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Prognostic value of high stanniocalcin 2 expression in solid cancers

A meta-analysis

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Abstract

Background: Several studies have explored the prognostic value of stanniocalcin 2 (STC2) in various cancers, but obtained inconsistent results. Therefore, this meta-analysis was performed to determine the prognostic and clinicopathologic significance of STC2 in various cancers.

Methods: Eligible studies were identified by searching the online databases PubMed, Embase, Web of Science, and the China National Knowledge Infrastructure up to March 2019. Hazard ratios (HRs) with 95% confidence intervals (CIs) and were calculated to clarify the correlation between STC2 expression and prognosis of different cancers. Odds ratios (ORs) with 95% CI were selected to appraise the correlation between STC2 with clinicopathologic characteristics of patients with cancer.

Results: A total of 16 eligible studies with 4074 patients with cancer were included in our meta-analysis. The results showed that high STC2 expression can predict poor overall survival (OS) for cancer (HR = 1.48, 95% CI: 1.15–1.90, $P = .002$). Subgroup analysis found that high STC2 expression was associated with worse OS in Asian (HR = 1.85, 95% CI: 1.35–2.55), the reported directly from articles group (HR = 1.39, 95% CI: 1.05–1.84), survival curves group (HR = 1.93, 95% CI: 1.36–2.74), and gastric cancer (HR = 1.43, 95% CI: 1.04–1.95). Furthermore, high STC2 expression was significantly related to advanced T stage (OR = 1.83, 95% CI: 1.17–2.86, $P = .008$), lymph node metastasis (OR = 2.29, 95% CI: 1.51–3.45, $P < .001$), lymphatic invasion (OR = 2.15, 95% CI: 1.53–3.02, $P < .001$), venous invasion (OR = 1.97, 95% CI: 1.30–2.99, $P = .001$), and more advanced clinical stage (OR = 2.36, 95% CI: 1.74–3.19, $P < .001$)

Conclusion: Elevated expression of STC2 suggested a poor prognosis in patients with cancer and may serve as a new tumor marker to monitor cancer development and progression.

Abbreviations: CI = confidence interval, HR = hazard ratio, IHC = immunohistochemistry, NOS = Newcastle–Ottawa scale, OR = odds ratio, OS = overall survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis, RT-qPCR = quantitative real-time reverse transcription polymerase chain reaction, STC = stanniocalcin, STC2 = stanniocalcin 2.

Keywords: cancer, meta-analysis, prognosis, stanniocalcin 2

1. Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide.[1] Despite enormous progress has been made in the diagnostic and treatment approaches, the prognosis of most cancers remains disappointing. Thus, it is very urgent to find better prediction biomarkers to fulfill the utility and precision of diagnostic tools of carcinoma.

Stanniocalcin (STC) is a glycoprotein hormone that were originally identified in the corpuscles of Stannius in bony fish.[2,3] STC2, a member of the STC family of molecules, is thought to modulate calcium and phosphate homeostasis.[4,5] STC2 has been found to play important roles in many physiologic processes such as bone development, reproduction, wound healing, angiogenesis, and modulation of inflammatory responses.[6,7]

An increasing number of studies have indicated that STC2 is overexpressed in various types of cancer, such as breast cancer,[8–10] colorectal cancer,[11,12] gastric cancer,[13,14] esophageal cancer,[15] gallbladder cancer,[16] hepatocellular cancer,[17] nasopharyngeal cancer,[18] laryngeal cancer,[19] cervical cancer,[20] ovarian cancer,[21] and endometrial cancer.[22] Besides, high expression of STC2 is significantly associated with poor prognosis in malignant tumors.[11–13,16,17,19–22] However, Todd et al found that high STC2 expression was prognostic for favorable overall survival (OS) in breast cancer.[9] Therefore, the prognostic value of STC2 expression in solid tumors is controversial. Given that a single study may lack the power to provide reliable conclusions because of the small sample size and methodologic limitations, we conducted a meta-analysis to

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estimate the prognostic value of STC2 in patients with solid cancers.

2. Materials and methods

2.1. Literature search and selection criteria

We searched PubMed, Embase, Web of Science, and the China National Knowledge Infrastructure up to March 2019 to identify relevant studies. The search strategy was generated by using the following keywords in various forms and combining key words related to "STC2, stanniocalcin 2" and "cancer, carcinoma, tumor, neoplasm, malignancy" and "prognosis (prognosis or prognostic), survival, outcome." The references of the retrieved articles were also checked to avoid missing relevant studies. Moreover, the present study was meta-analysis and did not involve the collection of samples. Therefore, ethical approval was not required.

