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Prognostic and clinicopathological impact of systemic inflammation response index (SIRI) on patients with esophageal cancer: a meta-analysis

Zhong Wu[1], Zongxin Zhang[2] and Chao Gu[3*]

Abstract

Background Although the systemic inflammation response index (SIRI) is often associated with prognostic significance in esophageal cancer (EC) patients, the results continue to be conflicting. We focused on identifying SIRI's precise role in forecasting EC prognosis through performing this meta-analysis.

Methods This work searched PubMed, Web of Science, Embase, Cochrane Library, and CNKI till November 16, 2024, and determined pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for evaluating EC prognosis forecasting efficiency of SIRI. The inclusion criteria: (1) pathologic confirmation of EC; (2) those reporting associations of SIRI with EC survival outcomes; (3) those reporting HRs and 95% CIs; (4) those with an available cut-off value of SIRI; and (5) no restriction in language. The exclusion criteria: (1) case reports, reviews, meeting abstracts, comments and letters; (2) those enrolling duplicate cases; and (3) animal studies.

Results We enrolled six studies comprising 2176 cases into the present work. Based on our combined findings, elevated SIRI showed significant relation to dismal overall survival (OS) (HR = 1.43, 95%CI = 1.20–1.71, $p < 0.001$; $I^2 = 48.8\%$, $p = 0.098$) and shortened progression-free survival (PFS) (HR = 2.00, 95%CI = 1.35–2.98, $p = 0.001$; $I^2 = 0$, $p = 0.409$) in EC. Moreover, high SIRI exhibited obvious relation to male gender (OR = 1.86, 95%CI = 1.07–3.22, $p = 0.027$; $I^2 = 69.4\%$, $p = 0.020$), TNM stage of III-IV (OR = 1.52, 95%CI = 1.18–1.94, $p = 0.001$; $I^2 = 24.3\%$, $p = 0.265$), T3-T4 stage (OR = 1.73, 95%CI = 1.12–2.69, $p = 0.014$; $I^2 = 61.0\%$, $p = 0.053$), and lymph node metastasis (OR = 1.29, 95%CI = 1.02–1.64, $p = 0.036$; $I^2 = 42.7\%$, $p = 0.155$). However, SIRI was not markedly related to age, tumor location, tumor differentiation, or smoking history.

Conclusion In summary, high SIRI is significantly related to dismal OS and shortened PFS of EC cases, together with advanced tumor stage, T3-T4 stage, and lymph node metastasis of EC. Due to some limitations, large prospective studies that utilize standardized threshold SIRI should be conducted to validate our results in the future.

Keywords Systemic inflammation response index, Meta-analysis, Evidence-based medicine, Prognosis, Biomarker

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Introduction

In 2022, esophageal cancer (EC) ranked as the eleventh most diagnosed cancer worldwide, with approximately 510,716 cases and 445,129 deaths, making it the seventh leading cause of cancer-related deaths globally [1]. The two major EC histological categories include esophageal squamous cell carcinoma (ESCC) and adenocarcinoma [2]. Of them, ESCC occupies more than 85% of all EC patients [3]. A multidisciplinary team typically guides EC treatment strategies, which involve a sequence of surgery, chemotherapy, radiotherapy, and immunotherapy [4]. However, the diagnosis of more than 66% of EC cases is made at the advanced and metastatic stages, with an overall 5-year survival rate as low as 20%-30% [5]. Furthermore, the prognosis is generally unfavorable, with the 5-year survival rate in advanced stage being just 5% [6]. In this regard, it is crucial to detect new and efficient biomarkers to forecast EC prognosis and improve the survival outcomes.

Current evidences have shown that inflammation significantly influences cancer's development, metastasis, and resistance to treatment, while changes in inflammatory cells related to tumors indicate the intensity of the tumor's inflammatory response [7]. Many studies have indicated that a series of inflammation-based indexes are significant prognostic factors for cancers, including platelet-to-lymphocyte (PLR) [8], C-reactive protein-to-albumin (CAR) [9], lymphocyte-to-monocyte (LMR) [10], and neutrophil-to-lymphocyte ratios [11]. As the new blood-test derived indicator, systemic inflammation response index (SIRI) is firstly put forward in 2016 [12]. SIRI was developed by neutrophil quantity × monocyte quantity/lymphocyte quantity [12]. SIRI was proposed as a prognostic marker for cancers. SIRI is previously suggested to be of significant prognostic impacts on different tumors like rectal cancer [13], gastric cancer [14], thyroid cancer [15], upper tract urothelial carcinoma [16], as well as breast cancer [17]. Besides, its efficiency in forecasting EC prognosis is reported, whereas the results were controversial due to variants among studies such as study region, sample size, and tumor stage etc. [18–23]. For example, some studies demonstrated that elevated SIRI independently forecast EC prognosis [18, 20, 21]. However, in other studies, SIRI was not apparently correlated with prognosis of EC [19, 23]. Consequently, this work focused on identifying prognostic and clinicopathological efficiency of SIRI for EC.

Materials and methods

Study guideline

We performed this study according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24].

