Medicine®

OPEN

Prognostic and clinicopathological significance of S100A14 expression in cancer patients
A meta-analysis

Lixia Hu, MS[a], Fanliang Kong, BS[a], Yueyin Pan, MD[b],*

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) severed 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.[1] Despite that diagnostic and treatment approaches, as well as supportive care, have greatly improved in the past few decades, the prognosis of most cancers remains very low. This may be because cancers can recur and few effective detection modes exist for cancer patients at the early stages. Early diagnosis and treatment is an important way to improve the prognosis of cancers. However, sensitivity and specificity of most of the cancer markers widely used now are not yet satisfactory.[2] Therefore, it is of great importance to discover new biomarkers to predict the prognosis and therapy targets for cancer.

The S100 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.[3] The S100 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.[4–6] The S100 protein family is related to many diseases such as inflammation, neurodegenerative disorders, depression, cystic fibrosis, and cancer.[6–9]

S100A14 is a recently identified member of the S100 protein family. Many studies have suggested that S100A14 is a new molecular marker closely related to the metastasis of malignant tumors.[10] S100A14 is downregulated in esophageal carcinoma and decreased S100A14 is correlated with poor differentiation.[11] S100A14 can act as a mediator of epithelialmesenchymal transformation, thereby promoting tumor metastasis.[12,13]

S100A14 blocks store-operated Ca2+ influx by inhibiting Orai1 and stromal interacting molecule 1 (STIM1) expression leading to FAK activation, MMP downregulation, and focal adhesion assembly.[14] Since Wang et al first identified the relationship between S100A14 expression and colorectal cancer patient's prognosis.[15] Researchers have found that high expression of S100A14 is negatively correlated with overall survival (OS) in different kinds of cancers.[16,17] However, there is no significant correlation in small intestinal adenocarcinoma[18] and lung adenocarcinoma.[19] 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.[20] 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.[21] 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 we 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.[22,23]

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 χ^2 test and the I^2 statistic were used to evaluate the heterogeneity among studies.[24] 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.[25] Publication bias was estimated by Egger linear regression test with a funnel plot.[26] 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.[12,15–19,27–31] Ten studies comprising 1443 patients investigated the relationship between S100A14 expression and OS in cancer.[12,15–19,27–30] 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 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 (I^2=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
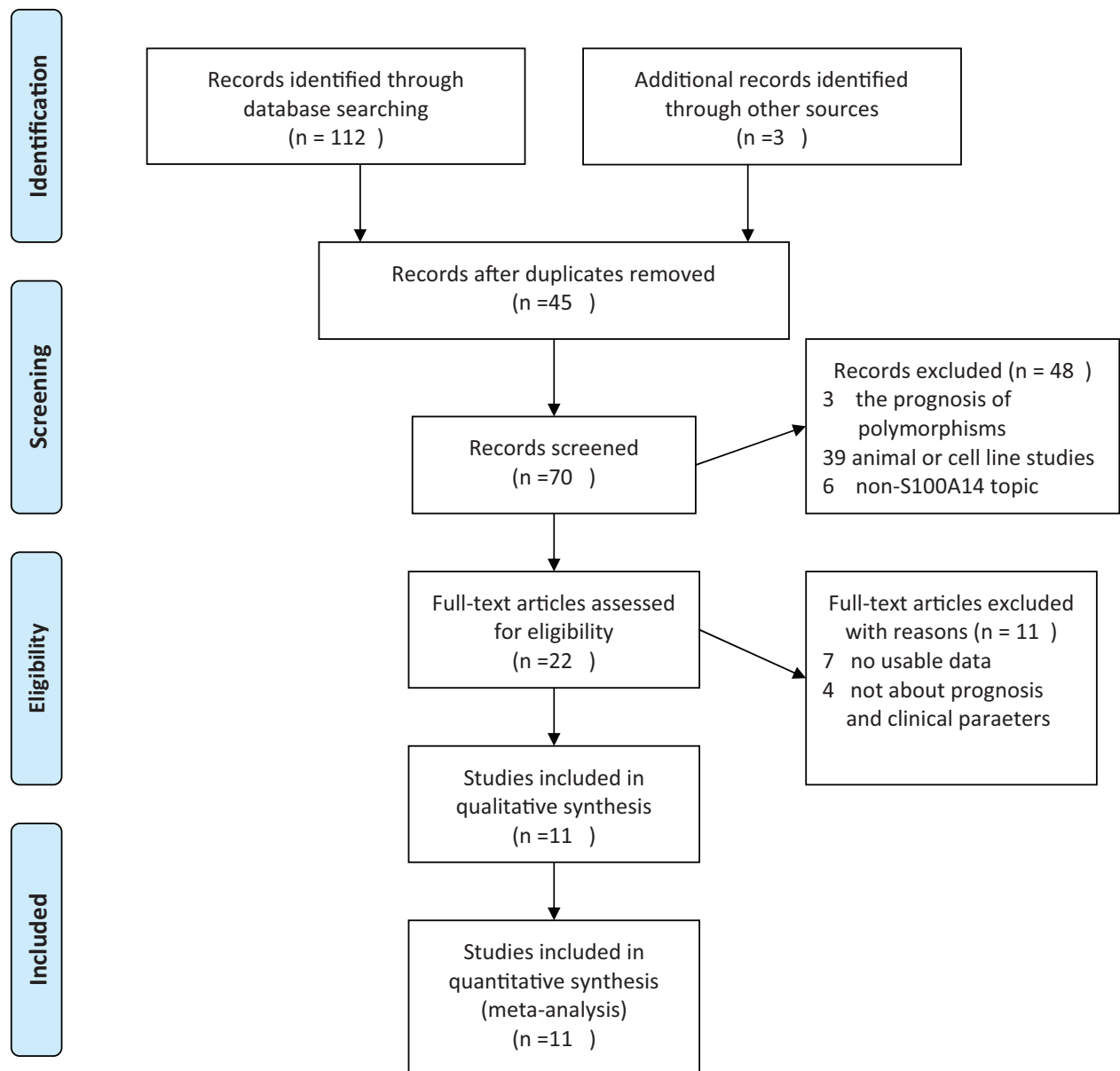
Figure 1. Flow diagram of the study selection.