2.2. Inclusion and exclusion criteria

The studies were included in our meta-analysis if they met the following inclusion criteria: STC2 expression evaluated in the human tissues; tumors should be confirmed by histologic or pathologic examinations; the main outcome of interest focus on prognostic factors; and full length paper with sufficient data to calculate the odds ratios (ORs) or hazard ratios (HRs) estimates and their 95% confidence intervals (95% CIs). The exclusion criteria were as follow: letters, case reports, reviews, and conference abstracts without original data; duplicate publications; and studies with insufficient data to calculate HR with 95% CI for survival from the paper.

2.3. Qualitative assessment

The Newcastle–Ottawa scale (NOS) was used to assess the quality of included studies.[23] Three aspects were considered in the NOS criteria: subject selection, 0 to 4; comparability of subject, 0 to 2; clinical outcome: 0 to 3. The range of NOS scores is from 0 to 9; and a score ≥6 means a good quality. Disagreements were resolved by discussion among all authors.

2.4. Data extraction

The studies information of this meta-analysis were retrieved by the reporting checklists of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[24] The following items were recorded: 1st author, publication year, ethnicity, cancer type, total number of patients, follow-up time, HR obtain method, test method, and NOS scores. When HRs and their 95% CIs were given in the articles, these data were extracted directly. If the prognosis was plotted as Kaplan–Meier survival curve, the data were digitized by the software Engauge Digitizer version 4.1 and calculated as described.[25,26]

2.5. Statistical analysis

The HRs with 95% CIs were calculated the association between STC2 expression and the OS of patients with cancer. ORs with 95% CIs were used to assess the association of STC2 expression with clinicopathologic characteristics. The evaluation of statistical heterogeneity was finished by using the Cochran Q statistic and I^2 tests.[27] If the heterogeneity was significant between studies ($I^2 > 50\%$ or $P < .10$), the random-effects model was used; otherwise, the fixed-effects model was used.[28] Both Begg test and Egger test were used to evaluate the potential publication bias.[29] Meanwhile, we performed the sensitivity analysis by omitting each study or specific studies to assess the influence of individual studies to the entire meta-analysis. The statistical analyses were performed using STATA version 12.0 software (Stata Corporation, Collage Station, TX). All P-values were 2-sided and $P < .05$ was considered statistically significant.

3. Results

3.1. Study selection and characteristics

The flowchart of the literature search is shown in Figure 1. Finally, 16 studies were included for further analysis.[8–22,30]Table 1 summarizes the identified studies and their main characteristics. A total of 4074 patients were included, and sample sizes for the included studies ranged between 49 and 1964. Five studies were conducted in Caucasian, and 11 in Asian. Cancer types of the patients included breast cancer, colorectal cancer, gastric cancer, esophageal cancer, gallbladder cancer, hepatocellular cancer, nasopharyngeal cancer, laryngeal cancer, cervical cancer, ovarian cancer, and endometrial cancer. The detection methods included immunohistochemistry, polymerase chain reaction (PCR), and reverse transcription quantitative PCR (RT-qPCR). Thirteen studies reported the HR data directly, and 3 studies provided Kaplan–Meier curve.

3.2. Meta-analysis results

The main results of this meta-analysis are listed in Table 2. Our analysis showed that high STC2 expression predicted poor survival in patients with cancer (HR = 1.48, 95% CI: 1.15–1.90, $P = .002$) for heterogeneity ($I^2 = 81.5\%$, $P < .001$; Fig. 2).

To lessen the impact of heterogeneity, subgroup analyses were performed for ethnicity, HR obtain method, and cancer type (Table 2). Subgroup analysis by ethnicity suggested that patients with high expression of STC2 predicted poor prognosis in Asian (HR = 1.85, 95% CI: 1.35–2.55, $P < .001$); however, no relationship between STC2 expression and OS was observed in Caucasian (HR = 0.99, 95% CI: 0.70–1.40, $P = .950$; Fig. 3). Subgroup analysis based on the HR obtain method suggested that the overexpression of STC2 predicted poor OS for both the reported directly from articles group (HR = 1.39, 95% CI: 1.05–1.84, $P < .001$) and survival curves group (HR = 1.93, 95% CI: 1.36–2.74, $P < .001$; Fig. 4).

Furthermore, the subgroup analyses classified by cancer type validated that high STC2 expression was an unfavorable prognostic factor in patients with gastric cancer (HR = 1.43, 95% CI: 1.04–1.95, $P = .028$). Nevertheless, there was no significant association between STC2 expression and OS in patients with breast cancer (HR = 0.77, 95% CI: 0.52–1.13, $P = .183$) and colorectal cancer (HR = 1.34, 95% CI: 0.70–2.57, $P = .381$).

