Original Paper

Prognostic Role of High Stathmin 1 Expression in Patients with Solid Tumors: Evidence from a Meta-Analysis

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Key Words

Stathmin 1 • Prognosis • Solid tumor • Biomarker • Meta-analysis

Abstract

Background/Aims: Several recent studies have demonstrated that Stathmin 1 expression may be closely associated with prognosis in patients with various types of cancers. In the present study, we conducted a meta-analysis of all available studies in the English literature to assess the prognostic value of Stathmin 1 expression in patients with solid cancers. **Methods:** The online databases PubMed, Embase, and Web of Science were searched for literature regarding Stathmin 1 and its association with patient outcomes associated with solid cancers. **Results:** A total of 23 articles including 26 studies that contained 5 335 patients were retrieved and analyzed. Our results indicated that high Stathmin 1 expression yielded a worse overall survival (OS) (hazard ratio [HR] = 2.17, 95% confidence interval [CI]: 1.81–2.60), disease-free survival (DFS) (HR = 2.46, 95% CI: 2.00–3.02), disease-specific survival (DSS) (HR = 1.98, 95% CI: 1.58–2.47) and progression-free survival (PFS)/recurrence-free survival (RFS) (HR = 2.09, 95% CI: 1.51–2.89). Furthermore, the association of high Stathmin 1 expression with poor survival was significant even for sub-group analyses of different tumor types, ethnicities, methods used to calculate HRs, detected methods, and analysis types. **Conclusion:** In summary, this meta-analysis determined that high Stathmin 1 expression is associated with poor prognosis in patients with solid cancers and expression of this protein could be a clinically useful prognostic biomarker.

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Introduction

Based on GLOBOCAN estimates, approximately 14.1 million new cancer cases and 8.2 million cancer-related deaths were reported in 2012 worldwide. The occurrence of cancer is increasing due to population growth and aging, as well as an increasing prevalence of established risk factors such as smoking, obesity, physical inactivity, and changing reproductive patterns associated with urbanization and economic development [1]. Prevention and early detection should be the mainstays of cancer control. Population screenings of asymptomatic

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individuals allows early detection when a cancer is localized and potentially curable, or the detection of precancerous lesions, which can be prevented from developing into invasive cancer [2]. Besides an early diagnosis, optimal therapeutic strategies that are based on the prediction of patient outcome also contribute to the successful management of cancer. Therefore, novel cancer biomarkers with improved sensitivity and specificity are essential for this fatal disease. Recently, the Stathmin 1 has emerged as a potential marker for cancer prognostication.

Stathmin 1, also known as oncoprotein 18 (Op18), p17, p18, p19, 19K, LAP 18, and metablastin, is a ubiquitous, highly conserved 18-kDa cytosolic phosphoprotein [3]. It is encoded by the human *STMN1* gene, which is located at chromosome 1p35-36.1 [4]. Stathmin 1 is composed of 149 amino acids organized into four domains (I–IV) as defined by limited proteolysis. The core region (amino acids 42–126) is the minimum fragment required for tubulin interaction with the additional requirement of either an N- or C-terminal extension. There are four phosphorylation domains, designated as Ser 16, 25, 38, and 63. Of the four phosphorylation sites, only Ser 16 is conserved throughout the Stathmin 1 family [5, 6]. As a major microtubule-destabilizing protein, it interacts directly with soluble tubulin to form a complex that sequesters free tubulin and impedes the polymerization of microtubules, which increases the upregulation of microtubule dynamics [7, 8]. It is involved in various cell functions such as cell cycle regulation, promoting cell proliferation, mobility, metastasis, and resistance to antimicrotubule therapy [7, 9]. Recently, numerous studies have demonstrated that Stathmin 1 is overexpressed in a variety of cancers, including urinary bladder, oral, ovarian, lung, nasopharyngeal, liver, esophageal, colorectal, and breast cancer; it has a positive correlation with nodal involvement, distant metastasis, clinical stage, and a poor prognosis [10–18]. Nevertheless, the reliability and prognostication of Stathmin 1 in solid tumors have not yet been methodically analyzed. Therefore, we conducted a meta-analysis to explore the relationship between Stathmin 1 expression and the prognosis of solid cancers. We hypothesized that high Stathmin 1 expression represents a biomarker of poor survival in patients with solid tumors.

