Prognostic and clinicopathological significance of S100A14 expression in cancer patients

A meta-analysis

Lixia Hu, MS, Fanliang Kong, BS, Yueyin Pan, MD

Abstract

Background: The prognostic significance of S100A14 for survival of cancer patients remains controversial. Therefore, we conducted this meta-analysis to explore the association between S100A14 expression and cancer prognosis.

Method: Eligible studies were identified by searching the online databases Pubmed and EMBASE up to August 2018. Odds ratios (ORs) with 95% confidence intervals (CIs) served as the summarized statistics for clinicopathological assessments and hazard ratios (HRs) with 95% CIs were calculated to clarify the correlation between S100A14 expression and prognosis of different cancers.

Results: A total of 11 studies with 1651 cancer patients were enrolled. The results indicated that S100A14 expression was not significantly associated with overall survival (OS) in total various cancers (HR= 1.54, 95% CI:0.89–2.67, P=.121). Further subgroup analysis stratified by tumor type showed that elevated S100A14 expression was associated with poor OS in breast cancer (HR= 3.66, 95% CI: 1.75–7.62, P<.001) and in ovarian cancer patients (HR=3.78, 95%CI: 1.63–8.73, P=.002). Interestingly, high S100A14 expression was correlated with poor tumor differentiation (OR=2.51, 95% CI: 1.52–4.13, P<.001). However, there were no significant correlations between S100A14 expression and other clinicopathologic characteristics. Begg funnel plot and Egger test showed that no publication bias was detected.

Conclusions: Our meta-analysis suggests that S100A14 overexpression might be a predictive biomarker for poor prognosis in patients with breast cancer and ovarian cancer. Large-scale studies are required to confirm these results.

Abbreviations: CI = confidence interval, HR = hazard ratio, IHC = Immunohistochemistry, NOS = Newcastle-Ottawa Scale, OR = Odds ratios, OS = overall survival, qRT-PCR = quantitative reverse transcription-polymerase chain reaction, STIM1 = stromal interacting molecule 1.

Keywords: cancer, meta-analysis, prognosis, S100A14

1. Introduction

Cancer is a leading cause of death worldwide. 

The $100$ family of proteins, a group of EF-hand calcium-binding proteins, are expressed in a cell- and tissue-specific manner and exert a broad range of intracellular and extracellular functions. The $100$ protein family performs multiple regulatory functions in cellular processes such as cell growth, differentiation, motility, contraction, transcription, signal transduction, protein phosphorylation, cell survival, apoptosis, and cell-cycle regulation. The $100$ protein family is related to many diseases such as inflammation, neurodegenerative disorders, depression, cystic fibrosis, and cancer.

S100A14 is a recently identified member of the $100$ protein family. Many studies have suggested that S100A14 is a new molecular marker closely related to the metastasis of malignant tumors. S100A14 is downregulated in esophageal carcinoma and decreased S100A14 is correlated with poor differentiation. S100A14 can act as a mediator of epithelialmesenchymal transformation, thereby promoting tumor metastasis.

S100A14 blocks store-operated Ca$2^+$ influx by inhibiting Orai1 and stromal interacting molecule 1 (STIM1) expression leading to FAK activation, MMP downregulation, and focal adhesion assembly. Since Wang et al first identified the relationship between S100A14 expression and colorectal cancer patient’s prognosis, researchers have found that high expression of S100A14 is negatively correlated with overall survival (OS) in different kinds of cancers. However, there is no significant correlation in small intestinal adenocarcinoma and lung adenocarcinoma. Therefore, we aimed to conduct a
meta-analysis to investigate the relationship between cancer and the clinicopathologic significance and prognostic value of S100A14.

2. Materials and methods

2.1. Literature search and selection criteria

We searched Pubmed and EMBASE up to August 2018 to identify relevant studies. The search strategy was: “S100A14” and “cancer or carcinoma or tumor or tumor, or neoplasm or malignancy”. The citation lists associated with the studies were used to identify additional eligible studies. The reviews and bibliographies were also manually inspected to find related articles. 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:
1. S100A14 expression evaluated in the human tissues;
2. tumors should be confirmed by histological or pathological examinations;
3. the main outcome of interest focus on prognostic factors and clinicopathological features;
4. full length paper with sufficient data to calculate the odds ratios (ORs) or hazard ratio (HRs) estimates and their 95% confidence intervals (95% CIs).