3.3. Association between STC2 expression and clinicopathologic characteristics

Meta-analysis of the relationship between STC2 expression and clinicopathologic characteristics (Table 3) failed to show a significant association of high STC2 expression with age (OR =

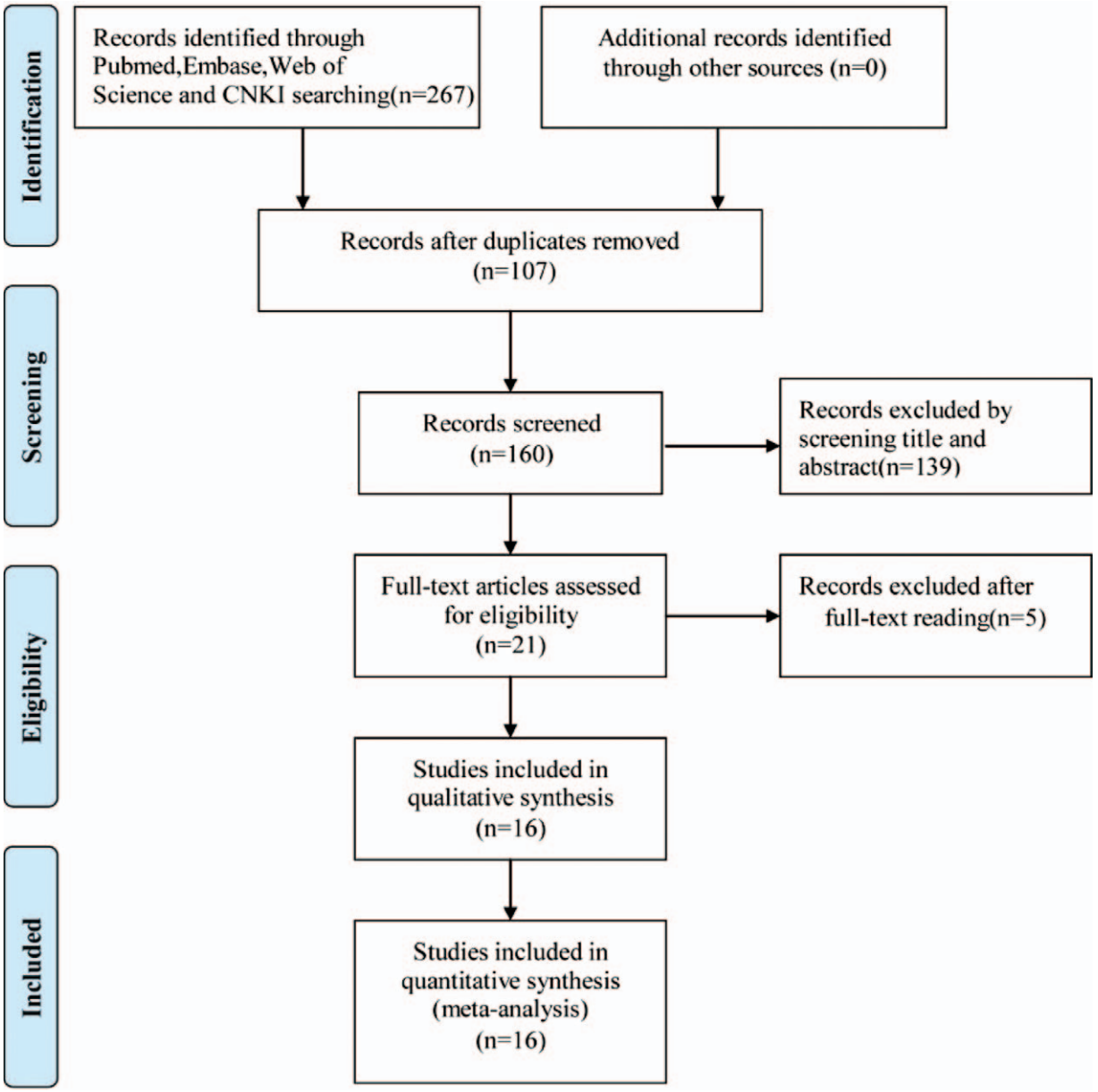

Figure 1. Flow diagram of study selection in present meta-analysis. CNKI = China National Knowledge Infrastructure.

Table 1

Characteristics of the included studies.

