World Journal of Surgical Oncology

RESEARCH

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The role of squamous cell carcinoma antigen and cytokeratin 19 fragment in predicting the outcome of esophageal cancer patients: insights from a meta-analysis

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Abstract

Background The accurate prognostication and recurrence monitoring of esophageal cancer (EC) are pivotal yet challenging. Despite the promising roles of squamous cell carcinoma antigen (SCC) and cytokeratin 19 fragment (CK19 Fragment) as cancer biomarkers in EC, their prognostic value remains unquantified. This meta-analysis is the first to quantitatively assess the relationship between serum levels of SCC and CK19 Fragment and EC prognosis, aiming to bridge this knowledge gap.

Methods We conducted a comprehensive and systematic literature search across PubMed, Web of Science, Cochrane Library, and Embase databases, and Hazard ratios (HRs) and 95% confidence intervals (CIs) for overall survival (OS) and other survival outcomes were extracted and analyzed using random-effects or fixed-effects models depending on heterogeneity among the studies.

Results 7309 patients from 29 studies were finally included in this meta-analysis. The quantitively summarized data revealed that elevated level of SCC and CK19 Fragment in serum was significantly correlated to poorer prognosis of EC patients with the pooled HR of OS was 1.25 (95%CI: 1.04–1.50, $P<0.05$) and 1.69 (95%CI: 1.25–1.27, $P<0.05$), respectively. Subgroup analyses indicated that the prognostic value of these biomarkers varied across different patient populations and treatment modalities.

Conclusion This meta-analysis demonstrated that SCC and CK19 Fragment levels in serum were both strong prognostic biomarkers of EC patients. The elevated level of SCC and CK19 Fragment in serum was significantly associated with worse survival outcomes, advocating for the integration of these biomarkers into prognostic assessments to improve decision-making processes in the management of EC.

Registration number CRD42022311617.

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Keywords Squamous cell carcinoma antigen, Cytokeratin 19 fragments, Esophageal cancer, Esophageal squamous cell carcinoma, Prognosis

Introduction

The incidence of esophageal cancer (EC) ranked ninth worldwide according to a recent statistic report [1], and the most common pathology subtypes of EC were esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Even though the technology in diagnosis and treatment has advanced rapidly, the prognosis of EC is still poor [2, 3]. Therefore, finding serum biomarkers for precisely predicting the prognosis of EC was of great necessity for clinicians.

So far, some tumor markers have been reported that could be tested into the peripheral circulation and were qualified in noninvasive detecting tumor progression and recurrence. Squamous cell carcinoma antigen (SCC) was first identified in uterine cervical cancer [4] and was primarily isolated from squamous cell carcinoma tissue [5]. Elevated SCC levels have been obversed to be linked with more advanced tumor stages, reflecting its potential as a biomarker for assessing disease progression. This relationship underscores the utility of SCC as a prognostic indicator [6, 7], and elevated level of SCC in serum was reported to correlate with worse prognosis [8, 9]. On the other hand, gathering evidence had shown that cytokeratin 19 fragment (CK19 Fragment), a cytoplasmic soluble protein debris of cytokeratin 19, had a prognostic value for head and neck cancer and other malignancies [10].

Recently, SCC and CK19 have emerged as novel biomarkers in clinical practice for monitoring tumor progression. These biomarkers are increasingly utilized to track disease development, offering valuable insights into tumor dynamics and potentially guiding therapeutic strategies [11, 12]. However, the prognosis value of SCC and CK19 Fragment in EC had not been clarified. This meta-analysis collected studies on these two biomarkers to quantitatively evaluate the prognostic value of SCC in EC. Furthermore, we also conducted a subgroup analysis to achieve a comprehensive investigation on the prognostic value of SCC and CK19 Fragment in EC among the diversity of different studies.

Materials and methods

Search design

We conducted a complete and systematic literature search through the following databases: PubMed, Web of Science, Cochrane library, and Embase. The search was updated to March 1, 2024. The main search keywords included squamous cell carcinoma antigen, cytokeratin 19 fragment, esophageal cancer, esophageal squamous cell carcinoma, esophageal adenocarcinoma, and prognosis. Together, the references list of included studies was also checked for other relevant literatures. The details of search strategy were shown in S1 File.

Inclusion and exclusion criteria

The inclusion criteria for selecting literature into this meta-analysis were as follows: (1) patients were pathologically confirmed as EC; (2) SCC and CK19 Fragment were detected in the peripheral circulation through serum methods; (3) patients in studies had been divided into high or low SCC, and CK19 Fragment groups based on their serum level; (4) studies provided sufficient data, relative information such as hazard ratio (HR) and 95% confidence interval (95%CI) was clarified in the literatures; (5) association of SCC and CK19 Fragment with EC survival outcomes was reported. Exclusion criteria were as follows: (1) duplicated studies; (2) animal experiments; (4) studies with insufficient data, the HR and 95%CI cannot be retrieved; (5) reviews, letters, case reports, and nonclinical studies; (6) the NOS score of studies < 6.