Ethical statement

Because this meta-analysis uses previously published data for analysis, ethical approval and informed consent are not required. This meta-analysis was performed in adherence to ethical principles in data. The PRISMA guideline was followed for data collection and selection.

Search strategy

PubMed, Web of Science, Embase, Cochrane Library, and CNKI were searched till November 16, 2024 using search items of (system inflammation response index or systemic inflammation response index or systemic inflammatory response index or SIRI) and (Esophageal Cancers or Esophageal Neoplasms or Oesophageal cancer Esophageal Cancer or Esophagus Cancer or Esophagus Cancers or Cancer of the Esophagus or Esophagus Neoplasms or Cancer of Esophagus or Esophageal Neoplasm or Esophagus Neoplasm or esophageal squamous cell carcinoma or Esophagus or ESCC). There was no restriction on languages of publications. Furthermore, we examined references in chosen studies for guaranteeing thorough coverage.

Inclusion and exclusion criteria

Following studies were included: (1) pathologic confirmation of EC; (2) those reporting associations of SIRI with EC survival outcomes; (3) those reporting hazard ratios (HRs) and 95% confidence intervals (CIs); (4) those with an available cut-off value of SIRI; and (5) no restriction in language. Studies below were eliminated: (1) case reports, reviews, meeting abstracts, comments and letters; (2) those enrolling duplicate cases; and (3) animal studies.

Information acquisition and quality analysis

Two researchers (Z.W. and Z.Z.) acquired information in eligible articles. Disputes between them were settled by negotiation with the third reviewer (C.G.). Information harvested included first author's name, year, country, sample size, age, gender, study period, study design, TNM stage, histology, study center, treatment, threshold SIRI, threshold determination, study outcomes, survival analysis, follow-up, together with HRs and 95%CIs. Overall survival (OS) served as our primary outcome, while progression-free survival (PFS) as our secondary outcome. Those enrolled cohort studies were independently evaluated for quality by two independent investigators (Z.W. and Z.Z.) with Newcastle–Ottawa Scale (NOS) [25] that measures cohort selection (0–4 score), comparability (0–2 score), and outcome evaluation (0–3 score). The NOS has a total score of 9 points, and ≥ 6 scores suggest high quality.

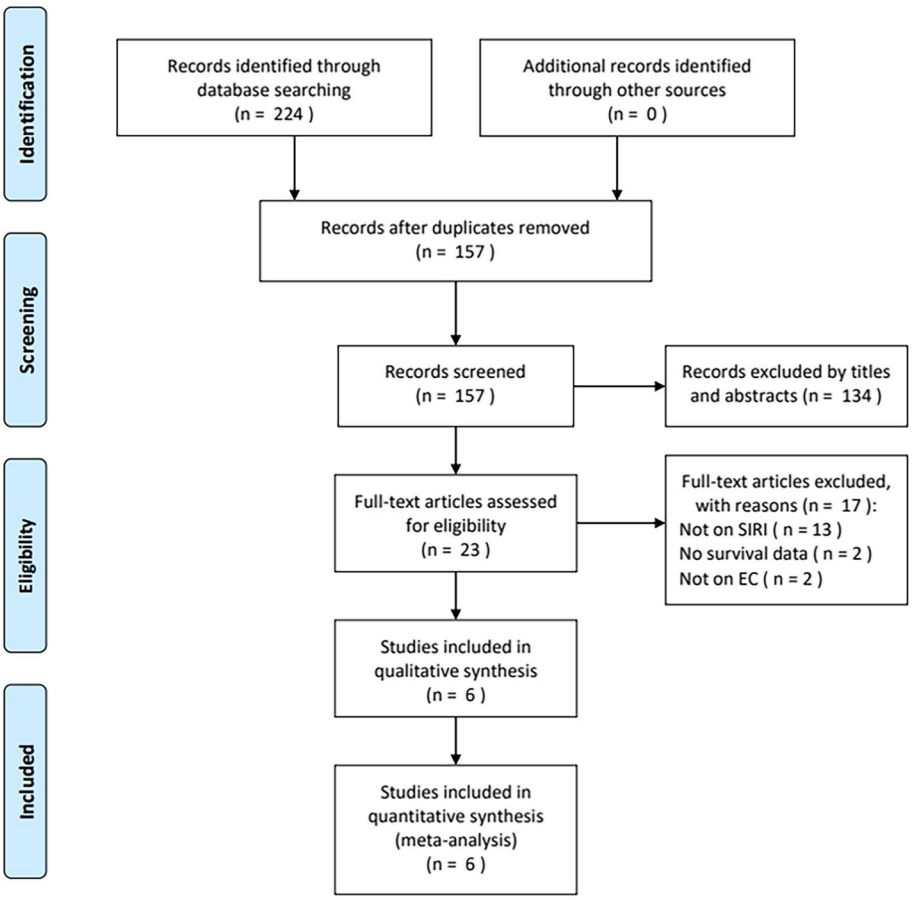

Fig. 1 PRISMA flow chart of this meta-analysis

Statistical analysis

This present work completed statistical analysis with Stata version 12.0 (StataCorp, College Station, TX, USA), and analyzed EC prediction efficiency of SIRI by combined HRs and 95%CIs. Among-studies heterogeneities were estimated through I^2 statistics along with Cochran's Q-test. $I^2 > 50\%$ and p-value < 0.10 (Q-test) indicate obvious heterogeneity, so we utilized a random-effects model; or else, we adopted a fixed-effects model [26]. Subgroup analyses based on diverse factors were completed for investigating SIRI's prognostic role in various patient populations. Also, associations of SIRI with EC clinicopathological features were assessed by pooling odds ratios (ORs) with 95%CIs. A sensitivity analysis was conducted to evaluate the robustness of the results by removing individual studies one at a time. We employed Begg's test and funnel plot for assessing publication bias. A $p < 0.05$ stood for significant differences.