First author (yr)	No. of patients	Cancer type	Ethnicity	HR obtain method	Follow-up time, mo	Test method	Cutoff	NOS score
Esseghir et al (2007)	245	Breast cancer	Caucasian	SC	NA	PCR	≥2	7
Ieta et al (2009)	139	Colorectal cancer	Asian	Reported	Median 33.6 (36–135.6)	RT-qPCR	>4.02	8
Yokobori et al (2010)	108	Gastric cancer	Asian	Reported	NA	RT-qPCR	NA	8
Kita et al (2011)	70	Esophageal cancer	Asian	Reported	NA	RT-qPCR	>0.356	8
Yuan et al (2013)	126	Gallbladder cancer	Asian	SC	24	IHC	≥25%	7
Arigami et al (2013)	93	Gastric cancer	Asian	Reported	Median 25 (1–74)	RT-qPCR	NA	8
Zhang et al (2014)	240	Hepatocellular cancer	Asian	Reported	60	IHC	≥7	8
Lin et al (2014)	94	Nasopharyngeal cancer	Asian	Reported	Median 51.9 (2.1–65.6)	IHC	≥4	7
Zhou et al (2014)	90	Laryngeal cancer	Asian	Reported	At least 24	IHC	≥5	8
Shen et al (2014)	92	Cervical cancer	Asian	Reported	NR	IHC	>4	7
Wu et al (2015)	95	Ovarian cancer	Caucasian	SC	120	IHC	>1	7
Chen et al (2016)	77	Colorectal cancer	Asian	Reported	62	IHC	>6	6
Todd et al (2016)	1964	Breast cancer	Caucasian	Reported	NR	RT-qPCR	NA	8
Coulson-Gilme et al (2018)	477	Breast cancer	Caucasian	Reported	Median 46.8 (0.96–294)	IHC	>90.5	7
Aydin et al (2019)	49	Endometrial cancer	Caucasian	Reported	Median 63 (1–141)	IHC	≥4	8
Zhang et al (2019)	115	Colorectal cancer	Asian	Reported	Median 42.8 (1–52)	IHC	≥2	8

IHC = immunohistochemistry, NOS = Newcastle–Ottawa scale, NR = not reported, RT-qPCR = quantitative real-time reverse transcription polymerase chain reaction, SC = survival curve.

Table 2

Main meta-analysis results of stanniocalcin 2 expression in patients with cancer.

Analysis	No. of studies	HR (95% CI)	*P*-value	Heterogeneity		
				χ^2	I^2,(%	*P*-value
Overall survival	16	1.48 (1.15–1.90)	.002	91.17	81.5	<.001
Ethnicity						
Asian	11	1.85 (1.35–2.55)	<.001	31.74	65.3	.001
Caucasian	5	0.99 (0.70–1.40)	.950	24.68	79.7	<.001
HR obtain method						
Survival curves	3	1.93 (1.36–2.74)	<.001	0.80	0.0	.850
Reported directly	13	1.39 (1.05–1.84)	.009	77.51	83.1	<.001
Cancer type						
Breast cancer	3	0.77 (0.52–1.13)	.183	16.28	81.6	.001
Colorectal cancer	3	1.34 (0.70–2.57)	.381	7.34	72.7	.025
Gastric cancer	2	1.43 (1.04–1.95)	.028	0.39	0.0	.530

CI = confidence interval, HR = hazard ratio.

1.52, 95% CI: 0.90–2.56, $P = .121$), gender (OR = 0.89, 95% CI: 0.67–1.18, $P = .419$), distant metastasis (OR = 1.03, 95% CI: 0.48–2.18, $P = .944$), or tumor differentiation (OR = 1.16, 95% CI: 0.65–2.07, $P = .609$). In contrast, high STC2 expression was significantly related to advanced T stage (OR = 1.83, 95% CI: 1.17–2.86, $P = .008$), lymph node metastasis (OR = 2.29, 95% CI: 1.51–3.45, $P < .001$), lymphatic invasion (OR = 2.15, 95% CI: 1.53–3.02, $P < .001$), venous invasion (OR = 1.97, 95% CI: 1.30–2.99, $P = .001$), and more advanced clinical stage (OR = 2.36, 95% CI: 1.74–3.19, $P < .001$).

3.4. Publication bias

In this meta-analysis, both Begg test and Egger test were used to check the potential publication bias. No publication bias was found in the meta-analysis with OS ($P = .256$) when tested by