Data extraction and quality assessment

All searched literatures were evaluated by two independent reviewers, and if disagreement occurred, two reviewers discussed with the third reviewer to arrive at a consensus. For the literatures which could not be decided whether to include or exclude based on titles and abstracts, full-texting reviewing was conducted. For each included literature, the following data were retrieved: first author, publication year, cancer type, sample size, sample type, detecting methods, survival outcomes, cut-off value, and HRs with 95% CI. The Newcastle-Ottawa Scale (NOS) was applied to assess the quality of all included studies. The NOS scores, including selection, comparability, and outcome, the NOS score ≥ 6 were assigned as studies with high quality.

Statistical analysis

We extracted HRs and the 95%CI from each study or used Engauge Digitizer version 4.1 software to analyze the survival curves. The HRs and the 95% CI were regarded as effect sizes to evaluate. When the HRs > 1 showed a worse prognosis in EC patients with high SCC and CK19 Fragment serum levels and HRs < 1 showed a better prognosis. Chi-square-based Q test and *I*-squared statistic were applied to assess the heterogeneity among the included studies. The $P < 0.05$ or $I^2 > 50\%$ showed significant heterogeneity among the studies, and the random-effect model was used to evaluate. Otherwise, the fixed-effect model was applied to analyze. Sensitivity analysis of the included studies was conducted by

removing one single study in turn to test the reliability of the primary outcomes in meta-analysis. We also assessed the publication bias among the studies by using Begg's funnel plot. *P*-value < 0.05 was believed statistically significant, and all statistical analyses of this meta-analysis were achieved by using Review Manager 5.3 and Stata 12.0 software.

Results

Study characteristics

Totally 1485 of literatures were selected out according to the initial search strategies. Founding duplications and checking titles and abstracts, 1423 were excluded because of the irrelevant research direction. After reviewing the full text of 62 literatures, 33 were further excluded because the relevant data could not be retrieved. Finally, 29 studies with an amount of 7309 patients were selected into this meta-analysis. In all incorporated studies of SCC, patients in 11 studies were Japanese, and in 7 studies were Chinese. Patients in 9 studies underwent surgery with oncological treatment, and patients in 9 studies underwent surgery therapy only. Twelve studies utilized overall survival (OS), two studies used cancer-specific survival (CSS), two studies utilized disease-specific survival (DSS), and two studies applied relapse-free survival (RFS) as survival outcomes. The cut-off value used in studies ranged from 1.0-2.3ng/ml. Testing methods of SCC in serum level were enzyme immunoassay (EIA), chemiluminescent microparticle immunoassay (CMI), and radioimmunoassay (RIA). In all included studies of CK19 Fragment, patients from Japan, China, France, and Germany. Patients in 8 studies underwent operation treatment only, and in the other three studies, patients only underwent oncological therapy. The cut-off value of included studies of CK19 Fragment was from 1.4-3.5ng/ml. Testing methods of CK19 Fragment in all incorporated studies were RIA, immunoradioassay (IRA), and EIA. Only the study conducted by Nobuki et al. testing methods was CMI. Table 1. showed the details and characteristics of all included studies (Fig. 1).

SCC and EC prognosis

Twelve studies investigated the association between SCC in serum level and OS in EC patients. According to the results of the Q test and I-square statistic test, heterogeneity ($I^2 = 39.0\%$, $P = 0.08$) was not detected among studies applied OS as survival outcomes, so we used the fixed-effect model to analyze. Six studies used CSS ($I^2 = 71.0\%$, $P = 0.06$), DSS ($I^2 = 66.0\%$, $P = 0.08$), and RFS ($I^2 = 57.0\%$, $P = 0.13$) as survival outcomes with significant heterogeneity detected, so the random-effect model was utilized to analysis. According to the results, this meta-analysis elucidated that high SCC in serum level was significantly associated with poorer prognosis of EC patients with the pooled HR was 1.25 (95%CI: 1.04–1.50, $P < 0.05$) for OS (Fig. 2). But no significant statistic difference was found in CSS (HR: 1.41, 95%CI: 0.93–2.15, $P > 0.05$), DSS (HR: 1.59, 95%CI: 0.98–2.57, $P > 0.05$), and RFS (HR: 1.47, 95%CI: 0.99–2.17, $P > 0.05$) (Fig. 3).

CK19 fragment and EC prognosis

In all selected studies, 11 studies detected the serum level of CK19 Fragment and the association between OS in EC patients. The Q test and I-square statistic test results showed there was significant heterogeneity among studies ($I^2 = 81.0\%$, $P < 0.001$), so the random-effect model was utilized for analysis. The pooled HR was 1.69 (95%CI: 1.25–2.27, $P < 0.05$) revealing that the elevated CK19 Fragment level in serum was associated with shorter OS (Fig. 4).

