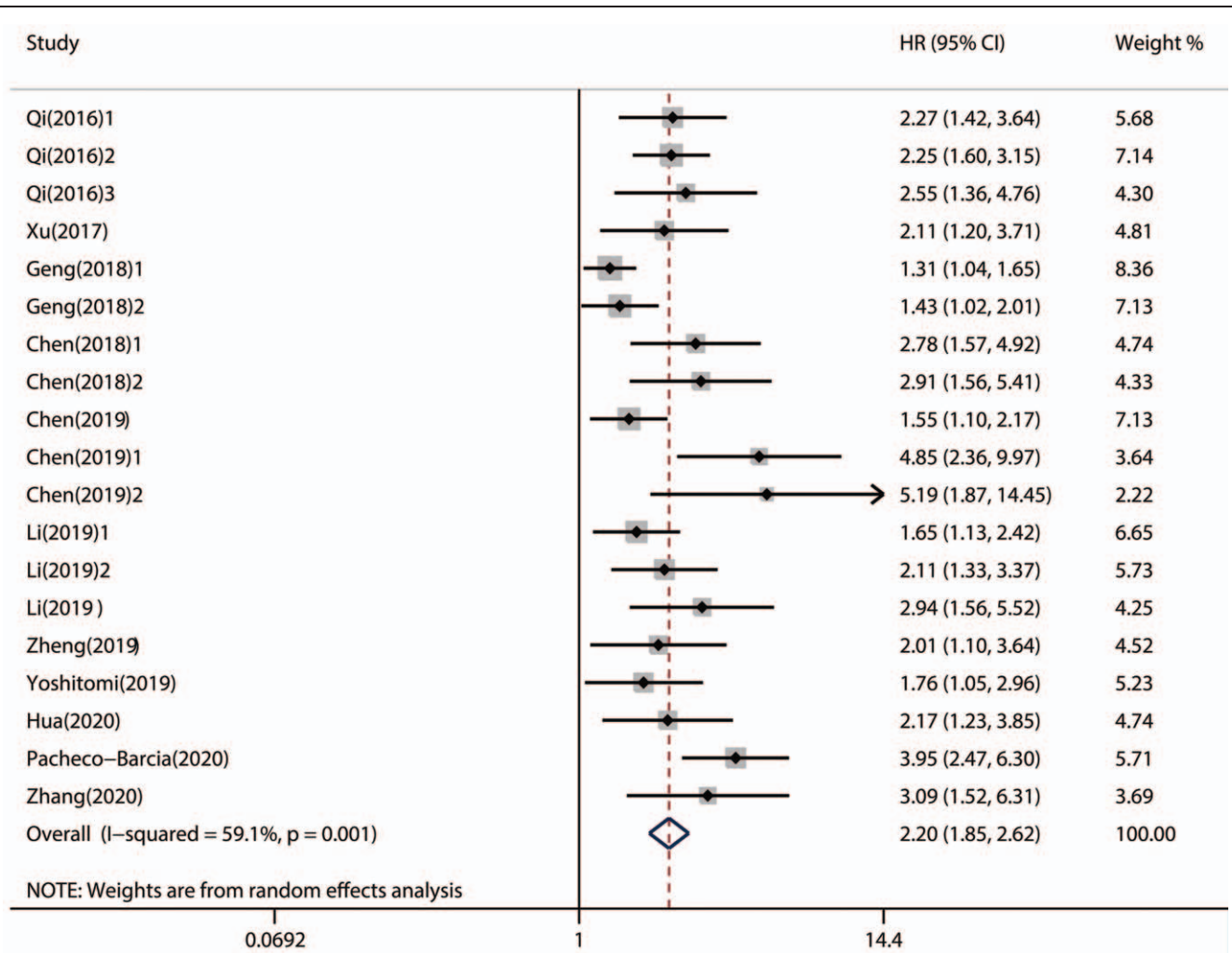


Figure 2. Forest plot for the association between SIRI and OS. OS = overall survival, SIRI = systemic inflammation response index.

Table 2

Stratification analysis for the meta-analysis with overall survival (OS) in patients with malignancy.