Materials and Methods

Search strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. A systematic search of PubMed, Embase, and Web of Science, for articles published in the English language, was performed by using the following search terms: “stathmin 1 or STMN1 or oncoprotein 18 or Op18 or p17 or p18 or p19 or 19K or LAP 18 or metablastin” (all fields), “cancer or carcinoma or tumor or neoplasm” (all fields), and “prognosis or prognostic or survival or outcome” (all fields). In addition, we also checked the references of all identified studies in order to retrieve unpublished but relevant studies.

Selection criteria

The inclusion criteria to select relevant published studies were as follows: (1) clinical study examining the association of high Stathmin 1 expression and cancer prognostic value; (2) studies that directly reported hazard ratios (HRs) and 95% confidence intervals (CIs), or allowed for their calculation; (3) patient prognostic outcomes, including overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), progression-free survival (PFS), and recurrence-free survival (RFS); and, (4) retrospective or prospective study design. Our exclusion criteria were: (1) publications related to meeting records, letters, review papers, comments, case reports, or clinical guidelines; (2) articles concerning cell lines or animal studies; (3) studies with sample sizes smaller than 40; and, (4) in case duplicate studies were retrieved, all but the study with the largest sample size were excluded.

Quality assessment

The eligible studies included in our meta-analysis were independently assessed by two researchers according to the Newcastle-Ottawa Scale (NOS) guidelines on a rating scale from 0 (lowest) to 9 (highest) [20]. Studies with scores of 6 or more were rated as being of high quality.

Data extraction and conversion

Relevant characteristics and outcome data were extracted from the literature by two independent reviewers. The main data of articles were tabulated as follows: (1) basic characteristics: first author's last name, publication year, country, and ethnicity; (2) clinical data: tumor type, gender, case number, age, treatment, tumor stage, follow-up duration, and detected method; (3) cut-off value and high expression number; and (4) HRs for OS, DFS, DSS, PFS, RFS, as well as their 95% CIs. In cases wherein the study provided the results of univariate and multivariate analyses, we chose the latter. Any disagreement was resolved by discussion among the investigators.

Most of the eligible studies included data pertaining to HRs and 95% CIs. If the HR and 95% CI were not available, we calculated the values by using the original data provided in the paper. If only Kaplan-Meier curves of Stathmin 1 were available, we were able to reconstruct the HRs and 95% CIs from the data extracted from the survival plots. All the calculation methods mentioned above were previously reported by Parmar et al. [21] and Tierney et al. [22]. We also communicated with the corresponding authors of the published studies by email to request any additional data that were required for the meta-analysis.

Statistical analysis

High or positive expression of Stathmin 1 was defined according to the cut-off values provided in the analyzed articles. Pooled HRs and 95% CIs were used to analyze the association between Stathmin 1 expression and the survival of patients with solid tumors. An observed HR >1 implied a poorer prognosis in patients with high Stathmin 1 expression, while HR <1 indicated a better prognosis. We used Cochran's Q test and Higgins I-squared statistic (I^2) for measuring the heterogeneity of the combined HRs. If the P value was less than 0.05 and/or I^2 was larger than 50%, the heterogeneity of the combined HRs was considered statistically significant. A random-effects model (DerSimonian-Laird method) was used. In the absence of heterogeneity among the studies, a fixed-effects model (the Mantel-Haenszel method) was applied. The factors that may have led to heterogeneity were further analyzed by subgroup analysis. Publication bias was assessed using Begg's and Egger's tests. All data analyses were performed with STATA version 12.0 (Stata Corporation, College Station, TX, USA). A P value lower than 0.05 was considered statistically significant on two-sided tests.