Results

Study screening

Our initial literature search identified 224 studies, among which, 157 were retained when duplicates were eliminate (Fig. 1). Later, we excluded 134 articles after title- and abstract-reading due to irrelevance or animal studies. Thereafter, full-texts of 23 articles were read, with 17 being discarded due to irrelevance to SIRI ($n = 13$), unavailable survival information ($n = 2$), and irrelevance to EC ($n = 2$). Ultimately, six studies comprising 2176 patients [18–23] were included in the present study (Fig. 1; Table 1).

Enrolled study features

All included studies [18–23] were published from 2018 to 2023 (Table 1). Six articles were performed in China, with ESCC patients being included [18–23]. Sample sizes were 51–916 (median, 281). There were five retrospective studies [18–21, 23] and one prospective trial [22]. Five studies were published in English [18–20, 22, 23] and one was in Chinese [21]. Four articles treated patients with surgery [18, 19, 21, 23], one study used radiotherapy [20], and one applied neoadjuvant chemoradiotherapy (CRT) and pembrolizumab [22]. The threshold SIRI was 0.485–1.39 (median, 0.985). All included studies [18–23] analyzed threshold by receiver operating characteristic

Table 1 Basic characteristics of included studies in this meta-analysis

Study	Year	Country	Sample size	Gender (M/F)	Age (years) Median(range)	Study period	Study design	TNM stage	Histology	Treatment	SIRI cut-off value	Cut-off determination	Survival outcomes	Survival analysis	Follow-up (months) Median(range)	NOS score
Geng, Y	2018	China	916	696/220	≤ 60y: 455 > 60y: 461	2002–2012	Retrospective	I-III	ESCC	Surgery	1.2	ROC curve	OS	Multivariate	1–150	8
Xu, X	2022	China	370	245/125	61(40–81)	2016–2018	Retrospective	I-IV	ESCC	Surgery	0.485	ROC curve	OS	Multivariate	1–60	8
Yan, K	2022	China	192	111/81	73(65–88)	2013–2016	Retrospective	II-III	ESCC	Radiotherapy	1.03	ROC curve	OS, PFS	Multivariate	21.3(3.8–95.1)	8
Kong, L. Y	2023	China	139	125/14	< 65y: 86 ≥ 65y: 53	2015–2018	Retrospective	I-IV	ESCC	Surgery	1.39	ROC curve	OS	Univariate	1–40	7
Qi, W. X	2023	China	51	44/7	62(39–75)	2019–2022	Prospective	II-IV	ESCC	CRT + ICIs	0.94	ROC curve	PFS	Multivariate	1–45	9
Wang, H. K	2023	China	508	340/168	< 65y: 283 ≥ 65y: 225	2013–2019	Retrospective	I-IV	ESCC	Surgery	0.901	ROC curve	OS	Multivariate	1–96	8

SIRI systemic inflammation response index, *ROC* receiver operating characteristic, *OS* overall survival, *PFS* progression-free survival, *CRT* chemoradiotherapy, *ICIs* immune checkpoint inhibitors, *M* male, *F* female, *NOS* Newcastle–Ottawa Scale, *ESCC* esophageal squamous cell carcinoma

Table 2 Subgroup analysis of prognostic value of SIRI for OS and PFS in patients with EC

Subgroups	No. of studies	No. of patients	Effects model	HR (95%CI)	*p*	Heterogeneity I^2(%) Ph	
OS							
Total	5	2125	Fixed	1.43(1.20–1.71)	< 0.001	48.8	0.098
Sample size							
< 200	2	331	Random	2.86(0.93–8.83)	0.067	64.9	0.091
≥ 200	3	1794	Fixed	1.28(1.05–1.57)	0.016	0	0.921
TNM stage							
I-IV	3	1017	Random	1.84(0.74–4.61)	0.192	62.4	0.070
I-III/II-III/II-IV	2	1108	Random	1.52(1.07–2.14)	0.018	59.6	0.116
Treatment							
Surgery	4	1933	Fixed	1.33(1.09–1.62)	0.005	44.2	0.146
Radiotherapy/CRT + ICIs	1	192	-	1.88(1.28–2.75)	0.001	-	-
SIRI cut-off value							
< 1.0	2	878	Fixed	1.20(0.78–1.83)	0.408	0	0.871
≥ 1.0	3	1247	Random	1.80(1.09–2.95)	0.020	71.2	0.031
Survival analysis							
Univariate	1	139	-	6.26(1.63–24.01)	0.008	-	-
Multivariate	4	1986	Fixed	1.39(1.17–1.67)	< 0.001	3.7	0.374
PFS							
Total	2	243	Fixed	2.00(1.35–2.98)	0.001	0	0.409

SIRI systemic inflammation response index, *OS* overall survival, *PFS* progression-free survival, *CRT* chemoradiotherapy, *ICIs* immune checkpoint inhibitors, *EC* esophageal cancer

(ROC) curve. Five articles reported SIRI's function in forecasting OS [18–21, 23] while two studies presented relation of SIRI with PFS [20, 22] in EC. The NOS scores of 7–9 suggested their high quality (Table 1).