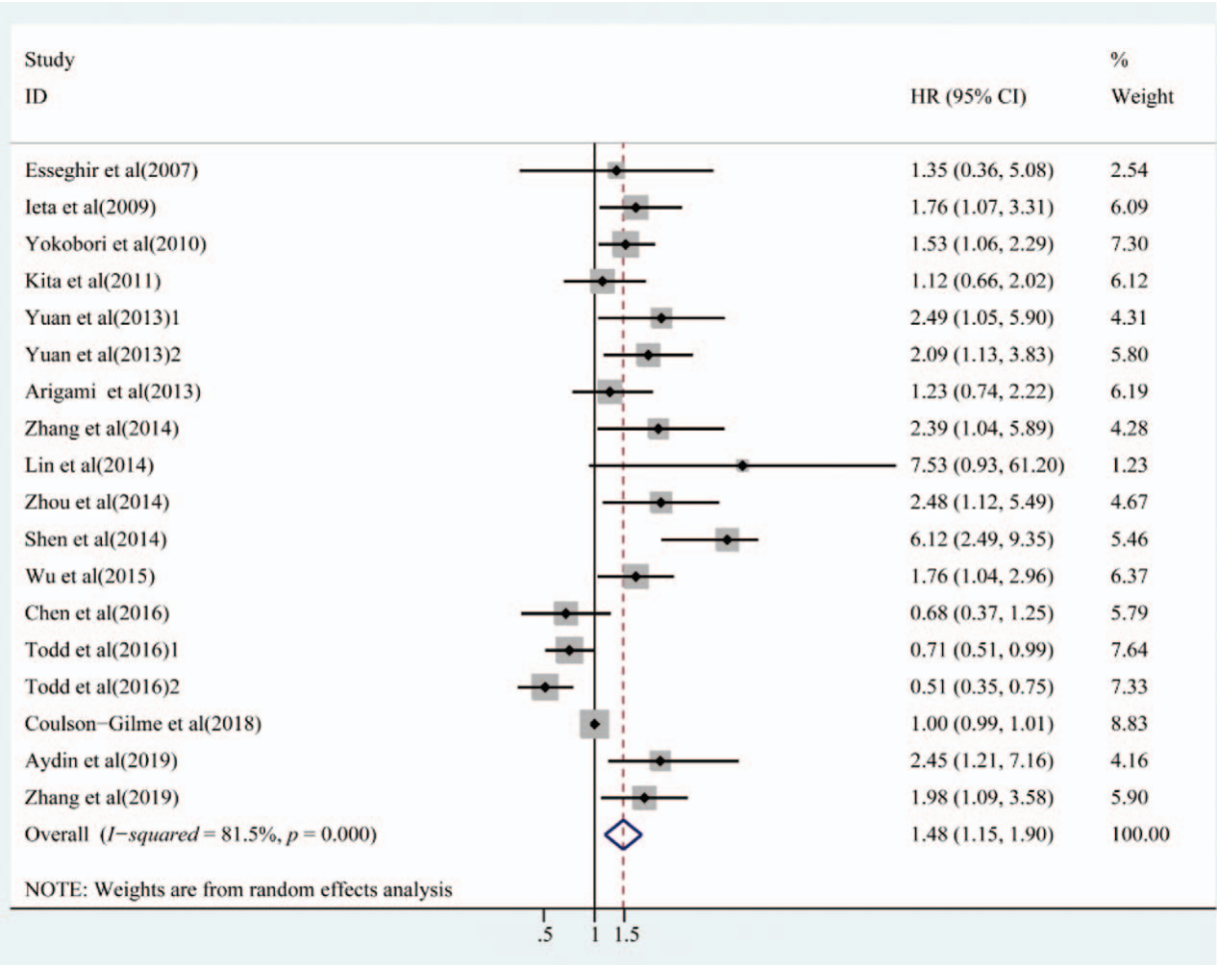

Figure 2. Forest plot of the relationship between stanniocalcin 2 expression and overall survival. CI = confidence interval, HR = hazard ratio.