Results

Search results

The process of searching and filtering the literature is shown in Fig. 1. A total of 698 records were retrieved in accordance with our search method. Following the screening of the titles, abstracts, publication categories, and full text of each article, only 42 articles qualified for the present analysis. Among these, 19 articles were excluded (9 lacked important data, 4 used continuous or two cut-offs for Stathmin 1 expression, and 6 reported only odds ratios or relative risk estimates). Finally, 23 articles including 26 studies, (because 3 articles included two independent cohort studies, respectively) which involved 5335 patients, were included in the final meta-analysis [10-18, 22-36].

Study characteristics

The characteristics of the studies are presented in Table 1. The 23 included articles were published between 2004 and 2017, and included patients from Sweden, Japan, China, Germany, Taiwan, Norway, Slovenia, and the USA. The category of cancers included oral squamous cell carcinoma (OSCC) (3 studies, 320 patients), ovarian cancer (2 studies, 398 patients), meningioma (2 studies, 191 patients), esophageal squamous cell carcinoma (ESCC) (3 studies, 436 patients), endometrial cancer (3 studies, 1433 patients), breast cancer (4

studies, 1214 patients), urinary bladder cancer (2 studies, 581 patients), non-small cell lung cancer (NSCLC) (1 study, 113 patients), nasopharyngeal carcinoma (NPC) (1 study, 98 patients), medulloblastoma (1 study, 180 patients), hepatocellular carcinoma (HCC) (1 study, 58 patients), gastric adenocarcinoma (1 study, 180 patients), colorectal cancer (CRC) (1 study, 149 patients), and colon cancer (1 study, 105 patients). The ethnicity of the patients was either Asian (35.3%, 1881) or Caucasian (64.7%, 3454). HRs were reported directly in 22 studies and estimated indirectly in the other 4 studies. The Stathmin 1 protein expression was assessed by immunohistochemistry (IHC) in 20 studies and by western blotting in 1 study, with the other 5 reports using quantitative real-time polymerase chain reaction (qRT-PCR) to detect STMN1 mRNA level. There were 18 studies that used multivariate analysis for statistical tests and 3 studies utilized univariate analysis, while the other 5 studies did not report a statistical technique. The cut-off values used in each study varied.

Fig. 1. Flow diagram of the patient selection process for this study.

Quality assessment

According to the Newcastle-Ottawa scale, we assessed the quality of the 26 eligible studies included in our meta-analysis. The quality scores of the studies varied from 4 to 9, with a mean score of 6. A higher score was indicative of a better methodology. All 26 studies were included in the subsequent analysis.

Meta-analysis of OS

The main results of this meta-analysis are shown in Table 2. Fourteen studies, which included 1855 patients, were analyzed in the current meta-analysis to assess the prognostic value of highly-expressed Stathmin 1 in solid tumors. As the studies evaluating OS were not of obvious statistical heterogeneity ($I^2 = 18.7\%$, $P = 0.249$), we used a fixed-effects model to pool the HRs. As shown in Fig. 2A, the pooled analysis demonstrated that high Stathmin 1 expression was significantly associated with unfavorable OS (HR = 2.17, 95% CI: 1.81–2.60, $P < 0.001$).

In the tumor type subgroup, as only one study analyzed OS for meningioma, endometrial cancer, breast cancer, NPC, medulloblastoma, CRC, and colon cancer, respectively, we combined them with the analysis of other cancers. High Stathmin 1 expression was associated with poorer OS for OSCC (HR = 2.47, 95% CI: 1.29–4.75, $P = 0.007$), ovarian cancer (HR = 3.12, 95% CI: 1.84–5.28, $P < 0.001$), ESCC (HR = 2.36, 95% CI: 1.51–3.67, $P < 0.001$), and other cancers (HR = 1.96, 95% CI: 1.56–2.46, $P < 0.001$) (Fig. 3A). Meanwhile, Stathmin 1 expression was significantly associated with worse OS in Caucasian patients (HR = 1.83, 95% CI: 1.42–2.35, $P < 0.001$) and Asian patients (HR = 2.61, 95% CI: 2.01–3.39, $P < 0.001$). High Stathmin 1 expression remained significantly associated with poor OS on subgroup analysis as well: HRs reported directly in text (HR = 2.10, 95% CI: 1.73–2.54, $P < 0.001$), HRs