OS and PFS forecasting value of SIRI

Five studies with 2125 patients [18–21, 23] mentioned the relation between SIRI and EC OS. We applied the fixed-effect model due to non-significant heterogeneity (I^2 = 48.8%, p = 0.098). HR = 1.43, 95%CI = 1.20–1.71, $p < 0.001$ were obtained, suggesting high SIRI as the significant prognostic marker for OS in EC (Table 2; Fig. 2). Based on subgroup analyses, SIRI remained to remarkably predict OS irrespective of treatment and survival analysis (Table 2). Moreover, elevated SIRI showed remarkable relation to poor OS of: sample size ≥ 200, TNM stage of I-III/II-III/II-IV, and cut-off value ≥ 1.0 subgroups (all $p < 0.05$; Table 2). Two studies consisting of 243 patients [20, 22] mentioned the PFS forecasting effect of SIRI on EC. The heterogeneity was non-significant ($I^2 = 0$, $p = 0.409$) and a fixed-effects model was applied. As a result, high SIRI showed close relation to dismal PFS in EC (HR = 2.00, 95%CI = 1.35–2.98, $p = 0.001$; Table 2; Fig. 3).

The relation of SIRI with EC clinicopathological factors

Four articles involving 1617 cases [18–21] investigated the relation of SIRI with EC clinicopathological factors. Based on our pooled findings, high SIRI was apparently related to male gender (OR = 1.86, 95%CI = 1.07–3.22, $p = 0.027$), TNM stage of III-IV (OR = 1.52, 95%CI = 1.18–1.94, $p = 0.001$), T3-T4 stage (OR = 1.73, 95%CI = 1.12–2.69, $p = 0.014$), together with presence of lymph node (LN) metastasis (OR = 1.29, 95%CI = 1.02–1.64, $p = 0.036$) (Table 3, Figs. 4 and 5). These results suggested that high SIRI was significantly correlated to features representing tumor development and metastasis of EC. However, there was no significant association between SIRI and the following clinicopathological factors: age (OR = 0.98, 95%CI = 0.75–1.27, $p = 0.856$), tumor location (OR = 2.06, 95%CI = 1.00–4.24, $p = 0.051$), tumor differentiation (OR = 1.57, 95%CI = 0.96–2.56, $p = 0.074$), and smoking history (OR = 1.65, 95%CI = 0.67–4.05, $p = 0.273$) (Table 3, Figs. 4 and 5).

Sensitivity analysis

The sensitivity analysis, which involved the separate removal of each study from the meta-analysis, did not alter any statistically significant conclusions (Fig. 6). These results confirmed the stability of our results in this meta-analysis.

Publication bias

This work adopted Begg's test and Funnel plots in detecting potential publication bias. Begg's test indicated no

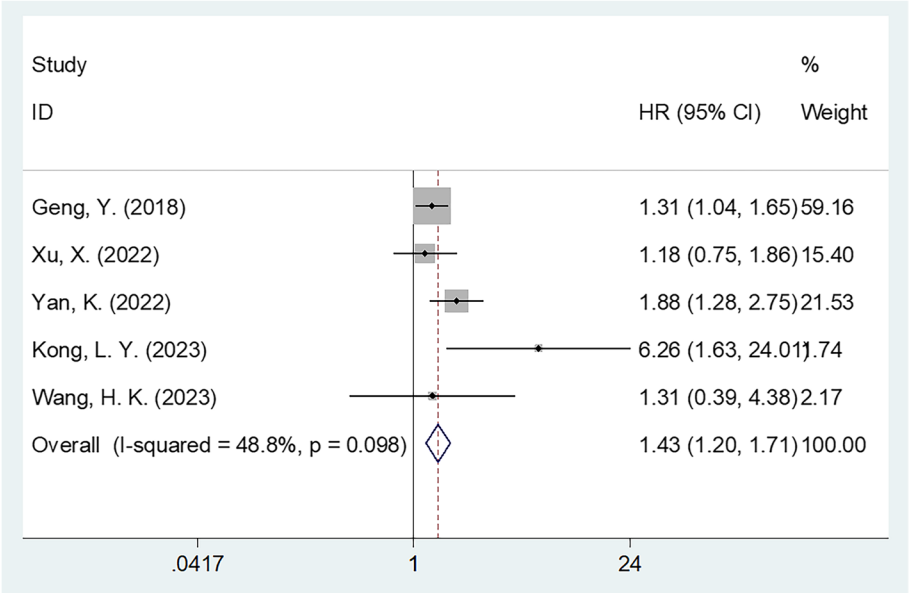

Fig. 2 Forest plots of the association between SIRI and overall survival in patients with EC. These results suggested high SIRI acted as the significant prognostic marker for OS in EC