The exclusion criteria were as follow:
1. letters, case reports, reviews, and conference abstracts without original data;
2. articles from which the relevant data could not be extracted;
3. duplicate publications.

2.3. Qualitative assessment

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of included studies. The score was based on subject selection, comparability of subject, clinical outcome in the NOS. NOS score of 0 to 9 was used to indicate the quality of studies, and a score ≥ 6 denoted a high quality.

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. The following items were recorded:
1. first author’s name, year of publication, ethnicity, cancer type, total number of patients, detection means, analysis model, and HR sources;
2. age, gender, tumor size, T stage, lymph node status, tumor stage, distant metastasis, tumor differentiation, vascular invasion.

Several of the included studies provided HRs and 95% CIs, which were pooled directly. Otherwise, we calculated the HR and its 95% CI from a Kaplan–Meier survival curve using Engauge Digitizer version 4.1, as previously reported.

2.5. Statistical analysis

HRs with 95% CIs were calculated the association between S100A14 expression and the OS of cancer patients. ORs with 95% CIs were used to assess the association of S100A14 expression with clinicopathological characteristics. The χ² test and the I² statistic were used to evaluate the heterogeneity among studies. If the heterogeneity was significant between studies (I² > 50% or P < .10), the random-effects model was used; otherwise, the fixed-effects model was used. Publication bias was estimated by Egger linear regression test with a funnel plot. The statistical analyses were performed using STATA version 12.0 software (Stata Corporation, Collage Station, Texas, USA). All P values were two-sided and P < .05 was considered statistically significant.

3. Results

3.1. Study selection and characteristics

The details of the study selection process are presented in Figure 1. Eventually 11 qualified studies containing 1651 cancer patients were enrolled for further analysis. Ten studies comprising 1443 patients investigated the relationship between S100A14 expression and OS in cancer. Table 1 listed the identified studies and their main characteristics. Eight studies evaluated patients from Asian and 2 evaluated patients from Caucasian. The types of cancers in these studies included colorectal cancer, breast cancer, small intestinal adenocarcinoma, gastric cancer, hepatocellular carcinoma, ovarian cancer, and lung adenocarcinoma. HR with 95%CI was reported directly in 8 studies, and for the remaining 2 studies, HR with 95%CI was extrapolated from survival curves. Immunohistochemistry (IHC) was used in the majority of all eligible studies to detect S100A14 expression, and quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was conducted in 1 study. The NOS scores ranged from 6 to 7.

In prognostic factors, 8 studies were identified the relationship between age and cancer prognosis, 6 studies about gender, 3 studies about tumor size, 3 studies about T stage, 7 studies about lymph node status, 7 studies about T tumor stage, 2 studies about distant metastasis, 3 studies about tumor differentiation, and 3 studies about vascular invasion (Table 2).

3.2. Meta-analysis results

The main results of this meta-analysis are listed in Table 2. Our analysis showed that high S100A14 expression did not indeed predict poor survival in cancer patients (HR = 1.54, 95% CI: 0.89–2.67, P = .121) for heterogeneity (I² = 83.4%, P < .001) (Fig. 2).

As shown in Table 3, the subgroup analyses were implemented based on ethnicity, cancer type, HR sources, analysis model, and detection means. Subgroup analysis by ethnicity suggested no association between S100A14 expression and OS was observed in the Asian patients (HR = 1.24, 95% CI: 0.70–2.19, P = .455) and in the Caucasian patients (HR = 5.92, 95% CI: 0.78–44.93, P = .085). When grouped according to cancer type, a significant relationship between S100A14 expression and OS was observed in breast cancer patients (HR = 3.66, 95% CI: 1.75–7.62, P < .001) and in ovarian cancer patients (HR = 3.78, 95% CI: 1.63–8.73, P = .002); however, no relationship between S100A14 expression and OS was observed in other cancer patients.
Records identified through database searching (n = 112)

Additional records identified through other sources (n = 3)

Records after duplicates removed (n = 45)

Records excluded (n = 48)
  3 the prognosis of polymorphisms
  39 animal or cell line studies
  6 non-S100A14 topic

Records screened (n = 70)

Full-text articles assessed for eligibility (n = 22)

Full-text articles excluded with reasons (n = 11)
  7 no usable data
  4 not about prognosis and clinical parameters

Studies included in qualitative synthesis (n = 11)

Studies included in quantitative synthesis (meta-analysis) (n = 11)

Figure 1. Flow diagram of the study selection.