| 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	295	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	128	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.

Table 2

S100A14 expression with clinicopathological parameter.

	S100A14 expression (high/low)																
	Age		Gender		T stage		Tumor size		Lymph node status		Distant metastasis		Tumor differentiation		Tumor stage		Vascular invasion	
Study	≥60	<60	Male	Female	T3–4	T1–2	≥5	<5	Yes	No	M1	M0	Poor	Well	III+ IV	I+ II	Present	Absent
Hongyi Wang	23/37	27/28	27/36	23/29	39/54	11/11	–	–	22/38	28/27	46/51	4/14	12/31	38/34	–	–	–	–
Gwangil Kim	20/64	27/64	28/83	19/45	40/119	7/9	–	–	16/74	31/54	–	–	8/32	39/96	16/74	31/54	–	–
Fu-Tao Zhao	9/10	43/58	47/57	5/11	–	–	31/46	21/22	–	–	–	–	–	–	29/25	30/36	40/35	18/27
Qingying Zhang	24/20	20/15	24/27	20/8	–	–	–	–	35/27	9/8	-	-	17/24	27/11	37/29	7/6	35/27	9/8
Mizuko Tanaka	18/31	65/53	–	–	11/6	72/78	–	–	61/54	22/30	–	–	–	–	18/9	65/75	–	–
Sidse Ehmsen	–	–	–	–	–	–	–	–	14/52	14/68	–	–	–	–	17/77	6/20	–	–
Haiyue Zhao	31/5	79/12	–	–	–	–	38/2	72/15	91/10	19/7	–	–	–	–	77/13	33/4	–	–
Ken Katono	–	–	50/37	32/47	–	–	13/3	69/81	29/14	53/70	–	–	–	–	–	–	42/15	29/60
Fang Ding	85/20	82/21	85/30	82/11	–	–	–	–	–	–	83/30	84/11	25/15	141/26	42/16	106/25	–	–

M = Distant metastasis.