Subgroup	No. of cohorts	No. of patients	Pooled HR (95% CI)	P	Heterogeneity	
					I ² (%)	P _h
Altogether	19	5253	2.20 (1.85–2.62)	<.001	59.1	.001
Publishing time						
<2019	8	2171	1.86 (1.44–2.29)	<.001	60.2	.014
≥2019	11	3082	1.98 (1.59–2.38)	<.001	54.7	.015
Country						
China	17	5006	2.13 (1.79–2.53)	<.001	54.0	.004
Japan	1	83	1.76 (1.05–2.95)	.032	NA	NA
Spain	1	164	3.95 (2.47–6.31)	<.001	NA	NA
Sample capacity						
<240	8	1295	2.65 (2.12–3.32)	<.001	14.2	.319
≥240	11	3958	1.95 (1.59–2.38)	<.001	58.8	.007
Cutoff value						
<1	8	2492	2.11 (1.73–2.57)	<.001	19.6	.274
≥1	11	2761	2.25 (1.73–2.92)	<.001	71.3	<.001
Cancer system						
Digestive	12	3134	1.96 (1.62–2.37)	<.001	60.0	.004
Respiratory	3	888	2.87 (2.02–4.07)	<.001	0	.990
Urinary	3	841	3.45 (1.79–6.67)	<.001	55.5	.106
Gland	1	390	2.17 (1.23–3.85)	.008	NA	NA
Primary therapy						
With-chemotherapy	8	1502	2.47 (2.08–2.94)	<.001	0	.465
With-surgery	11	3751	2.20 (1.60–2.54)	<.001	62.1	.003
Analytic method						
Multivariate	17	4854	2.12 (1.78–2.52)	<.001	58.7	.001
Univariate	2	399	3.66 (2.04–6.56)	<.001	0	.415