Subgroup analysis of SCC

In the subgroup analysis of treatment, seven studies investigated patients who underwent surgery therapy only with the pooled HR was 1.28 (95%CI: 0.98–1.67, $P > 0.05$), and five studies investigated surgery with oncological treatment, and the pooled HR was 1.21 (95%CI: 0.93–1.57, $P > 0.05$). In addition, regarding the subgroups analysis by SCC serum level detecting methods, this meta-analysis revealed that when serum samples were detected by EIA, the pooled HR was 1.07 (95%CI: 0.87–1.33, $P > 0.05$), however, when SCC was detected by CMI, the pooled HR was 1.50 (95%CI: 1.10–2.05, $P < 0.05$). When the studies were stratified by population, patients from Japan with the pooled HR of OS was 1.33 (95%CI: 1.06–1.67, $P < 0.05$) and 1.22 (95%CI: 0.92–1.61, $P > 0.05$) for Chinese patients (Table 2).

Subgroup analysis of CK19 fragment

When the included studies stratified by treatment methods, our meta-analysis results showed that 8 studies had investigated the EC patients who underwent surgery operation with the pooled HR was 1.67 (95%CI: 1.14–2.45, $P < 0.05$) and 3 studies had investigated patients who underwent oncological methods with the pooled HR was 1.69 (95%CI: 1.18–2.42, $P < 0.05$). According to the subgroup analysis results of test methods, the pooled HR of OS was 2.22 (95%CI: 0.98–5.04, $P > 0.05$) for IRA, 1.26 (95%CI: 1.00-1.59, $P < 0.05$) for EIA, 1.27 (95%CI: 0.96–1.68, $P > 0.05$) for RIA and 1.74 (95%CI: 1.20–2.52, $P < 0.05$) for CMI. In terms of population, the pooled HR of OS was 1.26 (95%CI: 1.06–1.49, $P < 0.05$) for patients from China and 1.71 (95%CI: 1.28–2.28, $P < 0.05$) for Japanese patients, respectively. (Table 3)

Publication bias and sensitivity analysis

The sensitivity analysis plot result showed no significant alteration by removing any one of the included studies

Table 1 Main characteristics of all the studies included in the meta-analysis

Name	Year	Population	Cancer type	Treatment	*N*	Male	Female	Age
SCC								
Nabeya [20]	2002	Japanese	ESCC	Surgery + oncological treatment	50	44	6	Average 66.5; 39–85
Shimada [21]	2003	Japanese	ESCC	Surgery	309	266	43	Average 63; 35–88
Kosugi [22]	2004	Japanese	ESCC	Surgery	245	213	32	Average 65.2; 40–91
Shimada [23]	2005	Japanese	ESCC	Surgery + oncological treatment	103	88	15	Average 64.5 (64.3 ± 8.2)
Cao M [24]	2009	Chinese	ESCC	Surgery	108	85	23	Average 58.9; 36–82;
Cao X [25]	2012	Chinese	ESCC	Surgery	379	221	158	< 60: 158; ≥60: 221
Yang [26]	2019	Chinese	ESCC	Surgery + oncological treatment	416	333	83	Median 60; 33–82
Kanda [27]	2019	Japanese	ESCC	Surgery + oncological treatment	427	362	65	66.4 ± 8
Kanie [28]	2021	Japanese	ESCC	Surgery + oncological treatment	139	103	36	NR
Kanie [28]	2021	Japanese	ESCC	Surgery + oncological treatment	138	111	27	NR
Kunizaki [29]	2018	Japanese	ESCC	Surgery	133	112	21	< 70: 88; ≥70: 45
Shishido [30]	2021	Japanese	ESCC	Surgery + oncological treatment	66	58	8	Median 65; 51–79
Ma[31]	2016	Chinese	ESCC	Surgery	725	539	186	< 65: 656; ≥65: 69
Okamura [32]	2020	Japanese	ESCC	Surgery + oncological treatment	304	240	64	High group: median 64; 34–78 Low group: median 62; 32–78
Okamura [32]	2020	Japanese	ESCC	Surgery + oncological treatment	325	259	66	Middle group: median 64; 40–79 Low group: median 62; 32–78
Wu[33]	2020	Chinese	ESCC	Surgery	308	230	78	58 ± 8.3
Yin[34]	2020	Chinese	ESCC	Surgery	267	219	48	< 60: 132; ≥60: 135
Qiao[35]	2019	Chinese	ESCC	Surgery	315	261	54	< 60: 149; ≥60: 166
CK19 Fragment								
Quillien [36]	1998	French	ESCC	Surgery	96	86	10	NR
Brockmann [37]	2000	German	EC	Surgery	50	40	10	Average 58.9
Jiang[38]	2012	Chinese	ESCC	Oncological treatment	192	123	69	< 60: 101; ≥60: 91
Ishioka [39]	2021	Japanese	ESCC	Surgery	412	325	87	Average 66; 39–83;
Ishioka [39]	2021	Japanese	ESCC	Oncological treatment	486	NA	NA	NR
Ishioka [39]	2021	Japanese	ESCC	Oncological treatment	149	NA	NA	NR
Qiao[35]	2019	Chinese	ESCC	Surgery	315	261	54	< 60: 149; ≥60: 166
Yang[26]	2019	Chinese	ESCC	Surgery	416	333	83	Median 60; 33–82
Tsuchiya [40]	1998	Japanese	ESCC	Surgery	66	57	9	Median 63; 42–81
Shimada [23]	2005	Japanese	ESCC	Surgery	103	88	15	64.3 ± 8.2
Yin [34]	2020	Chinese	ESCC	Surgery	267	219	48	< 60: 132; ≥60: 135