Table 1
Main characteristics and results of the eligible studies.

| Study            | Year | Country | Ethnicity | Cancer type                     | Number of patients | Method       | Source of HR | Analysis model            | Scores |
|------------------|------|---------|-----------|---------------------------------|--------------------|--------------|--------------|--------------------------|--------|
| Hongyi Wang      | 2010 | China   | Asian     | colorectal cancer               | 115                | IHC          | reported     | multivarate analysis     | 7      |
| Eadaoin McKiernan| 2011 | Ireland | Caucasian | breast cancer                   | 205                | qRT-PCR      | reported     | univariate analysis      | 6      |
| Gwangil Kim      | 2013 | Korea   | Asian     | small intestinal adenocarcinoma | 175                | IHC          | Survival curves | univariate analysis      | 6      |
| Fu-Tao Zhao      | 2013 | China   | Asian     | hepatocellular cancer           | 120                | IHC          | reported     | multivarate analysis     | 6      |
| Hanbyoul Cho     | 2014 | Korea   | Asian     | ovarian cancer                  | 71                 | IHC          | reported     | multivarate analysis     | 6      |
| Qingying Zhang   | 2015 | China   | Asian     | gastric cancer                  | 79                 | IHC          | Survival curves | univariate analysis      | 6      |
| Mizuko Tanaka    | 2015 | Japan   | Asian     | breast cancer                   | 167                | IHC          | reported     | univariate analysis      | 7      |
| Sidse Ehmsen     | 2015 | Denmark | Caucasian | triple-negative breast cancer   | 129                | IHC          | reported     | multivarate analysis     | 7      |
| Haiyue Zhao      | 2016 | China   | Asian     | ovarian cancer                  | 127                | IHC          | reported     | multivarate analysis     | 6      |
| Ken Katono       | 2018 | Japan   | Asian     | lung adenocarcinoma             | 166                | IHC          | reported     | multivarate analysis     | 7      |
| Fang Ding        | 2018 | China   | Asian     | lung adenocarcinoma             | 208                | IHC          | –            | –                        | 6      |

HR = hazard ratio, IHC = immunohistochemistry, qRT-PCR = quantitative reverse transcription-polymerase chain reaction.
When stratifying by HR sources, no significant relevance was observed in reported directly from articles subgroup (HR = 2.00, 95%CI: 0.97–4.14, \(P = .062\)) and in survival curves subgroup (HR = 0.78, 95% CI:0.37–1.67, \(P < .001\)). Regarding analysis model, no statistically evident correlation was detected between S100A14 expression neither when using multivariate analysis model (HR = 1.47, 95%CI: 0.66–3.25, \(P = .349\)) nor when using univariate analysis model (HR = 1.75, 95%CI: 0.69–4.46, \(P = .523\)). Regarding the detection means, there was no significant association between S100A14 expression and OS in patients with IHC (HR = 1.35, 95%CI: 0.79–2.29, \(P = .271\)).

| Study          | Age | Gender | T stage | Tumor size | Lymph node status | Distant metastasis | Tumor differentiation | Tumor stage | Vascular invasion | HR(95% CI)   | Weight |
|---------------|-----|--------|---------|------------|-------------------|--------------------|----------------------|-------------|-------------------|-------------|--------|
| Wang 2010     |     |        |         |            |                   |                    |                      |             |                   | 0.39 (0.19, 0.79) | 11.00   |
| McKiernan 2011 |     |        |         |            |                   |                    |                      |             |                   | 21.19 (2.81, 159.80) | 4.75    |
| Kim 2013      |     |        |         |            |                   |                    |                      |             |                   | 1.11 (0.81, 1.51) | 12.83   |
| Zhao 2013     |     |        |         |            |                   |                    |                      |             |                   | 1.98 (1.14, 3.46) | 11.77   |
| Cho 2014      |     |        |         |            |                   |                    |                      |             |                   | 4.53 (1.16, 17.69) | 7.33    |
| Zhang 2015    |     |        |         |            |                   |                    |                      |             |                   | 0.51 (0.29, 0.90) | 11.71   |
| Tanaka 2015   |     |        |         |            |                   |                    |                      |             |                   | 3.32 (1.78, 6.81) | 11.15   |
| Ehmsen 2015   |     |        |         |            |                   |                    |                      |             |                   | 2.56 (1.23, 5.33) | 10.80   |
| Zhao 2016     |     |        |         |            |                   |                    |                      |             |                   | 3.38 (1.17, 9.80) | 8.90    |
| Katono 2018   |     |        |         |            |                   |                    |                      |             |                   | 0.45 (0.18, 1.12) | 9.76    |
| Overall (I−squared = 83.4%, \(P = 0.000\)) |     |        |         |            |                   |                    |                      |             |                   | 1.54 (0.89, 2.67) | 100.00 |