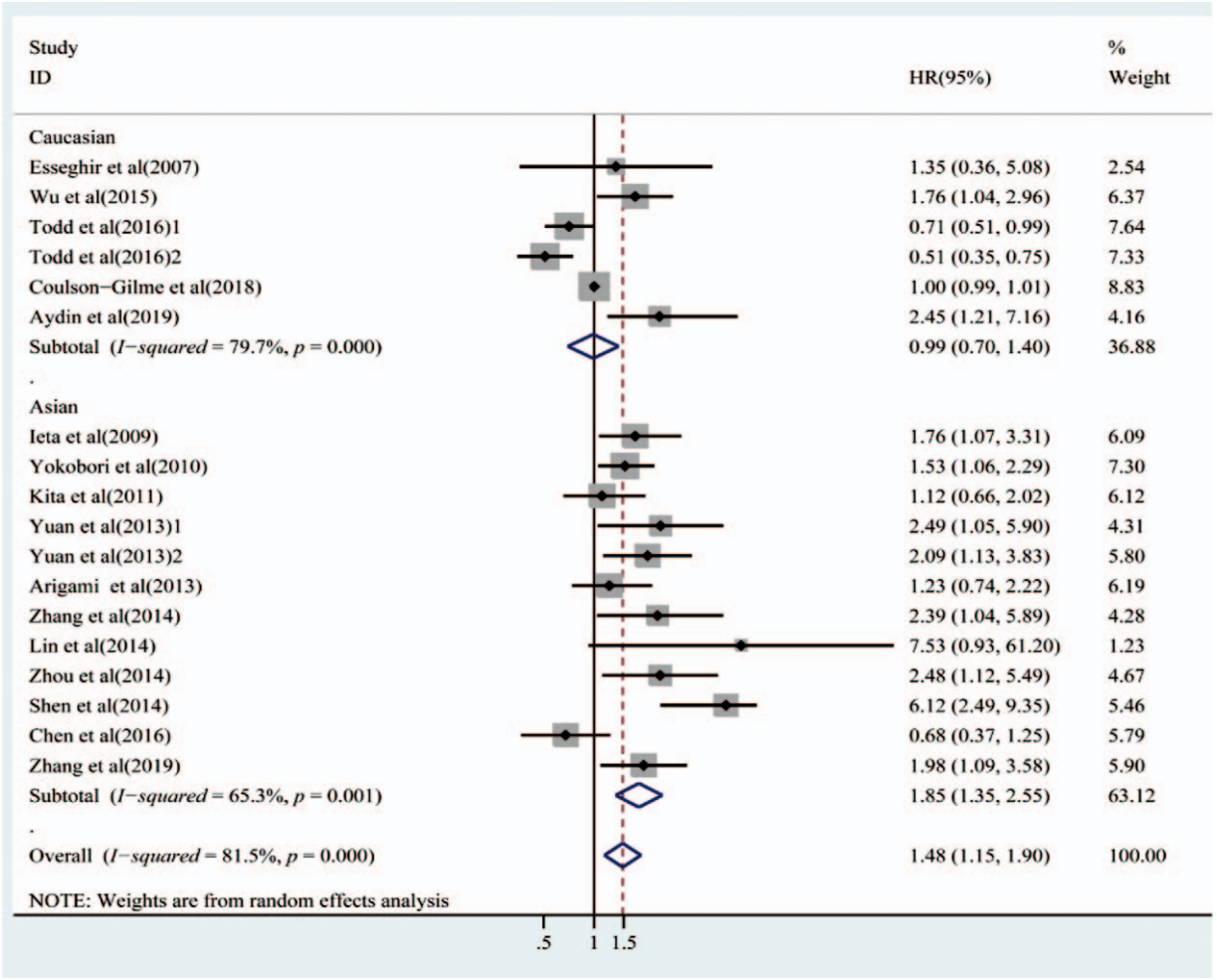

Figure 3. Forest plots of studies evaluating stanniocalcin 2 expression level and patients' overall survival with regard to ethnicity. CI = confidence interval, HR = hazard ratio.

Begg test. However, publication bias was found in the meta-analysis with OS ($P = .012$) when tested by Egger test.

3.5. Sensitivity analysis

Moreover, sensitivity analysis was carried out to assess the influence of individual studies on the overall results of OS. No individual study dominated this meta-analysis, and the removal of any single study had no significant effect on the overall conclusion (Fig. 5).

4. Discussion

The stanniocalcin (STC) family consists of 2 proteins, STC1 and STC2, which are expressed in various human tissues, such as pancreas, spleen, kidney, and skeletal muscle.[31] STC2 plays an important role in the tumorigenesis or progression. For example, Yang et al[32] suggested that high expression of STC2 promotes the migration and invasion of head and neck squamous cell carcinoma cells in vitro and in vivo through the PI3K/AKT pathway may. Wang et al[33] speculated that STC2 promoted lymphatic metastasis through VEGF-C/VEGF-D/VEGFR-3 pathway and EMT-related molecules in colorectal cancer. One study elaborated that STC2 contributes to hepatocellular carcinoma progression and metastasis by affecting cells viability, colony formation, and migration ability in a dominant-positive manner.[34] Based on these results, it would be of great interest to explore the prognostic value of STC2 in various malignant solid tumors.[8–22] However, the results remain controversial for many conditions. No meta-analysis has been conducted to assess the prognostic values of STC2 overexpression so far.

To the best of our knowledge, this is the 1st meta-analysis focused on the association between STC2 expression and patient survival. Our data indicated that high expression of STC2 could predict poor OS for cancers (HR = 1.48, 95% CI: 1.15–1.90, $P = .002$). Subgroup analysis in OS was performed to explore the source of heterogeneity based on ethnicity, HR obtain method, and cancer type. Subgroup analysis by ethnicity suggested that patients with high STC2 expression predicted poor prognosis in Asian; however, no relationship between STC2 expression and OS was observed in Caucasian. Based on the HR obtain method, we found that high expression of STC2 is related to poorer OS in the HR reported directly from articles group and survival curves group.

The subgroup analyses classified by cancer type validated that high STC2 expression was an unfavorable prognostic factor in