SCC: squamous cell carcinoma antigen; CK19 Fragment: cytokeratin 19 fragment; OS: overall survival; CSS: cancer-specific survival; DSS: disease-specific survival; RFS: relapse-free survival; Multi: multivariate analysis; Uni: univariate analysis; NR: not reported; EIA: enzyme immunoassay; CMI: chemiluminescent microparticle immunoassay; RIA: radioimmunoassay; IRA: immunoradioassay

of SCC and CK19 Fragment, respectively (Fig. 5A, B). In addition, Begg's funnel plots were performed to assess the publication bias, and publication bias was not detected in the included studies with OS of SCC and CK19 Fragment with the P value of Begg' 's test was 0.399 (Fig. 5C) and 0.305(Fig. 5D).

Discussion

Serum biomarkers play vital roles in tumor detecting and monitoring. Among the biomarkers, SCC was first reported in 1977 [13], which was produced from cervical squamous epithelium, and its level in serum increasing during the neoplastic transformation of the cervical squamous epithelium. Elevated SCC levels in serum could be detected in most patients with cervical carcinoma [14]. Apart from cervical carcinoma, SCC was also widely investigated in hepatocellular carcinoma (HCC), some research proved that SCC still had value in HCC diagnosis [15, 16] and its expression level in serum was correlated with HCC prognosis [17]. The K19 fragment is a well-established biomarker designed to detect a soluble fragment of cytokeratin 19 in serum. It has demonstrated high sensitivity in non-small cell lung cancer (NSCLC) and serves as a valuable marker for clinical monitoring during and after cancer treatment [18]. CK19 fragment has been extensively studied as a promising prognostic biomarker across various types of cancer. Its potential role in predicting disease outcomes has garnered attention due to its ability to reflect tumor presence and progression. Elevated levels of CK19 fragment in serum have been associated with adverse prognosis, making it a valuable tool in assessing the aggressiveness of the disease, monitoring therapeutic responses, and predicting recurrence in cancer patients [19]. Despite the established