Table 1. Main characteristics of all studies included in the meta-analysis. NR: not report; IHC: immunohistochemistry; DSS: disease-specific survival; OSCC: oral squamous cell carcinoma; OS: overall survival; DFS: disease-free survival; SC: survival curve; qRT-PCR: quantitative real-time polymerase chain reaction; PFS: progression-free survival; NSCLC: non-small cell lung cancer; NPC: nasopharyngeal carcinoma; HCC: hepatocellular carcinoma; ESCC: esophageal squamous cell carcinoma; RFS: recurrence-free survival; mix: mixed treatment including chemotherapy, hormonal therapy, surgery, radiotherapy; CRC: colorectal cancer

Study	Country	Ethnicity	Tumor type	Sample/female	Age (years)	Treatment	Tumor stage	Follow-up (months)	High expression n (%)	Detected method	Cut-off value	Survival analysis	Multivariate analysis	HR
Herndin [10] 2014	Sweden	Caucasian	urinary bladder cancer	cohort I: 134/83 cohort II: 123/93	cohort I: 72years: 51.2% cohort II: >65years: 59.0%	surgery	cohort I: T1a: 115 T1b: 115 T2: 4 cohort II: T1: 13 T2: 100 T3: 108 T4: 28	cohort I: mean 54.2; range 1–223 cohort II: mean 48.5; range 1–126	NR	IHC	score category=2	DSS	yes	report
Harada [11] 2017	Japan	Asian	OSCC	49/19	median 69; range 36–83	chemotherapy+surgery	L5 IL25 III: 12 IV: 7	NR	17(94.7)	IHC	score=57.2	OS	yes	report
Ma [23] 2016	China	Asian	OSCC	109/38	>60years: 52.3%	chemotherapy	I: IL63 II: IL46	NR	55(50.5)	IHC	values>150	OS	yes	report
Kozu [24] 2006	Japan	Asian	OSCC	81/33	>70years: 40.7%	surgery	I: IL63 II: IL39	median 30.3; range 3–60	53(65.4)	IHC	score=86.16	OS, DFS	NR	SC
Su [12] 2009	USA	Caucasian	ovarian cancer	178/178	median 57.4; range 26–82	surgery+chemotherapy	I: IL33 II: IL20 III: 13	NR	59(33.1)	qRT-PCR	Median	OS, PFS	NR	report
Wei [25] 2008	China	Asian	ovarian cancer	42/42	median 35.6; range 24–45	surgery+chemotherapy	I: IL6 IL22 III: 4	NR	22(52.4)	qRT-PCR	median	OS	NR	SC
Nie [13] 2015	China	Asian	NSCLC	113/41	median 55	surgery	I: IL: 74 III: 39	median 43.4; range 8.4–88.2	52(46.0)	IHC	score>3	DSS	yes	report
Cheng [14] 2008	China	Asian	NPC	98/32	>50years: 30.6%	radiotherapy	II: 10 III: 53 IV: 35	mean 48.1; range 6–72	29(29.6)	IHC	score 5–6	OS	no	report
Wang [26] 2017	China	Asian	meningioma	73/42	mean 49.9 ± 14.7	surgery	WHO grade I–41 WHO grade II: 23 WHO grade III: 9	NR	NR	qRT-PCR	score=2.97	DFS	yes	Report
Liu [27] 2017	China	Asian	meningioma	59/26	mean 55.8 ± 13.2	surgery+radiotherapy	WHO grade II: 59	NR	NR	qRT-PCR	NR	OS, DFS	yes	report
Neben [28] 2004	Germany	Caucasian	medulloblastoma	180/62	>16years: 32.2%	surgery+chemotherapy	NR	median 34; range 3–130	82(45.6)	IHC	immunostaining>10%	OS	yes	report