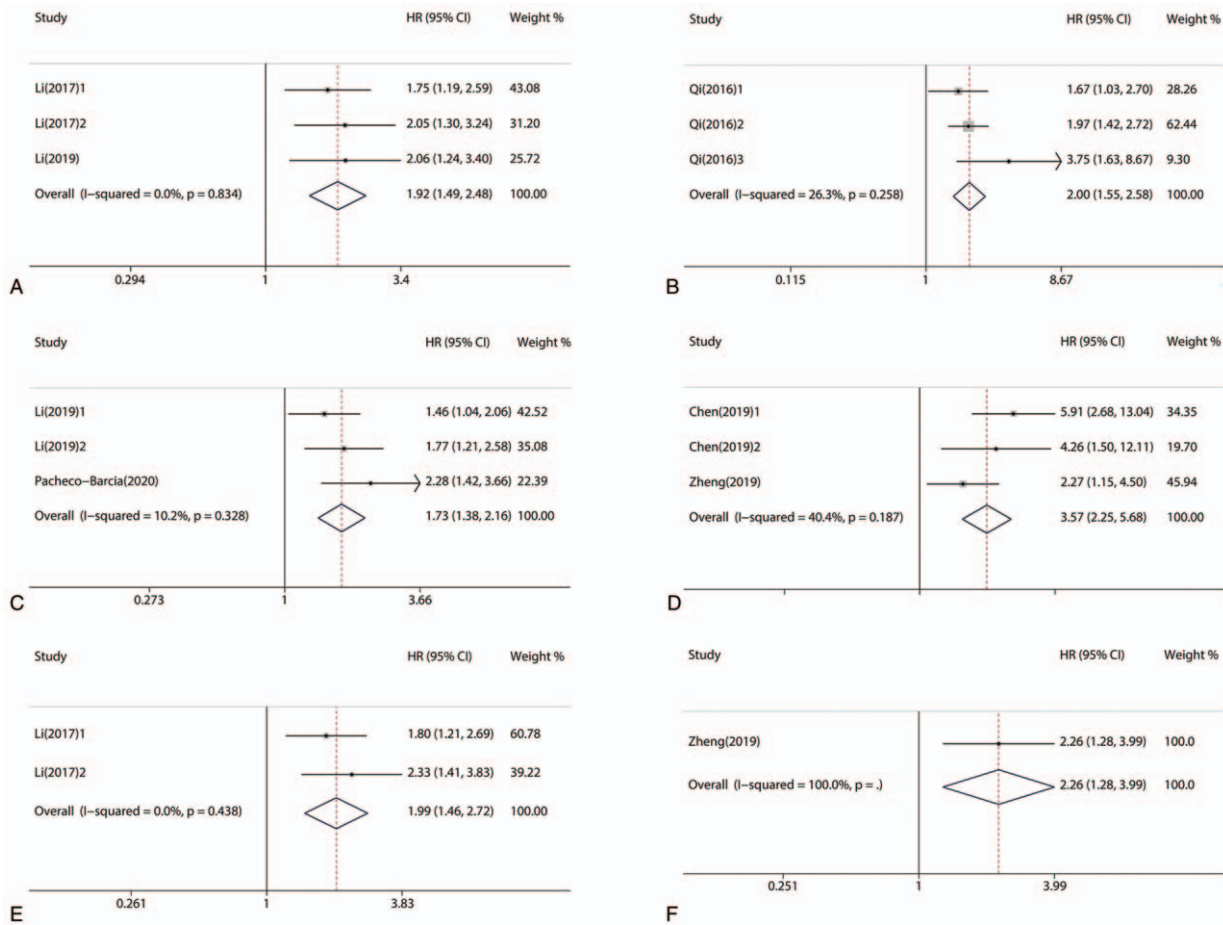


Figure 3. Forest plot for the association between SIRI and other outcomes. Notes: A, forest plot for DFS; B, forest plot for TTP; C, forest plot for PFS; D, forest plot for CSS; E, forest plot for DSS; F, forest plot for MFS. CSS = cancer-specific survival, DFS = disease-free survival, DSS = disease-specific survival, MFS = metastatic-free survival, PFS = progression-free survival, SIRI = systemic inflammation response index, TTP = time-to-progression.

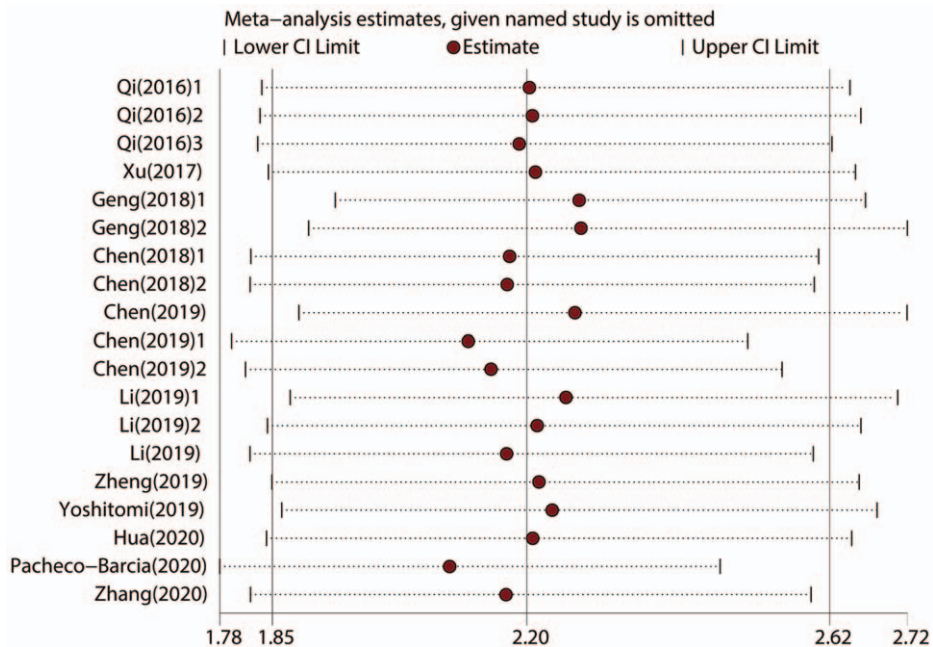


Figure 4. Sensitivity analysis for the association between SIRI and OS. OS = overall survival, SIRI, systemic inflammation response index.