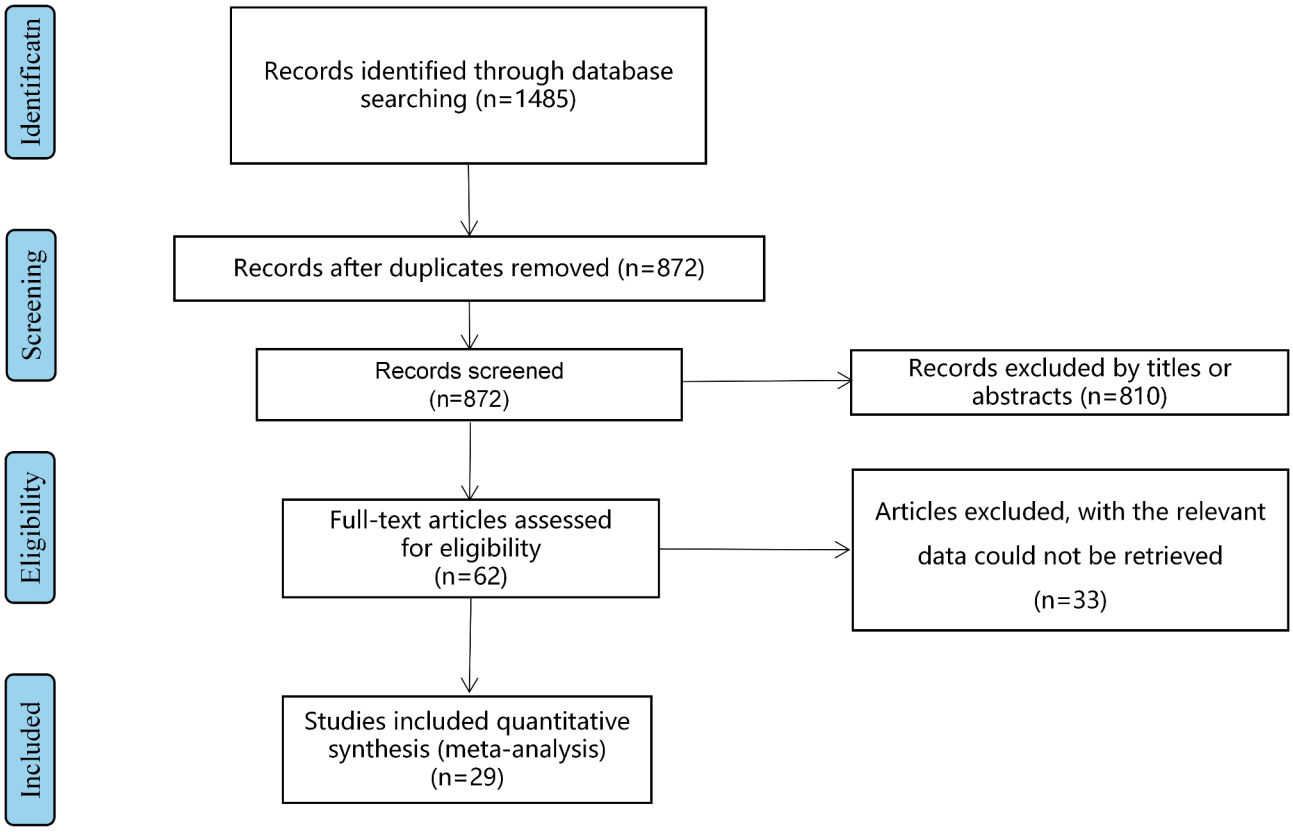

Fig. 1 The flow diagram indicates the process of study selection

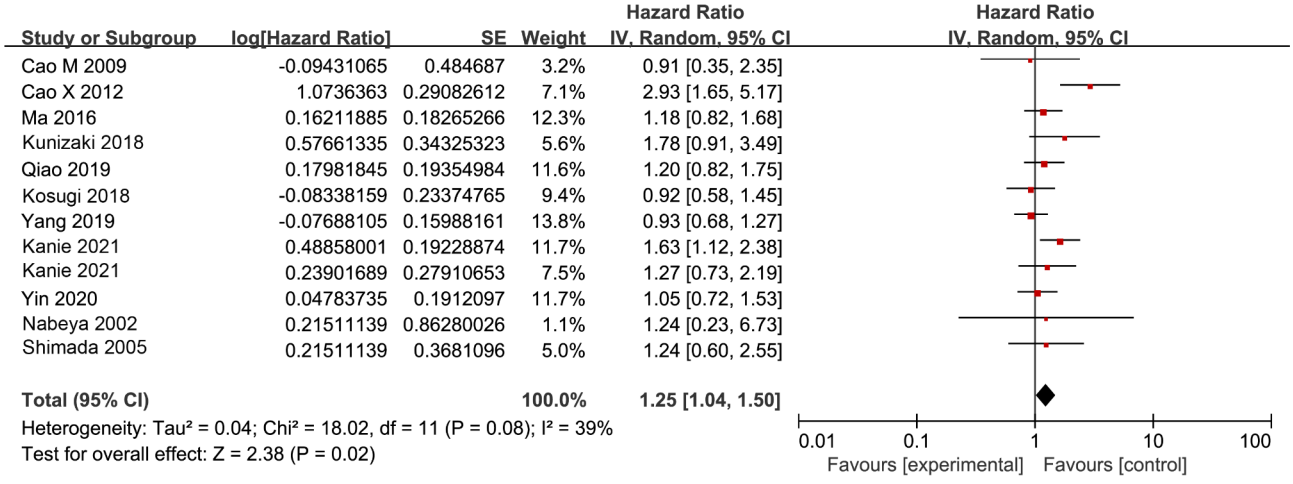

Fig. 2 Forest plot of studies evaluating hazard ratios of SCC and the overall survival of esophageal cancer

importance of serum biomarkers like SCC and CK19 Fragment in the detection and monitoring of various cancers, their prognostic value in EC has not been fully elucidated. This meta-analysis aggregates existing research to quantitatively assess the impact of SCC on the prognosis of EC. Moreover, we have performed a subgroup analysis to delve into the prognostic significance of both SCC and CK19 Fragment in EC, considering the diversity of the studies examined.

Our meta-analysis collected all the data of 7309 EC patients from 29 individual studies and illustrated that high SCC and CK19 Fragment in serum level were significantly associated with poorer OS in EC. Specifically, the data showed that a high level of SCC in serum was associated with poor OS of EC patients with the pooled