Hsieh [15] 2010	Taiwan	Asian	HCC	58/18	>60years: 46.6%	surgery	T1: 138 T2: 5 T3: 14 T4: 1	mean 41; range 2–96	43(74.1)	qRT-PCR	threefold or more	DFS	yes	report
Yoshida [29] 2010	Japan	Asian	gastric adenocarcinoma	59/21	mean 62; range 40–87	surgery	I: IL42 II: IL17	median 36; range 4–46	30(50.8)	IHC	score 2–3	DFS	NR	SC
Akhtar [16] 2014	China	Asian	ESCC	174/40	mean 59.8	surgery	T1: 12 T2: 70 T3: 92	mean 48.4 ± 1.3	100(57.5)	IHC	IHS ≥ 4	RFS	yes	report
Alkhatir [30] 2014	China	Asian	ESCC	162/36	mean 59.8	surgery	T2: 70 T3: 92	mean 48.4 ± 1.3	94(58.0)	IHC	IHS ≥ 4	OS	yes	report
Wang [31] 2014	China	Asian	ESCC	100/46	mean 64	surgery	I: IL39 II: IL61	NR	73(73.0)	IHC	score>3	OS	yes	report
Reyes [32] 2017	USA	Caucasian	endometrial cancer	69/69	high stathmin: mean 60.83; low stathmin: mean 62.45 ± 10.25	NR	I: 14 I: 226 I: 327 N/A: 2	NR	7(10.1)	IHC	H-score=50	OS, PFS	NR	SC
Trovik [33] 2011	Norway	Caucasian	endometrial cancer	1076/1076	mean 66; range 28–94	mix	I: 784 II: 105 III: 136 IV: 51	mean 30; range 0–90	curettage specimens: 302(36.9) hysterectomy specimens: 84(17.6)	IHC	upper quartile	DSS	yes	report
Zhong [17] 2010	China	Asian	CRC	149/53	>50years: 71.7%	NR	I: IL: 73 II: IL: 69	NR	48(32.2)	IHC	score=8	OS	yes	report
Zhang [34] 2016	China	Asian	colon cancer	105/36	median 53.8; range 22–79	surgery+chemotherapy	I: IL: 35 II: IL: 70	NR	66(62.9)	IHC	point=2	OS	yes	report
Kuang [18] 2015	China	Asian	breast cancer	training set: 204/204 validation set: 106/106	training set: median 51; range 29–84 validation set: median 55; range 34–85	surgery+chemotherapy	training set: I: IL: 9 II: IL: 7 III: 37 N/A: 1 validation set: I: IL: 3 II: IL: 26 N/A: 1	training set: median 102; range 0–144 validation set: median 79; range 2–	145(46.8)	IHC	score=0	DFS	no	report
Baquero [35] 2012	USA	Caucasian	breast cancer	474/474	NR	surgery	NR	NR	276(58.2)	western blotting	AQUA score=25	OS	yes	report
Golouh [36] 2008	Slovenia	Caucasian	breast cancer	215/215	median 67.9; range 36–83	surgery+hormonal therapy	G1: 24 G2: 105 G3: 85 unknown: 1	median 84; range 5–133	89(41.4)	IHC	staining intensity≥3	DFS, DSS	yes	report

Table 2. Pooled hazard ratios for OS according to subgroup analyses. OS: overall survival; HR: hazard ratio; CI: confidence intervals; OSCC: oral squamous cell carcinoma; ESCC: esophageal squamous cell carcinoma; IHC: immunohistochemistry; qRT-PCR: quantitative real-time polymerase chain reaction; NR: not report. * indicates that the difference was statistically significant