(HR = 0.76, 95%CI:0.43–1.35, P = .355). 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).
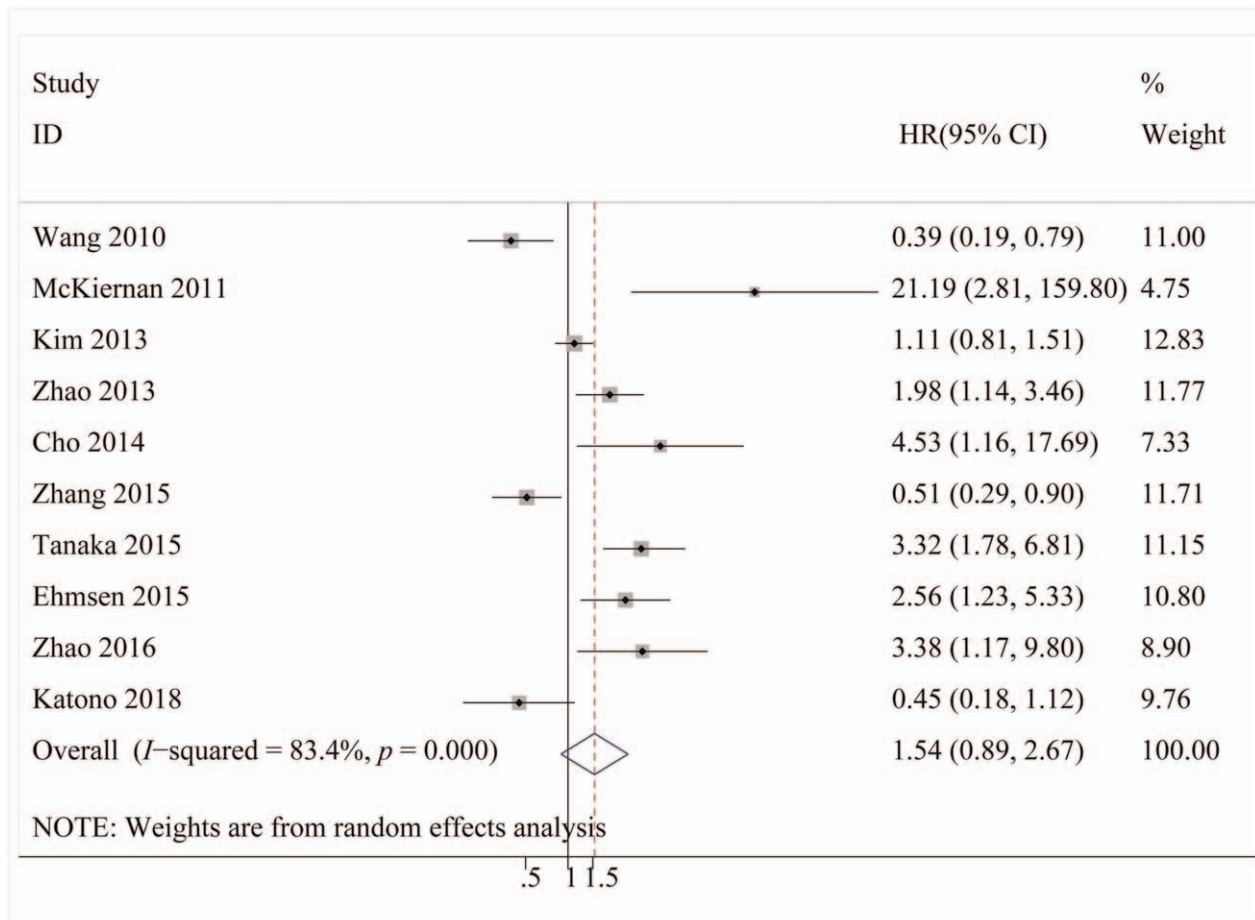

Study ID		HR(95% CI)	% Weight
Wang 2010		0.39 (0.19, 0.79)	11.00
McKiernan 2011		21.19 (2.81, 159.80)	4.75
Kim 2013		1.11 (0.81, 1.51)	12.83
Zhao 2013		1.98 (1.14, 3.46)	11.77
Cho 2014		4.53 (1.16, 17.69)	7.33
Zhang 2015		0.51 (0.29, 0.90)	11.71
Tanaka 2015		3.32 (1.78, 6.81)	11.15
Ehmsen 2015		2.56 (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

.5   1 1.5

Figure 2. Forest plot of the relationship between S100A14 and overall survival.

Table 3

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

Analysis	Numbers of studies	HR (95%CI)	P value	Heterogeneity		
				χ^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						
Multivarate 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.