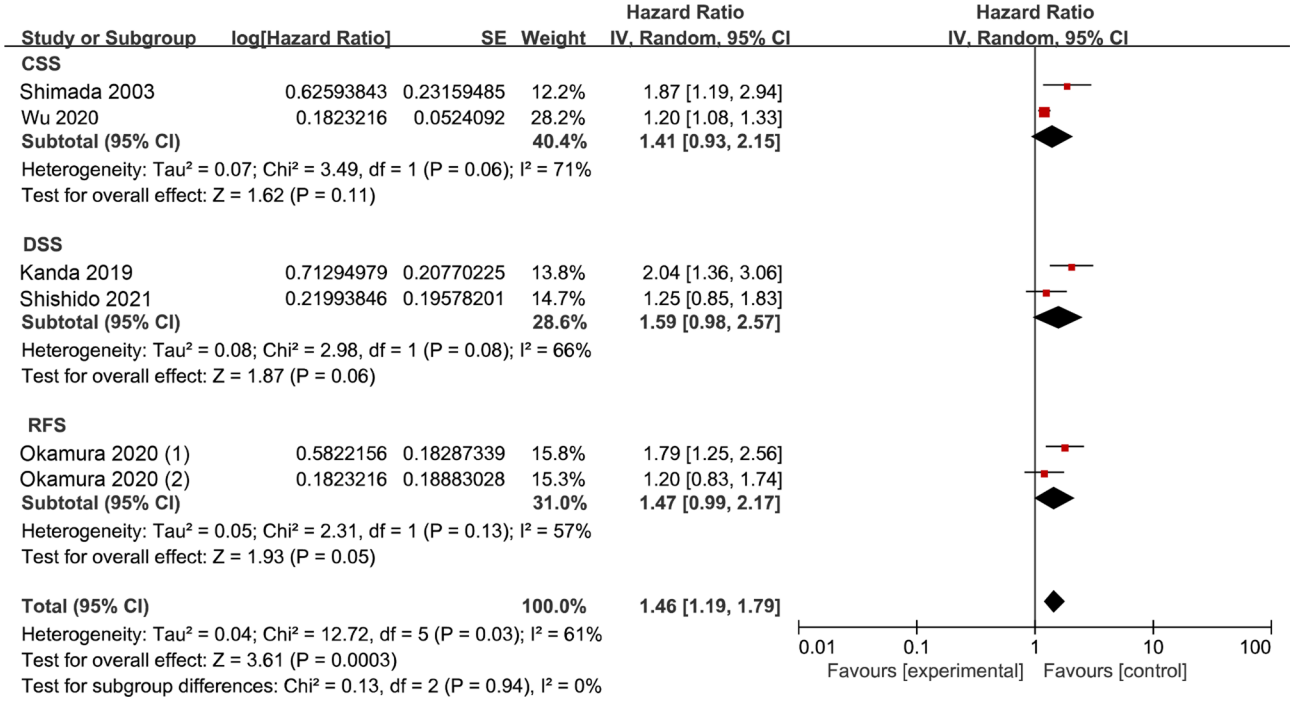

Fig. 3 Forest plot of studies evaluating hazard ratios of SCC and the cancer-specific survival, disease-specific survival, and relapse-free survival of esophageal cancer

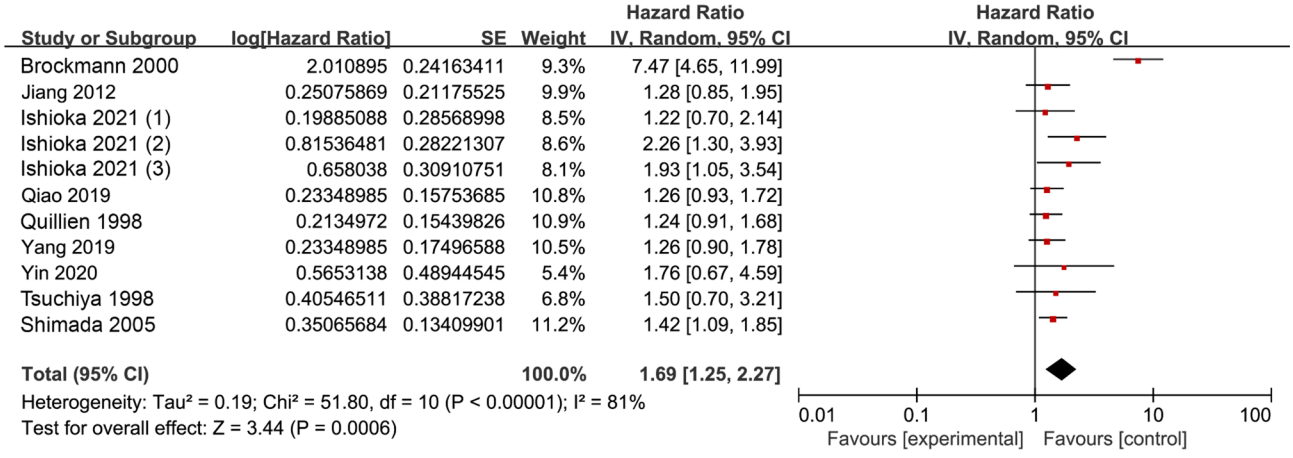

Fig. 4 Forest plot of studies evaluating hazard ratios of SCC and the cancer-specific survival, disease-specific survival, and relapse-free survival of esophageal cancer

HR was 1.25 (95%CI: 1.04–1.50, $P<0.05$). This suggests that SCC could be a valuable prognostic marker for EC. Moreover, the pooled HR for the EC patients who underwent surgery therapy only was 1.28 (95%CI: 0.98–1.67, $P>0.05$) and for those patients treated with surgery with oncology therapy, the pooled HR of OS was 1.21 (95%CI: 0.93–1.57, $P>0.05$). The distinction between patient groups based on the type of treatment (surgery alone vs. surgery with oncology therapy) did not yield statistically significant differences in HR for OS. This could imply that the prognostic value of SCC levels might be independent of the primary treatment modality. However, the lack of statistical significance could also result from sample size limitations, variability in treatment protocols, or heterogeneity among the included studies. For Japanese patients, a statistically significant association between higher SCC levels and poorer OS was identified, which was not observed in Chinese patients. This raises interesting questions about potential biological or genetic differences in EC between populations, or it could reflect variations in healthcare systems, disease management strategies, or environmental factors. The findings also suggest that the method of SCC detection (CMI vs. EIA) could influence the observed associations.