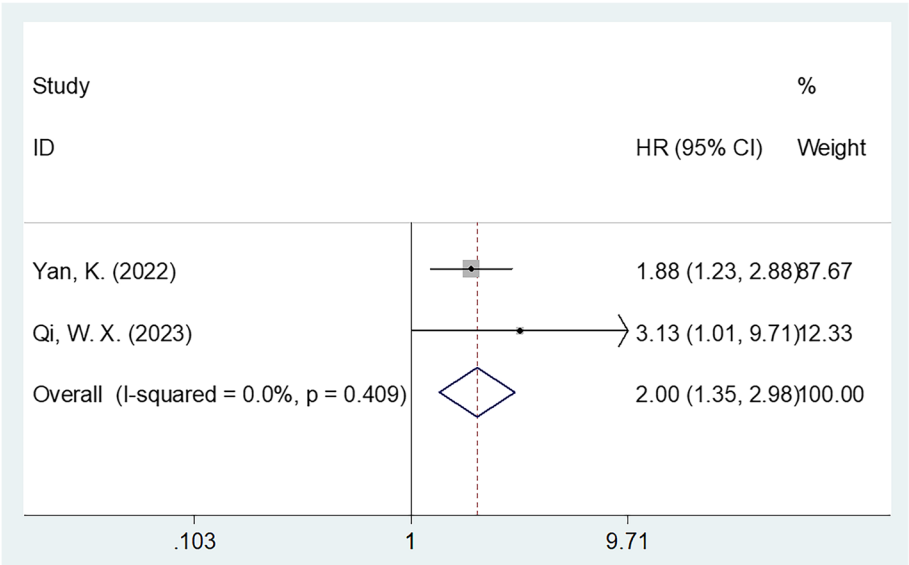

Fig. 3 Forest plots of the association between SIRI and progression-free survival in patients with EC. High SIRI showed close relation to dismal PFS in EC

obvious publication for OS ($p=0.221$) and PFS ($p=1.000$) (Fig. 6). As observed, funnel plots were symmetrical for OS and PFS (Fig. 7).

Discussion

SIRI is widely analyzed for its value in forecasting EC prognosis, whereas findings remain controversial. The current work synthetized data in six articles with 2176 patients [18–23] and suggested the obvious effect of SIRI on forecasting poor OS and PFS of EC. Furthermore, elevated SIRI was also significantly associated with male gender, advanced tumor stage, T3-T4 stage, and LN metastasis of EC. Taken together, SIRI significantly predicted short- and long-time prognoses of EC. The present work provides the initial meta-analysis evidence of the EC prognostic effect of SIRI.

Table 3 The association between SIRI and clinicopathological features of patients with EC

Clinicopathological factors	No. of studies	No. of patients	Effects model	OR (95%CI)	p	Heterogeneity I^2(%) Ph	
Gender (male vs female)	4	1617	Random	1.86(1.07–3.22)	0.027	69.4	0.020
Age (years) (> 60 vs ≤ 60)	3	1425	Fixed	0.98(0.75–1.27)	0.856	29.8	0.241
TNM stage (III-IV vs I-II)	4	1617	Fixed	1.52(1.18–1.94)	0.001	24.3	0.265
T stage (T3-T4 vs T1-T2)	4	1617	Random	1.73(1.12–2.69)	0.014	61.0	0.053
LN metastasis (yes vs no)	4	1617	Fixed	1.29(1.02–1.64)	0.036	42.7	0.155
Tumor location (middle + lower vs upper)	4	1617	Random	2.06(1.00–4.24)	0.051	67.0	0.028
Tumor differentiation (poor vs well + moderate)	3	1425	Random	1.57(0.96–2.56)	0.074	56.8	0.099
Smoking history (yes vs no)	2	509	Random	1.65(0.67–4.05)	0.273	77.6	0.035

LN lymph node, *SIRI* systemic inflammation response index, *EC* esophageal cancer