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 (≥60 vs <60) (OR = 0.78, 95% CI: 0.58–1.55, P = .093), gender (male vs female) (OR = 0.85, 95% CI: 0.48–1.53, P = .590), T stage (T3–4 vs T1–2) (OR = 0.85, 95% CI: 0.36–1.98, P = .705), tumor size (≥5 vs <5) (OR = 2.20, 95% CI: 0.53–9.26, P = .281), lymph node status (yes vs no) (OR = 1.20, 95% CI: 0.66–2.19, P = .552), distant metastasis (M1 vs M0) (OR = 0.98, 95% CI: 0.12–8.21, P = .987), tumor stage (III+ IV vs I+ II) (OR = 0.87, 95% CI: 0. 53–1.43, P = .589), vascular invasion (present vs absent) (OR = 2.36, 95% CI: 0.90–6.20, P = .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

Table 4

Results of the association of S100A14 expression with clinicopathological features.

Clinicopathological parameter	N	OR (95% CI)	P value	Heterogeneity test (Q, I^2, P-value)
Age (≥60 vs <60)	8	0.78 (0.58–1.55)	.093	4.22, 0.648, .0%
Gender (male vs female)	6	0.85 (0.48–1.53)	.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 (≥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 (0.90–6.20)	.082	7.91, 0.019, 74.7%

CI = confidence interval, N = Numbers of studies, OR = odds ratio.
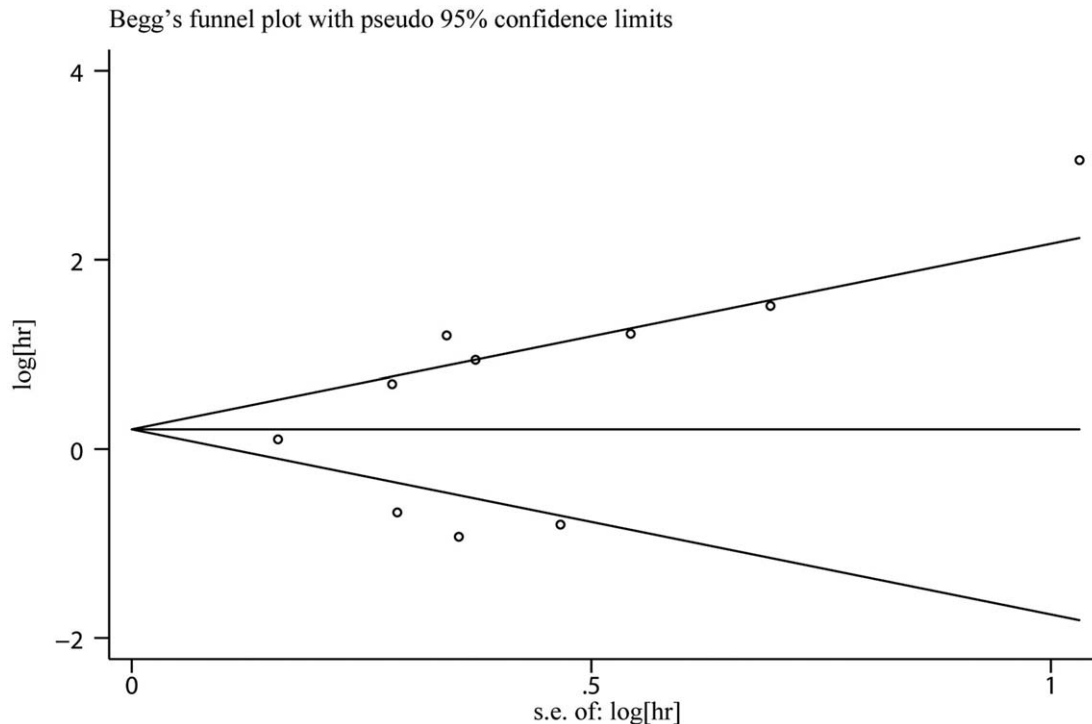
Figure 3. Begg test for publication bias on the relationship between S100A14 and overall survival.

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.

References

[1] Torre LA, Siegel RL, Ward EM, et al. Global cancer incidence and mortality rates and trends–an update. Cancer Epidemiol Biomarkers Prev 2016;25:16–27.

[2] Cui Z, Chen Y, Xiao Z, et al. Long noncoding RNAs as auxiliary biomarkers for gastric cancer screening: a pooled analysis of individual studies. Oncotarget 2016;7:25791–800.

[3] Hernandez JL, Padilla L, Dakhel S, et al. Therapeutic targeting of tumor growth and angiogenesis with a novel anti-S100A4 monoclonal antibody. PLoS One 2013;8:e72480.

[4] Marenholz I, Heizmann CW, Fritz G. S100 proteins in mouse and man: from evolution to function and pathology (including an update of the nomenclature). Biochem Biophys Res Commun 2004;322:1111–22.