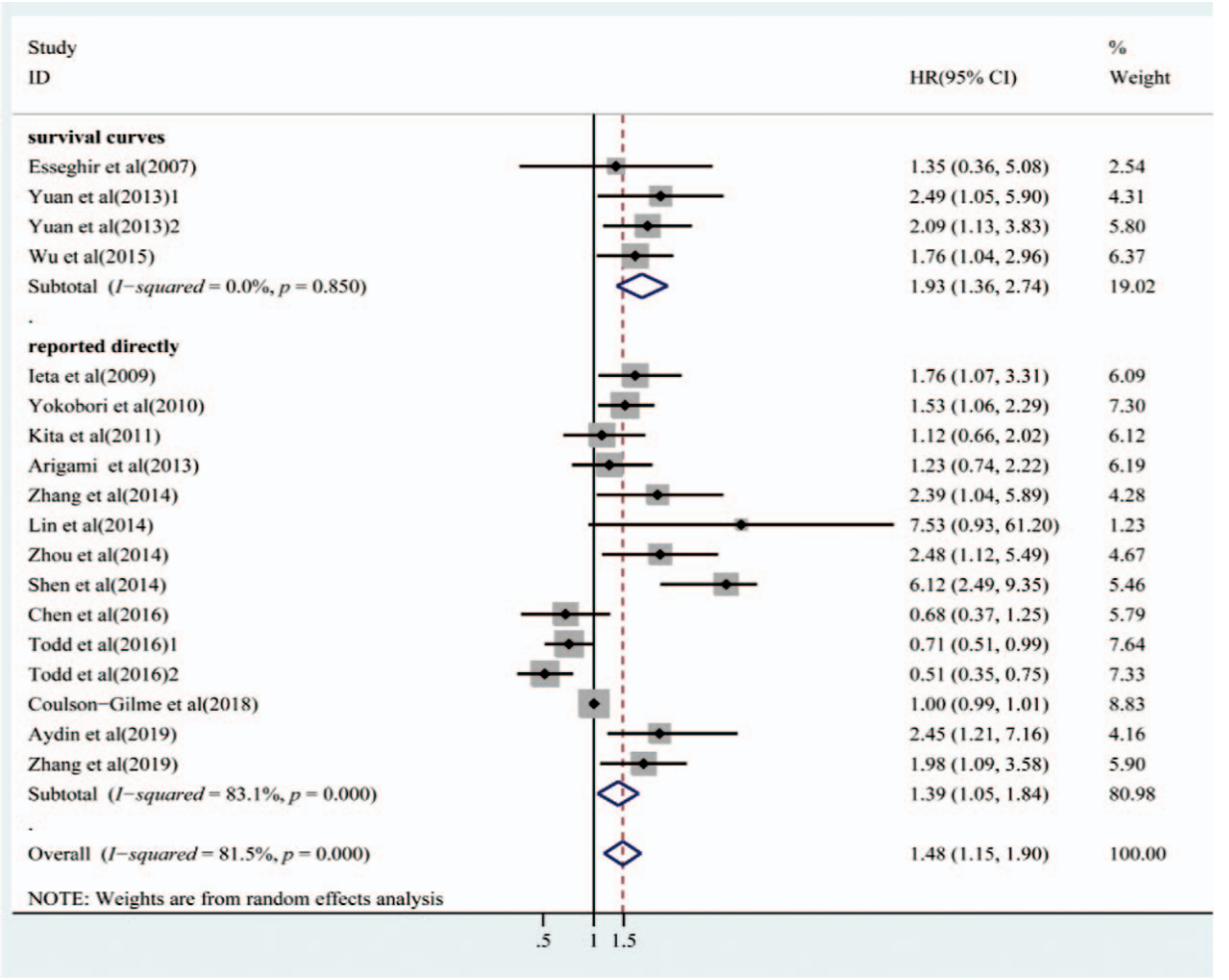

Figure 4. Forest plots of studies evaluating stanniocalcin 2 expression level and patients' overall survival with regard to hazard ratio (HR) obtain method. CI = confidence interval.

patients with gastric cancer, not in breast cancer and colorectal cancer. We suspected that the differences in STC2 behavior in different cancer types may be due in part to unique pathogenic mechanisms in each cancer type and differences in the contribution of STC2 to tumor biology.

Moreover, we carried out meta-analysis with respect to pathologic characteristics. We found that high STC2 expression was correlated with advanced T stage, lymph node metastasis, lymphatic invasion, venous invasion, and more advanced clinical stage. No statistically significant correlations were found for such as age, gender, distant metastasis, or tumor differentiation.

This meta-analysis also has some limitations, and the results should be interpreted with caution. First, the definition of high STC2 expression was not the same in the included studies, which may cause potential bias. Second, part of the HR value was calculated using a survival curve, which may lead to some error.

Table 3

Results of the association of stanniocalcin 2 expression with clinicopathologic features.

Clinicopathologic parameter	N	OR (95% CI)	*P*-value	Heterogeneity test (*Q*, I^2, *P*-value)
Age (≤50 vs >50 yrs)	4	1.52 (0.90–2.56)	.121	6.83, 56.1%, .078
Gender (male vs female)	7	0.89 (0.67–1.18)	.419	6.03, 0.0%, .644
T stage (T3–4 vs T1–2)	8	1.83 (1.17–2.86)	.008	17.11, 59.1%, .017
Lymph node metastasis (present vs absent)	10	2.29 (1.51–3.45)	<.001	18.44, 51.2%, .030
Distant metastasis (present vs absent)	6	1.03 (0.48–2.18)	.944	13.99, 64.2%, .016
Lymphatic invasion (present vs absent)	6	2.15 (1.53–3.02)	<.001	3.74, 0.0%, .588
Venous invasion (present vs absent)	5	1.97 (1.30–2.99)	.001	2.80, 0.0%, .591
Stage (stage 3–4 vs stage 1–2)	8	2.36 (1.74–3.19)	<.001	7.44, 5.9%, .385
Tumor differentiation (poor vs well)	8	1.16 (0.65–2.07)	.609	21.00, 66.7%, .004

CI = confidence interval, N = numbers of studies, OR = odds ratio.