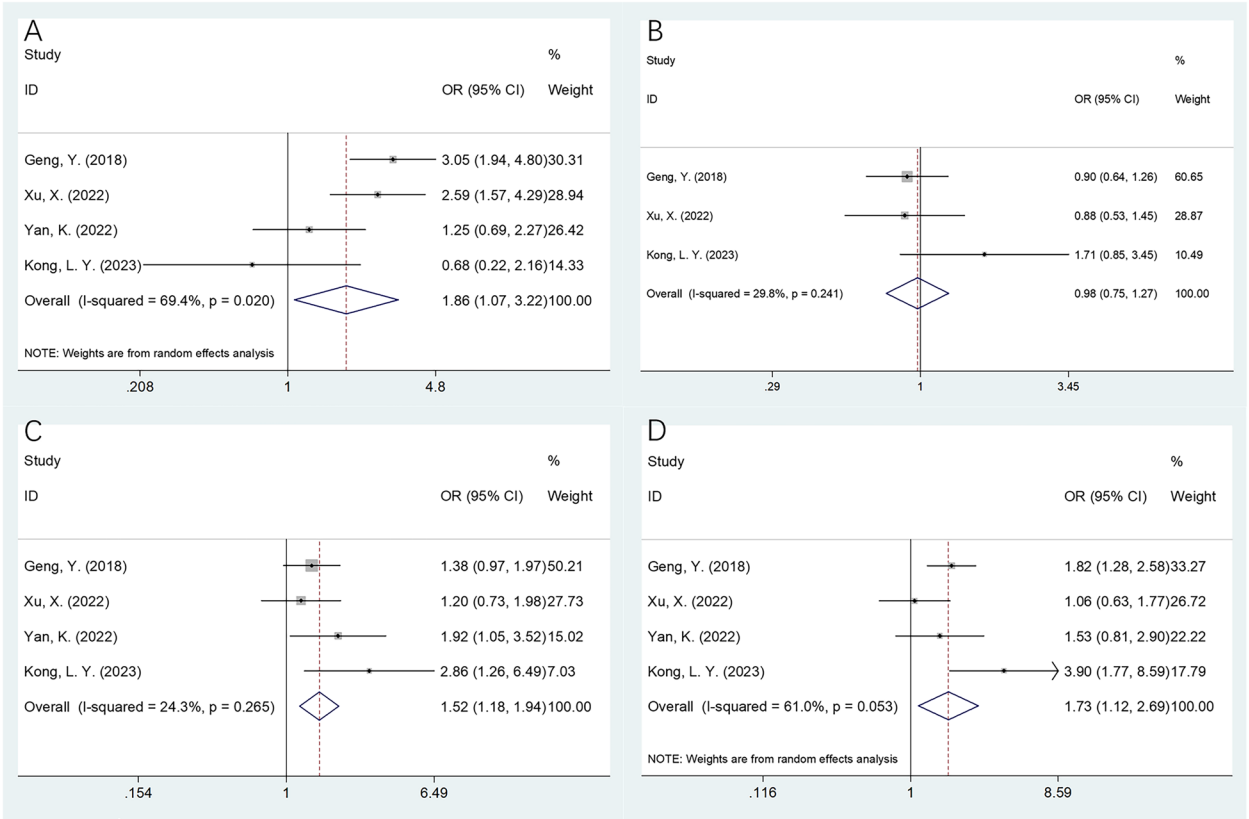

Fig. 4 The correlation between SIRI and clinicopathological features of EC. **A** Gender (male vs female); (**B**) Age (years) (> 60 vs ≤ 60); (C) TNM stage (III-IV vs I-II); and (D) T stage (T3-T4 vs T1-T2)

SIRI includes three elements: neutrophils, lymphocytes and monocytes. The high SIRI could be the results of increased neutrophil quantity, increased monocyte quantity, and/or decreased lymphocyte quantity. The EC prognostic mechanism of SIRI has not been comprehensively explored, which is interpreted as follows. Firstly, Neutrophils contribute to tumor cell proliferation by producing proteolytic enzymes such as matrix metalloproteinase and serine proteinase, and they also release vascular endothelial growth factor and matrix metalloproteinase 9 to promote tumor angiogenesis [27]. Neutrophils present in cancer patients are related to a negative prognosis because they can stimulate endothelial and parenchymal cells, which help in the spread of circulating tumor cells [28]. Secondly, blood monocytes have the ability to transform to tumor-associated