[5] Donato R. S100: a multigenic family of calcium-modulated proteins of the EF-hand type with intracellular and extracellular functional roles. Int J Biochem Cell Biol 2001;33:637–68.

[6] Donato R. Functional roles of S100 proteins, calcium-binding proteins of the EF-hand type. Biochim Biophys Acta 1999;1450:191–231.

[7] Salama I, Malone PS, Mihaimeed F, et al. A review of the S100 proteins in cancer. Eur J Surg Oncol 2008;34:357–64.

[8] Jiang H, Hu H, Tong X, et al. Calcium-binding protein S100P and cancer: mechanisms and clinical relevance. J Cancer Res Clin Oncol 2012;138:1–9.

[9] Tirkos S, Newbigging S, Nguyen V, et al. Expression of S100A8 correlates with inflammatory lung disease in congenic mice deficient of the cystic fibrosis transmembrane conductance regulator. Respir Res 2006;7:51.

[10] Leth-Larsen R, Terp MG, Christensen AG, et al. Functional heterogeneity within the CD44 high human breast cancer stem cell-like compartment reveals a gene signature predictive of distant metastasis. Mol Med 2012;18:1109–21.

[11] Chen H, Yu D, Luo A, et al. Functional role of S100A14 genetic variants and their association with esophageal squamous cell carcinoma. Cancer Res 2009;69:3451–7.

[12] Ehmsen S, Hansen LT, Bak M, et al. S100A14 is a novel independent prognostic biomarker in the triple-negative breast cancer subtype. Int J Cancer 2015;137:2093–103.

[13] Wang X, Yang J, Qian J, et al. S100A14 a mediator of epithelial-mesenchymal transition, regulates proliferation, migration and invasion of human cervical cancer cells. Am J Cancer Res 2015;5:1484–95.

[14] Zhu M, Wang H, Cui J, et al. Calcium-binding protein S100A14 induces differentiation and suppresses metastasis in gastric cancer. Cell Death Dis 2017;8:e2938.

[15] Wang HY, Zhang JY, Cui JT, et al. Expression status of S100A14 and S100A4 correlates with metastatic potential and clinical outcome in colorectal cancer after surgery. Oncol Rep 2010;23:45–52.

[16] Zhao FT, Jia ZS, Yang Q, et al. S100A14 promotes the growth and metastasis of hepatocellular carcinoma. Asian Pac J Cancer Prev 2013;14:3831–6.

[17] Cho H, Shin HY, Kim S, et al. The role of S100A14 in epithelial ovarian tumors. Oncotarget 2014;5:3482–96.

[18] Kim G, Chung JY, Jun SY, et al. Loss of S100A14 expression is associated with the progression of adenocarcinomas of the small intestine. Pathobiology 2013;80:95–101.

[19] Katono K, Sato Y, Kobayashi M, et al. Clinicopathological significance of S100A14 expression in lung adenocarcinoma. Oncol Res Treat 2017;40:594–602.

[20] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.

[21] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339: b2700.

[22] Williamson PR, Smith CT, Hutton JL, et al. Aggregate data meta-analysis with time-to-event outcomes. Stat Med 2002;21:3337–51.

[23] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.

[24] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[25] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

[26] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[27] McKiernan E, McDermott EW, Evoy D, et al. The role of S100 genes in breast cancer progression. Tumour BiolV 32 2011;441–50.

[28] Tanaka M, Ichikawa-Tomikawa N, Shishito N, et al. Co-expression of S100A14 and S100A16 correlates with a poor prognosis in human breast cancer and promotes cancer cell invasion. BMC Cancer 2015;15:53.

[29] Zhang Q, Zhu M, Cheng W, et al. Downregulation of 425G>a variant of calcium-binding protein S100A14 associated with poor differentiation and prognosis in gastric cancer. J Cancer Res Clin Oncol 2015;141:691–703.

[30] Zhao H, Guo E, Hu T, et al. KCNN4 and S100A14 act as predictors of recurrence in optimally debulked patients with serous ovarian cancer. Oncotarget 2016;7:43924–38.

[31] Ding F, Wang D, Li XK, et al. Overexpression of S100A14 contributes to malignant progression and predicts poor prognosis of lung adenocarcinoma. Thorac Cancer 2018;9:827–35.

[32] Timulak L. Meta-analysis of qualitative studies: a tool for reviewing qualitative research findings in psychotherapy. Psychother Res 2009;19:591–600.