Table 2 Summary of the subgroup analysis results of SCC

Analysis	*N*	HR (95%CI) of OS	Effects model	I^2	Q test *P*
Subgroup 1: Treatment					
Surgery	7	1.28 (0.98–1.67)	Random	52.9%	0.047
Surgery + oncological treatment	5	1.21 (0.93–1.57)	Random	23.2%	0.183
Subgroup 2: Method					
EIA	6	1.07 (0.87–1.33)	Fixed	0.0%	0.957
CMI	2	1.50 (1.10–2.05)	Fixed	0.0%	0.462
Subgroup 3: Population					
Japanese	6	1.33 (1.06–1.67)	Random	0.0%	0.494
Chinese	6	1.22 (0.92–1.61)	Random	60.5%	0.027

SCC: squamous cell carcinoma antigen; EIA: enzyme immunoassay; CMI: chemiluminescent microparticle immunoassay

Table 3 Summary of the subgroup analysis results of CK19 fragment

Analysis	*N*	HR (95%CI) of OS	Effects model	I^2	Q test *P*
Subgroup 1: Treatment					
Surgery	8	1.67 (1.14–2.45)	Random	85.6%	0.000
Oncological treatment	3	1.69 (1.18–2.42)	Random	30.9%	0.235
Subgroup 2: Method					
IRA	4	2.22 (0.98–5.04)	Random	92.5%	0.000
EIA	2	1.26 (1.00-1.59)	Random	0.0%	1.000
RIA	2	1.27 (0.96–1.68)	Random	0.0%	0.646
CMI	3	1.74 (1.20–2.52)	Random	20.5%	0.284
Subgroup 3: Population					
Japanese	5	1.71 (1.28–2.28)	Fixed	0.0%	0.619
Chinese	4	1.26 (1.06-1.49)	Fixed	0.0%	0.999

CK19 Fragment: cytokeratin 19 fragment; EIA: enzyme immunoassay; CMI: chemiluminescent microparticle immunoassay; RIA: radioimmunoassay; IRA: immunoradioassay

The CMI method showed a significant association with OS, whereas the EIA method did not. This difference might stem from the sensitivity, specificity, or overall performance of these methods in detecting SCC levels. It highlights the need for standardization in biomarker measurements in oncology research.

As for CK19 Fragment, the data showed that a high level of CK19 Fragment in serum was associated with poor OS of EC patients with the pooled HR was 1.69 (95%CI: 1.25–2.27, $P<0.001$). This indicates that CK19 Fragment could serve as a potential biomarker for assessing the prognosis of patients with EC. The study also conducted subgroup analyses and found that high levels of CK19 Fragment were indicative of poor prognosis, regardless of whether the treatment was surgical or oncological. Particularly in patient subgroups from China and Japan, those with high levels of CK19 Fragment exhibited pooled HR for OS of 1.26 (95% CI: 1.06–1.49, $P<0.05$) and 1.71 (95% CI: 1.28–2.28, $P<0.05$), respectively. These findings further emphasize the broad applicability of this biomarker across different treatments and populations.

According to the results of our meta-analysis, SCC and CK19 Fragment in serum levels may play a vital role in predicting EC prognosis. Utilizing biomarkers such as SCC and CK19 Fragment allows for a more precise stratification of EC patients based on their disease prognosis. This approach aims to provide each patient with a personalized treatment plan, thereby enhancing treatment outcomes and minimizing unnecessary side effects. Key aspects of enhancing treatment stratification include (1) Disease stage refinement: The current cancer staging system primarily relies on tumor size, lymph node metastasis, and distant metastasis. Incorporating levels of SCC and CK19 Fragment enables physicians to more finely assess the aggressiveness of the tumor and the overall prognosis of the patient. This refinement may reveal cancers that appear early-stage in traditional staging but are biologically more aggressive, and these patients could benefit from more aggressive treatment strategies; (2) Optimal treatment selection: Based on the levels of SCC and CK19 Fragment, physicians can choose the most appropriate treatment plan for the disease characteristics of the patient. For instance, patients with higher levels of these biomarkers may be recommended more aggressive postoperative chemotherapy, addition of new targeted therapies, or immunotherapy to improve treatment outcomes; (3) More accurate survival prediction: By analyzing levels of SCC and CK19 Fragment, physicians can provide patients with more accurate survival predictions. This not only helps patients and their families make more informed medical decisions but also guides the selection of clinical treatments to some extent.

There were several limitations in our meta-analysis. First, lacking a uniform standard cut-off value of SCC and CK19 Fragment in serum level may lead the conclusion to deviate from the true outcomes. Second, the number of included studies that applied the same survival outcome OS was only 12 and 10, lacking other survival outcome indexes like DFS, DSS, PFS, et al., which may not totally reflect the prognostic situation of EC patients. One other limitation in this meta-analysis is the lack of explicit information regarding the timing of biomarker measurement across the included studies. The majority of the studies did not provide detailed descriptions of when the biomarkers were measured in relation to the patient's treatment course. The absence of standardized timing of measurement across the studies leads to potential bias