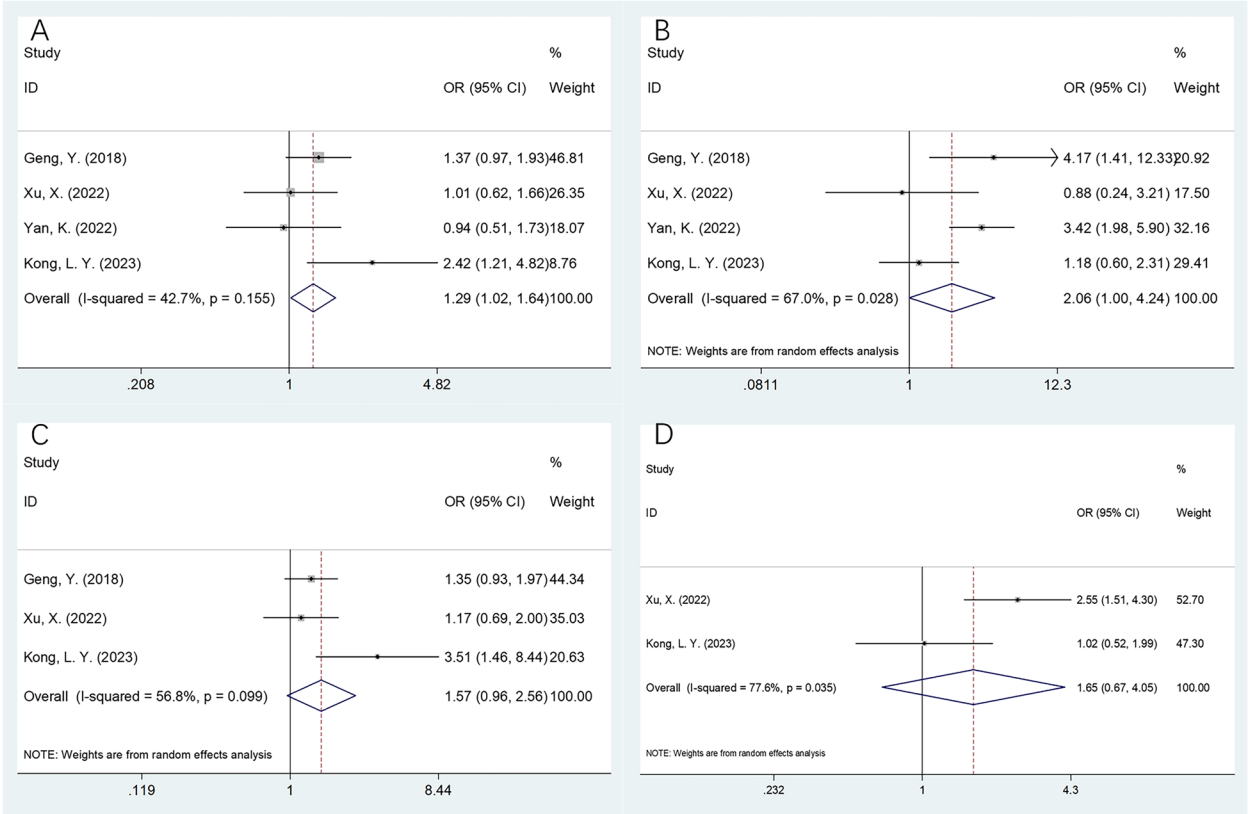

Fig. 5 The correlation between SIRI and clinicopathological features of EC. **A** LN metastasis (yes vs no); **B** Tumor location (middle + lower vs upper); **C** Tumor differentiation (poor vs well + moderate); and (**D**) Smoking history (yes vs no)

macrophages (TAMs), which are vital for tumor development [29]. TAMs have the ability to modify the tumor microenvironment and enhance tumorigenesis, recurrence, and metastasis through the release of various inflammatory mediators and cytokines [30, 31]. Additionally, TAMs can assist cancer cells in escaping immune attack and facilitate aggressive invasion [32]. Thirdly, lymphocytes, as a significant component of human immune system, can prevent tumor formation and recurrence while regulating immune functions by generating cytokines and causing cytotoxic death [33]. Lymphocytes are essential for the adaptive immune response and are active in cancer immunosurveillance and immunoediting [34]. Lymphopenia often reflects the seriousness of the disease and aids cancer cells in evading the immune response from tumor-infiltrating lymphocytes, which form as lymphocytes migrate to the tumor microenvironment [35]. In addition, a decrease in peripheral lymphocytes can compromise anti-tumor responses, which may lead to tumor cell growth and metastasis [36]. Therefore, SIRI is a reasonable prognostic parameter for EC based on these elements.

In the previous studies investigating the prognostic value of SIRI in EC, the results were inconsistent [18–23]. The contradictory findings may be caused by the following factors. First, the sample size varied among studies. Sample sizes were 51 to 916, with a median value of 281. Second, the inclusion and exclusion of each individual study were not uniform in this meta-analysis. Therefore, selection bias in patients may exist. Third, the cut-off values of SIRI were inconsistent among included studies.

The results of this meta-analysis provided some clinical implications. First, this meta-analysis suggested that elevated SIRI was a significant prognostic marker for poor OS and PFS of EC. Therefore, patients with EC measured with high pretreatment SIRI should be treated with more radical regimen. Second, SIRI could be applied as an index during follow-up to indicate tumor progression. Third, elevated SIRI was also significantly associated with advanced tumor stage and LN metastasis of EC. Therefore, distant metastasis should be monitored in EC patients with high SIRI.

The prognostic effect of SIRI for EC was shown in this meta-analysis. There were some similarities between