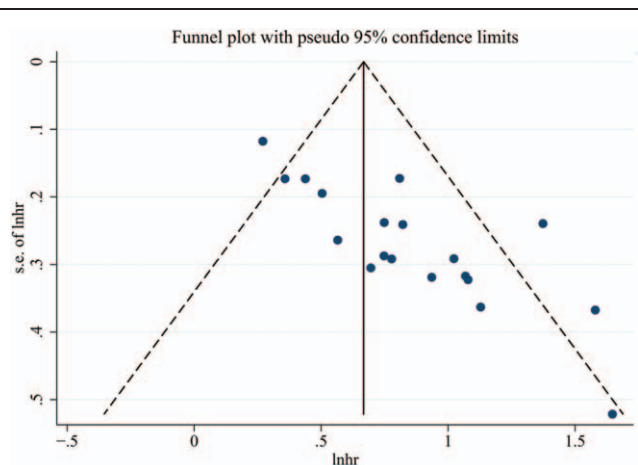


Figure 5. Begg funnel plot for the assessment of potential publication bias according to OS. OS = overall survival.

these three cell types may better reflect the balance between host inflammation and immune status.

Some limitations to our meta-analysis should be noted. First, there was apparent heterogeneity in the analysis of the relationship between SIRI and OS. We speculate through subgroup analysis and meta-regression that the heterogeneity might be caused by the differences in primary therapy used in different studies. Furthermore, we verified the reliability of our meta-analysis through sensitivity analysis. Second, the studies included were all retrospective studies; therefore, potential bias was more likely to occur. Large-scale multicenter prospective cohort studies are needed to verify our results. Third, we found publication bias in the meta-analysis of OS, which may be due to the difficulty of publishing studies with negative results. However, the comprehensive meta-analysis effect of SIRI did not change in the sensitivity analysis. Despite these limitations, we provide valuable support for the prognostic value of SIRI in patients with malignancies, based on available evidence.

In conclusion, our meta-analysis demonstrates that SIRI is associated with poor prognosis of malignancies, and could be used as a useful predictor in the treatment of cancer. However, due to the limited number of studies included in the analysis, large-scale prospective studies are required to confirm our results.

Author contributions

Conceptualization: Ping Yan

Data curation: Lishuang Wei, Hailun Xie

Formal analysis: Lishuang Wei, Hailun Xie

Writing – original draft: Lishuang Wei, Hailun Xie

Writing – review & editing: Ping Yan

References

- [1] Freddie , Bray , Jacques , et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
- [2] Rosenberg SA. Progress in human tumour immunology and immunotherapy. *Nature* 2001;411:380–4.
- [3] Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. *Nature* 2008;454:436–44.