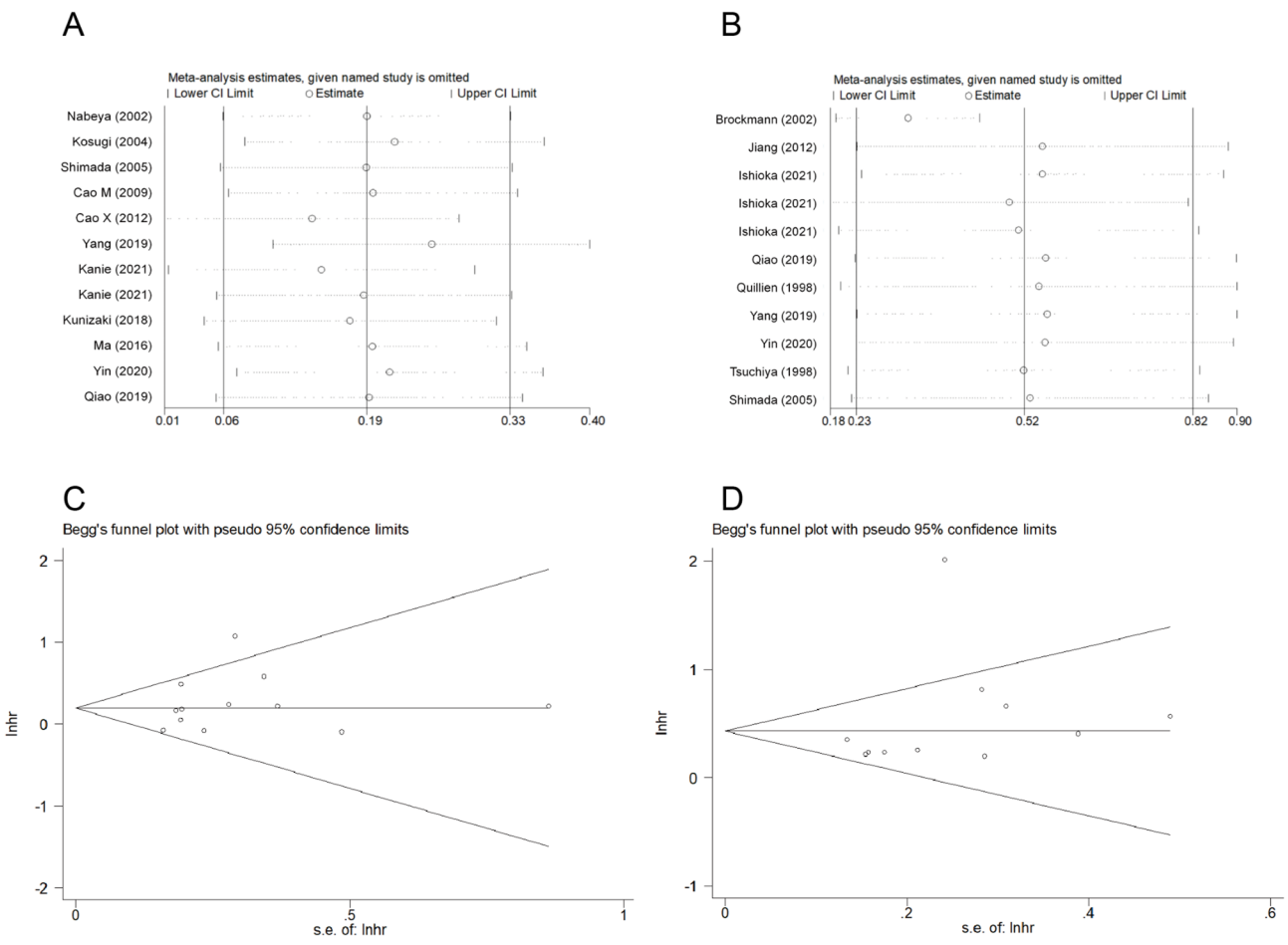

Fig. 5 (**A**) Sensitivity analysis for meta-analysis of SCC for OS. (**B**) Sensitivity analysis for meta-analysis of CK19 Fragment for OS. (**C**) Funnel plots of publication bias for meta-analysis of SCC for OS. (**D**) Funnel plots of publication bias for meta-analysis of CK19 Fragment for OS

and limits our ability to conduct subgroup analyses based on treatment stages. In addition, the majority of studies included patients from specific regions (e.g., Japan and China), which might limit the applicability of the findings to other populations with different genetic backgrounds, lifestyles, and healthcare systems.

In conclusion, this meta-analysis showed that high SCC and CK19 Fragment levels in serum might be negative biomarkers predicting a poorer prognosis of EC patients. Considering the exact mechanism of these two biomarkers involved in EC was lacking, more well-designed clinical trials should be completed to clarify the role of SCC and CK19 Fragment in EC.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03776-4.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
Not applicable.

Author contributions
JZ and CX conceptualized the study, revised the manuscript, and supervised the study. XZ and LY conceptualized the study, drafted the manuscript, and made the figures. JD, WG, and DL collected the data and revised the manuscript. All authors read and approved the final manuscript.

Funding
None.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All analyses were based on previous published studies thus no ethical approval and patient consent are required.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 6 November 2024 / Accepted: 23 March 2025
Published online: 21 April 2025

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