Prognostic value of high stanniocalcin 2 expression in solid cancers
A meta-analysis

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1. Introduction
Cancer is one of the leading causes of morbidity and mortality worldwide.\textsuperscript{11} 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.\textsuperscript{2,3} STC2, a member of the STC family of molecules, is thought to modulate calcium and phosphate homeostasis.\textsuperscript{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.\textsuperscript{6,7}

An increasing number of studies have indicated that STC2 is overexpressed in various types of cancer, such as breast cancer,\textsuperscript{8–10} colorectal cancer,\textsuperscript{11,12} gastric cancer,\textsuperscript{13,14} esophageal cancer,\textsuperscript{15} gallbladder cancer,\textsuperscript{16} hepatocellular cancer,\textsuperscript{17} nasopharyngeal cancer,\textsuperscript{18} laryngeal cancer,\textsuperscript{19} cervical cancer,\textsuperscript{20} ovarian cancer,\textsuperscript{21} and endometrial cancer.\textsuperscript{22} Besides, high expression of STC2 is significantly associated with poor prognosis in malignant tumors.\textsuperscript{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.\textsuperscript{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...
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 Disagreements were resolved by discussion among all authors. The studies information of this meta-analysis were retrieved by selecting the relevant data from the full text of the included studies. Three aspects were considered in high STC2 expression and the OS of patients with cancer. 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 (I² = 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         |
| Nakajima 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 1.1 (2.1–56.3) | 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         |
| Coulon-Gimé et al (2018) | 477           | Breast cancer   | Caucasian | Reported | Median 48.8 (196–294) | IHC           | >90.5  | 7         |
| Aydin et al (2019) | 49               | Endometrial cancer | 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.
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...
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. 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.\(^{18-22}\) 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 3. Forest plots of studies evaluating stanniocalcin 2 expression level and patients’ overall survival with regard to ethnicity. CI = confidence interval, HR = hazard ratio.](image-url)
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**

| Clinicopathologic parameter | N  | OR (95% CI) | P-value | Heterogeneity test (Q, I², 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.
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**

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