Variables	Studies	Patients	HR (95% CI)	P value	Model	Heterogeneity I ²	P
All	14	1855	2.17 (1.81, 2.60)	<0.001*	fixed	18.7%	0.249
Tumor type							
OSCC	3	239	2.47 (1.29, 4.75)	0.007*	fixed	23.0%	0.273
Ovarian cancer	2	220	3.12 (1.84, 5.28)	<0.001*	fixed	0.0%	0.404
ESCC	2	262	2.36 (1.51, 3.67)	<0.001*	fixed	0.0%	0.808
Other cancers	7	1134	1.96 (1.56, 2.46)	<0.001*	fixed	38.5%	0.135
Ethnicity							
Caucasian	4	901	1.83 (1.42, 2.35)	<0.001*	fixed	45.6%	0.138
Asian	10	954	2.61 (2.01, 3.39)	<0.001*	fixed	0.0%	0.655
HR obtain method							
Reported in text	11	1663	2.10 (1.73, 2.54)	<0.001*	fixed	17.8%	0.275
Data extrapolated	3	192	2.97 (1.67, 5.31)	<0.001*	fixed	22.5%	0.275
Detected method							
IHC	10	1102	2.26 (1.78, 2.88)	<0.001*	fixed	8.5%	0.364
qRT-PCR	3	279	2.97 (1.95, 4.52)	<0.001*	fixed	0.0%	0.676
western blotting	1	474	1.57 (1.09, 2.25)	0.015*	-	-	-
Analysis type							
Multivariate	9	1387	1.95 (1.59, 2.40)	<0.001*	fixed	0.0%	0.509
Univariate	1	98	5.88 (2.38, 20.00)	<0.001*	-	-	-
NR	4	370	2.87 (1.90, 4.35)	<0.001*	fixed	0.0%	0.456

Fig. 2. Forest plots of studies evaluating the hazard ratios of high Stathmin 1 expression in solid cancers for (A) OS, (B) DFS, (C) DSS, and (D) PFS/RFS.

estimated indirectly by data extrapolated (HR = 2.97, 95% CI: 1.67–5.31, $P < 0.001$); IHC for Stathmin 1 protein (HR = 2.26, 95% CI: 1.78–2.88, $P < 0.001$), qRT-PCR for STMN1 mRNA (HR = 2.97, 95% CI: 1.95–4.52, $P < 0.001$); multivariate analysis (HR = 1.95, 95% CI: 1.59–2.40, $P < 0.001$), and analysis type not reported (HR = 2.87, 95% CI: 1.90–4.35, $P < 0.001$).

Meta-analysis of DFS

Eight studies that included 855 patients provided suitable data for DFS analysis. The main results are listed in Table 3. In the absence of heterogeneity among the studies ($I^2 = 0.0\%$, $P = 0.612$), we also used a fixed-effects model to pool the HRs. The pooled analysis demonstrated that high Stathmin 1 expression was significantly associated with worse DFS (HR = 2.46, 95% CI: 2.00–3.02, $P < 0.001$) (Fig. 2B). The negative effect of high Stathmin 1 expression on DFS was verified in the tumor type subgroup with breast cancer (HR = 2.27, 95% CI: 1.55–3.31, $P < 0.001$), meningioma (HR = 2.53, 95% CI: 1.94–3.31, $P < 0.001$), and other cancers (including OSCC, HCC, and gastric adenocarcinoma) (HR = 2.59, 95% CI: 1.43–4.70, $P = 0.002$) (Fig. 3B). In addition, differences were significant in other subgroup analyses: Asian patients (HR = 2.45; 95% CI: 1.97–3.04; $P < 0.001$); HRs reported directly in article text (HR = 2.50, 95% CI: 2.02–3.09, $P < 0.001$); IHC for Stathmin 1 protein (HR = 2.21, 95% CI: 1.57–3.10, $P < 0.001$), qRT-PCR for STMN1 mRNA (HR = 2.61, 95% CI: 2.02–3.38, $P < 0.001$); multivariate analysis (HR = 2.60, 95% CI: 2.06–3.30, $P < 0.001$), and univariate analysis (HR = 2.09, 95% CI: 1.28–3.42, $P = 0.003$). However, subgroup analysis did not show a significant difference in HRs estimated indirectly by data extrapolated (HR = 1.97, 95% CI: 0.92–4.25, $P = 0.083$) or analysis type not reported (HR = 1.97, 95% CI: 0.92–4.25, $P = 0.083$).