NOTE: Weights are from random effects analysis.
### 3.3. Association of S100A14 expression with prognosis factors

High S100A14 expression was correlated with poor tumor differentiation (OR = 2.51, 95% CI: 1.52–4.13, \( P < .001 \)). However, S100A14 expression was not significant related to prognosis factors, such as age (\( \geq 60 \) vs \(< 60 \)) (OR = 0.78, 95% CI: 0.58–1.55, \( P = 0.93 \)), gender (male vs female) (OR = 0.85, 95% CI: 0.48–1.53, \( P = 0.59 \)), T stage (T3−4 vs T1–2) (OR = 0.85, 95% CI: 0.36–1.98, \( P = 0.70 \)), tumor size (\( \geq 5 \) vs \(< 5 \)) (OR = 2.20, 95% CI: 0.53–9.26, \( P = 0.28 \)), lymph node status (yes vs no) (OR = 1.20, 95% CI: 0.66–2.19, \( P = 0.52 \)), distant metastasis (M1 vs M0) (OR = 0.98, 95% CI: 0.12–8.21, \( P = 0.98 \)), tumor stage (III+ IV vs I+ II) (OR = 0.87, 95% CI: 0.53–1.43, \( P = 0.59 \)), vascular invasion (present vs absent) (OR = 2.36, 95% CI: 0.90–6.20, \( P = 0.082 \)) (Table 4).

### 3.4. Publication bias

The shape of the funnel plot did not reveal any evidence of obvious asymmetry (Fig. 3). Egger test also indicated that there was no significant publication bias in the meta-analysis (\( P = .283 \)).

### 4. Discussion

In recent years, the correlation between S100A14 expression and the survival of patients has been explored in many studies due to the key role of S100A14 in tumorigenesis. The prognostic value of high S100A14 expression remained inconclusive. To address the prognostic value of S100A14 expression, we conducted this meta-analysis.

To the best of our knowledge, this is the first meta-analysis focused on the association between S100A14 expression and patient survival. Meta-analysis is a useful tool to detect effects that may be missed by individual studies.\[32\] The present study pooled the survival data of 1443 cancer patients that from 10 studies, and found that that S100A14 expression was not associated with OS in cancer patients (HR = 1.54, 95% CI: 0.89–2.67, \( P = .121 \)). To determine the prognostic role of S100A14 in different cancers, we conducted subgroup analysis by cancer types. The results showed that elevated S100A14 expression was significantly associated with worse OS in patients with breast cancer (HR = 3.66, 95% CI: 1.75–7.62, \( P < .001 \)) and with ovarian cancer (HR = 3.78, 95% CI: 1.63–8.73, \( P = .002 \)). However, no relationship between S100A14 expression and OS was observed in other cancer patients. The reason for this discrepancy may be that the number of subgroups contain was small. Thus, S100A14 could serve as a novel prognostic marker for breast cancer and ovarian cancer aforementioned. We suspected that the differences in S100A14 behavior in different cancer types may be due in part to unique pathogenic mechanisms in each cancer type and differences in the contribution of S100A14 to tumor biology. However, the

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**Table 3**

Main meta-analysis results of S100A14 expression in cancer patients.