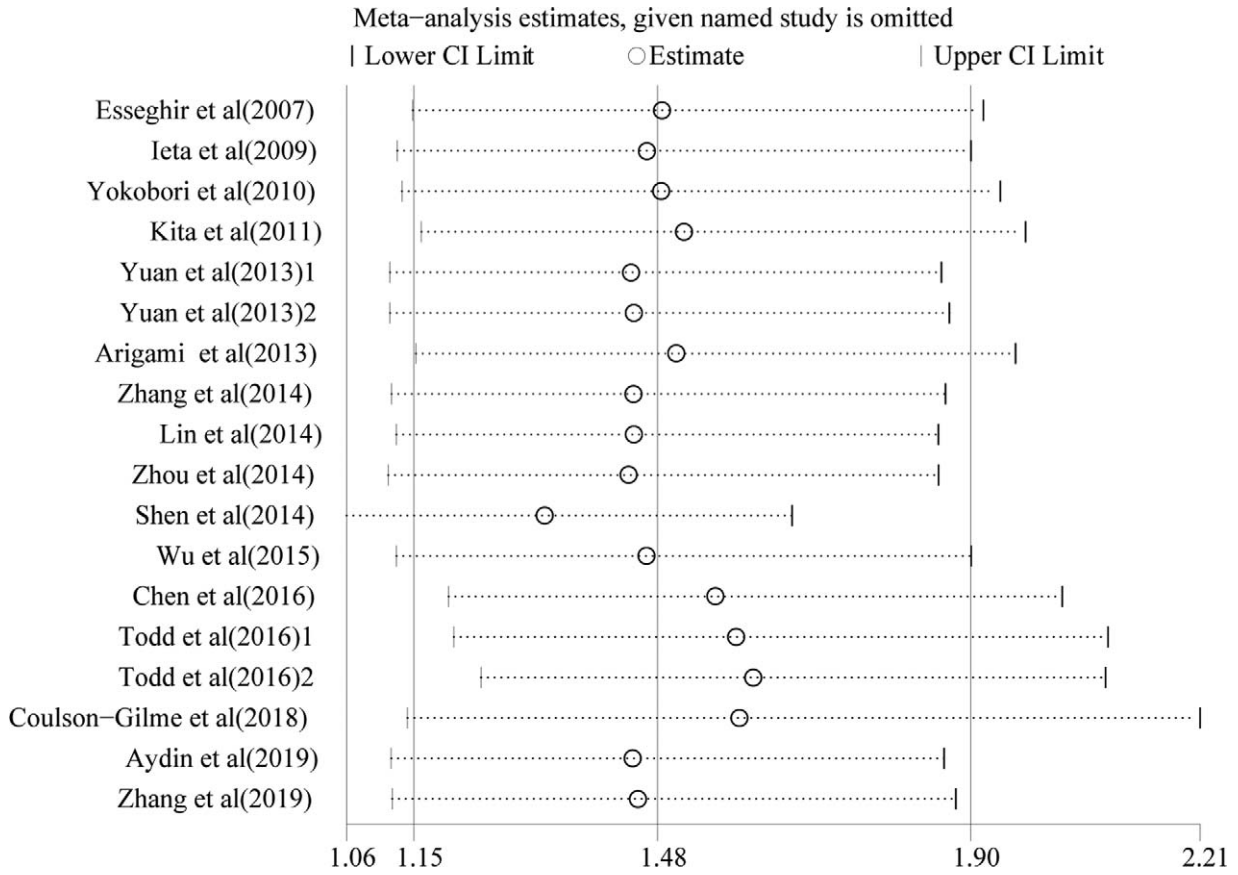

Figure 5. Sensitivity analysis of this meta-analysis. CI = confidence interval.

Third, the Egger test suggested the probability of publication bias because positive results are more easily accepted by journals than negative or null results. Fourth, large heterogeneity still exists in our study despite the random-effects model being used to conduct the analysis.

In conclusion, despite the limitations of the present study and heterogeneity across the included studies, our meta-analysis demonstrated that high expression of STC2 was significantly correlated with poor OS and may serve as a new tumor marker to monitor cancer development and progression. Future larger scale prospective and standard investigations should be conducted to confirm our results.

Author contributions

Conceptualization: Yueyin Pan.
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Writing – original draft: Lixia Hu, Yanyan Zha.
Writing – review & editing: Yueyin Pan.

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