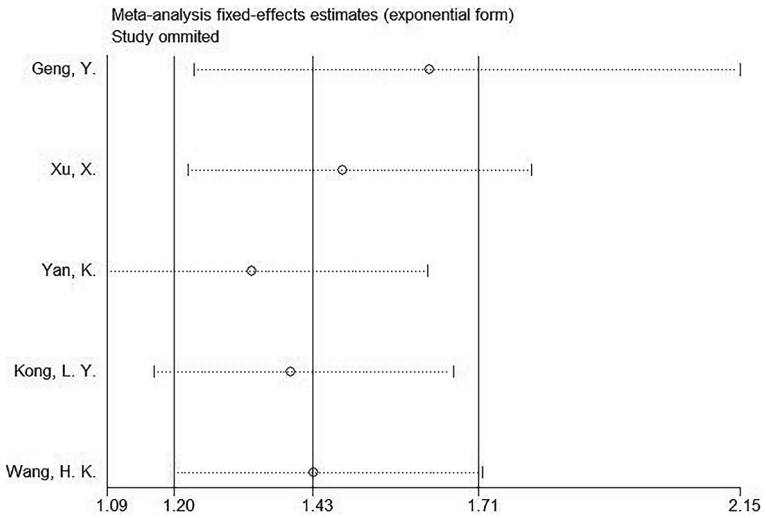

Fig. 6 Sensitivity analysis

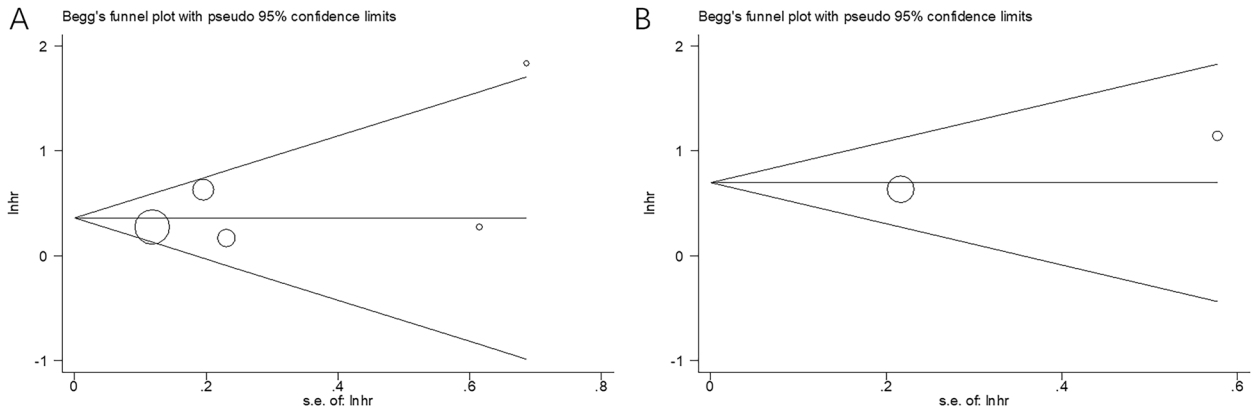

Fig. 7 Publication bias by Begg's test. **A** Begg's test for OS, $p = 0.221$; and (**B**) Begg's test for PFS, $p = 1.000$

SIRI and other prognostic markers such as PLR, LMR, and CAR. First, they are all derived from laboratory tests and are easily available. Second, they all can reflect the immune status of patients. Third, they are all reported to have prognostic value for various cancer types.

Many studies have also revealed that SIRI is significant for forecasting cancer prognosis via meta-analysis [37–41]. As reported by Ye et al. through the meta-analysis 3728 cases, an increased SIRI was remarkably related to OS and PFS of non-small cell lung cancer [37]. Yang et al. showed the relation between high SIRI and worse OS in oral cancer patients through the meta-analysis involving 17 articles [38]. A recent meta-analysis indicated that an elevated SIRI exhibited obvious relations to OS and PFS of cancer cases receiving PD-1/PD-L1 immune checkpoint inhibitors [39]. Zhang et al. performed the meta-analysis comprising 2997 patients and demonstrated that an increased SIRI predicted dismal OS of breast cancer [40]. As reported by Menyhart and colleagues in a recent meta-analysis, the increased SIRI predicted worse OS and disease-free survival/recurrence-free survival of colorectal cancer [41]. Results from the present work in EC conformed to results obtained from additional cancers. However, a recent meta-analysis showed that there was no significant association between SIRI and OS in patients with glioma [42].

Certain limitations should be noted. Firstly, only six articles were enrolled, regardless of no language restriction and a broad search time interval. Secondly, the majority of enrolled articles were of retrospective design. Confounder factors in included studies such as treatment variations and sample heterogeneity could cause selection bias. Therefore, there might be selection bias because of our retrospective design. Thirdly, threshold SIRI was inconsistent among the enrolled articles.

Conclusions

In summary, this meta-analysis indicated that an increased SIRI is significantly related to dismal OS and shortened PFS of EC. Moreover, elevated SIRI was also significantly associated with advanced tumor stage, T3-T4 stage, and LN metastasis of EC. Due to some limitations, large prospective studies that utilize standardized threshold SIRI should be conducted to validate our results in the future.

Abbreviations

SIRI	Systemic inflammation response index
EC	Esophageal cancer
HR	Hazard ratio
CI	Confidence interval
OS	Overall survival
PFS	Progression-free survival
ESCC	Esophageal squamous cell carcinoma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NOS	Newcastle–Ottawa Scale
OR	Odds ratio
CRT	Chemoradiotherapy
ROC	Receiver operating characteristic
LN	Lymph node
TAMs	Tumor-associated macrophages

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02847-7.

Supplementary Material 1.

Acknowledgements

None.

Authors' contributions

Z.W. and Z.Z. extracted the data and assessed the quality of the literature. Z.W. and Z.Z. wrote the main manuscript text and prepared Figures. Z.Z. and C.G. designed the study and prepared Tables. C.G. revised the manuscript. All authors have approved the final version of the manuscript.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no conflict of interest.

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