| Analysis                        | Numbers of studies | HR (95% CI) | \( P \) value | \( \chi^2 \) | \( I^2 \) (%) | \( P \) value |
|---------------------------------|--------------------|-------------|----------------|-------------|----------------|----------------|
| Overall survival (OS)           | 10                 | 1.54 (0.89–2.67) | .121 | 54.21 | 83.4 | <.001 |
| Ethnicity                       |                    |             |                |             |                |                |
| Asian                           | 8                  | 1.24 (0.70–2.19) | .455 | 42.09 | 83.4 | <.001 |
| Caucasian                       | 2                  | 5.92 (0.78–44.93) | .085 | 3.72 | 73.1 | .054 |
| Analysis model                  |                    |             |                |             |                |                |
| Multivariate analysis           | 6                  | 1.47 (0.66–3.25) | .349 | 28.16 | 82.2 | <.001 |
| Univariate analysis             | 4                  | 1.75 (0.69–4.46) | .523 | 25.49 | 88.2 | <.001 |
| Survival curves                 | 2                  | 0.78 (0.37–1.67) | .062 | 5.56 | 82.0 | .018 |
| Reported directly               | 8                  | 2.00 (0.97–4.14) | <.001 | 39.85 | 82.4 | <.001 |
| Cancer type                     |                    |             |                |             |                |                |
| Breast cancer                   | 3                  | 3.66 (1.75–7.62) | <.001 | 3.72 | 46.2 | 156 |
| Ovarian cancer                  | 2                  | 3.78 (1.63–8.73) | .002 | 0.11 | 0 | .739 |
| Other cancer                    | 5                  | 0.76 (0.43–1.35) | .355 | 20.92 | 80.9 | <.001 |
| Detection means                 |                    |             |                |             |                |                |
| Immunohistochemistry            | 9                  | 1.35 (0.79–2.29) | .271 | 46.53 | 82.8 | <.001 |

CI = confidence interval, HR = hazard ratio.

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**Table 4**

Results of the association of S100A14 expression with clinicopathological features.

| Clinicopathological parameter | N   | OR (95% CI)   | \( P \) value | Heterogeneity test (\( Q, \bar{I}^2, P \)-value) |
|-------------------------------|-----|--------------|---------------|------------------------------------------|
| Age (\( \geq 60 \) vs \(< 60 \)) | 8   | 0.78 (0.58–1.55) | .093 | 4.22, 0.648, 0%  |
| Gender (male vs female)       | 6   | 0.89 (0.49–1.63) | .590 | 16.33, 0.006, 69.4%  |
| T stage (T3–4 vs T1–2)        | 3   | 0.85 (0.36–1.98) | .705 | 4.26, 0.119, 53.0%  |
| Tumor size (\( \geq 5 \) vs \(< 5 \)) | 3   | 2.20 (0.53–9.26) | .281 | 8.94, 0.011, 77.6%  |
| Lymph node status (yes vs no) | 7   | 1.20 (0.66–2.19) | .552 | 23.42, 0.001, 74.4%  |
| Distant metastasis (M1 vs M0) | 2   | 0.98 (0.12–8.21) | .987 | 9.20, 0.002, 89.1%  |
| Tumor stage (III–IV vs I–II)  | 7   | 0.87 (0.53–1.43) | .589 | 13.18, 0.040, 54.5%  |
| Tumor differentiation (well vs poor) | 3   | 2.51 (1.52–4.13) | <.001 | 1.55, 0.460, 0%  |
| Vascular invasion (Present vs Absent) | 3   | 2.36 (0.30–6.20) | .082 | 7.91, 0.019, 74.7%  |

CI = confidence interval, \( N \) = Numbers of studies, OR = odds ratio.
analysis found no significant correlations between high S100A14 expression and OS in subgroups including ethnicity, HR sources, analysis model, and detection means. Moreover, we carried out meta-analyses with respect to pathological characteristics. We found that high S100A14 expression was correlated with poor tumor differentiation. No statistically significant correlations were found for such as age, gender, T stage, tumor size, lymph node status, distant metastasis, tumor stage, and vascular invasion.

This meta-analysis also has some limitations, and the results should be interpreted with caution. First, the ethnicities of most studies were Asian populations with only 2 study carried out in Caucasian, which deserves further confirmations in other ethnicities. Second, the definition of high S100A14 expression was not the same across studies; thus, it was difficult to define S100A14 overexpression in various cancers. Third, not all of the HRs with 95% CIs was directly extracted from the studies, so we had to evaluate the HRs from the survival curves and these calculated HRs and 95% CIs might be less reliable than the directly given data. Most of studies detected S100A14 expression by IHC, the use of different antibody concentrations and variable cutoff values might have influenced the results.

Our meta-analysis suggests that S100A14 overexpression might be a significantly prognostic indicator for patients with breast cancer and ovarian cancer. More multi-center clinical investigations with larger sample sizes should be conducted to confirm these findings.

**Author contributions**

Conceptualization: Yueyin Pan.

Data curation: Lixia Hu, Fanliang Kong

Formal analysis: Lixia Hu, Fanliang Kong, Yueyin Pan.

Methodology: Lixia Hu, Fanliang Kong.

Project administration: Yueyin Pan.

Validation: Fanliang Kong.

Software: Lixia Hu.

Writing – original draft: Lixia Hu.

Writing – review & editing: Yueyin Pan.

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