- [4] Virchow R. An address on the value of pathological experiments. *Br Med J* 1881;2:198–203.
- [5] Hanahan D, Weinberg Robert A. Hallmarks of Cancer: The Next Generation. *Cell* 2011;144:646–74.
- [6] Ostan R, Lanzarini C, Pini E, et al. Inflammaging and cancer: a challenge for the Mediterranean diet. *Nutrients* 2015;7:2589–621.
- [7] McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat Rev* 2013;39:534–40.
- [8] Templeton AJ, McNamara MG, Seruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014;106:dju124.
- [9] Zhou WJ, Wu J, Li XD, et al. Effect of preoperative monocyte-lymphocyte ratio on prognosis of patients with resectable esophago-gastric junction cancer. *Zhonghua Zhong Liu Za Zhi* 2017;39:178–83.
- [10] Qi Q, Zhuang L, Shen Y, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. *Cancer* 2016;122:2158–67.
- [11] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151:W65–94.
- [12] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
- [13] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
- [14] Li S, Lan X, Gao H, et al. Systemic Inflammation Response Index (SIRI), cancer stem cells and survival of localised gastric adenocarcinoma after curative resection. *J Cancer Res Clin Oncol* 2017;143:2455–68.
- [15] Xu L, Yu S, Zhuang L, et al. Systemic inflammation response index (SIRI) predicts prognosis in hepatocellular carcinoma patients. *Oncotarget* 2017;8:34954–60.
- [16] Geng Y, Zhu D, Wu C, et al. A novel systemic inflammation response index (SIRI) for predicting postoperative survival of patients with esophageal squamous cell carcinoma. *Int Immunopharmacol* 2018;65:503–10.
- [17] Chen Y, Jiang W, Xi D, et al. Development and validation of nomogram based on SIRI for predicting the clinical outcome in patients with nasopharyngeal carcinomas. *J Investig Med* 2019;67:691–8.
- [18] Chen Y, Jin M, Shao Y, et al. Prognostic value of the systemic inflammation response index in patients with adenocarcinoma of the oesophagogastric junction: a propensity score-matched analysis. *Dis Markers* 2019;2019:4659048.
- [19] Chen Z, Wang K, Lu H, et al. Systemic inflammation response index predicts prognosis in patients with clear cell renal cell carcinoma: a propensity score-matched analysis. *Cancer Manag Res* 2019;11:909–19.
- [20] Li S, Xu H, Wang W, et al. The systemic inflammation response index predicts survival and recurrence in patients with resectable pancreatic ductal adenocarcinoma. *Cancer Manag Res* 2019;11:3327–37.
- [21] Li S, Yang Z, Du H, et al. Novel systemic inflammation response index to predict prognosis after thoracoscopic lung cancer surgery: a propensity score-matching study. *ANZ J Surg* 2019;89:E507–13.
- [22] Zheng Y, Chen Y, Chen J, et al. Combination of systemic inflammation response index and platelet-to-lymphocyte ratio as a novel prognostic marker of upper tract urothelial carcinoma after radical nephroureterectomy. *Front Oncol* 2019;9:914.
- [23] Pacheco-Barcia V, Mondejar Solis R, France T, et al. A systemic inflammation response index could be a predictive factor for mFOLFIRINOX in metastatic pancreatic cancer. *Pancreas* 2019;48:e45–7.
- [24] Hua X, Long ZQ, Huang X, et al. The preoperative systemic inflammation response index (SIRI) independently predicts survival in postmenopausal women with breast cancer. *Curr Probl Cancer* 2020;100560.
- [25] Pacheco-Barcia V, Mondejar Solis R, France T, et al. A systemic inflammation response index (SIRI) correlates with survival and predicts oncological outcome for mFOLFIRINOX therapy in metastatic pancreatic cancer. *Pancreatol* 2020;20:254–64.
- [26] Zhang J, Ding Y, Wang W, et al. Combining the fibrinogen/albumin ratio and systemic inflammation response index predicts survival in resectable gastric cancer. *Gastroenterol Res Pract* 2020;2020:3207345.
- [27] Grivnennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010;140:883–99.

- [28] Gregory AD, Houghton AM. Tumor-associated neutrophils: new targets for cancer therapy. *Cancer Res* 2011;71:2411–6.
- [29] Liao R, Jiang N, Tang ZW, et al. Systemic and intratumoral balances between monocytes/macrophages and lymphocytes predict prognosis in hepatocellular carcinoma patients after surgery. *Oncotarget* 2016;7:30951–61.
- [30] Yu PF, Huang Y, Han YY, et al. TNF α -activated mesenchymal stromal cells promote breast cancer metastasis by recruiting CXCR2(+) neutrophils. *Oncogene* 2017;36:482–90.
- [31] Wan S, Zhao E, Kryczek I, et al. Tumor-associated macrophages produce interleukin 6 and signal via STAT3 to promote expansion of human hepatocellular carcinoma stem cells. *Gastroenterology* 2014;147:1393–404.
- [32] Takaishi S, Okumura T, Tu S, et al. Identification of gastric cancer stem cells using the cell surface marker CD44. *Stem Cells* 2009;27:1006–20.
- [33] Heinzel S, Marchingo JM, Horton MB, et al. The regulation of lymphocyte activation and proliferation. *Curr Opin Immunol* 2018;51:32–8.