Meta-analysis of DSS

Six studies that included 2204 patients were included in this part of the meta-analysis. High Stathmin 1 expression yielded a worse DSS ($I^2 = 0.0\%$, $P = 0.573$, fixed-effects model; HR = 1.98, 95% CI: 1.58–2.47, $P < 0.001$) (Fig. 2C). In addition, Stathmin 1 was significantly associated with worse DSS in endometrial cancer (HR = 1.68, 95% CI: 1.18–2.39, $P = 0.004$), urinary bladder cancer (HR = 1.88, 95% CI: 1.27–2.79, $P = 0.002$), and other cancers (included

Table 3. Pooled hazard ratios for DFS according to subgroup analyses. DFS: disease-free survival; HR: hazard ratio; CI: confidence intervals; IHC: immunohistochemistry; qRT-PCR: quantitative real-time polymerase chain reaction; NR: not report. * indicates that the difference was statistically significant

Variables	Studies	Patients	HR (95% CI)	P value	Model	Heterogeneity I^2	P
All	8	855	2.46 (2.00, 3.02)	<0.001*	fixed	0.0%	0.612
Tumor type							
Breast cancer	3	525	2.27 (1.55, 3.31)	<0.001*	fixed	0.0%	0.649
Meningioma	2	132	2.53 (1.94, 3.31)	<0.001*	fixed	39.4%	0.199
Other cancers	3	198	2.59 (1.43, 4.70)	0.002*	fixed	23.9%	0.269
Ethnicity							
Caucasian	1	215	2.55 (1.41, 4.61)	0.002*	-	-	-
Asian	7	640	2.45 (1.97, 3.04)	<0.001*	fixed	0.0%	0.496
HR obtain method							
Reported in text	6	715	2.50 (2.02, 3.09)	<0.001*	fixed	0.0%	0.601
Data extrapolated	2	140	1.97 (0.92, 4.25)	0.083	fixed	28.8%	0.236
Detected method							
IHC	5	665	2.21 (1.57, 3.10)	<0.001*	fixed	0.0%	0.668
qRT-PCR	3	190	2.61 (2.02, 3.38)	<0.001*	fixed	17.2%	0.299
Analysis type							
Multivariate	4	405	2.60 (2.06, 3.30)	<0.001*	fixed	0.0%	0.49
Univariate	2	310	2.09 (1.28, 3.42)	0.003*	fixed	0.0%	0.435
NR	2	140	1.97 (0.92, 4.25)	0.083	fixed	28.8%	0.236

Fig. 3. Forest plot of the relationship between high Stathmin 1 expression and (A) OS, (B) DFS, and (C) DSS, in patients with various types of cancers.

breast cancer and NSCLC) (HR = 2.65, 95% CI: 1.74–4.03, $P < 0.001$) (Fig. 3C), and other subgroup analyses.

Meta-analysis of PFS/RFS

Considering the similarities between RFS and PFS, we merged them together to conduct this analysis. Three studies that included 421 patients revealed a significant positive association between high Stathmin 1 expression and poor PFS/RFS ($I^2 = 0.0\%$, $P = 0.778$, fixed-effects model; HR = 2.09, 95% CI: 1.51–2.89, $P < 0.001$) (Fig. 2D). Likewise, a similar result was found in different subgroups.

Sensitivity analysis

The sensitivity analysis was conducted to assess the consistency of the above results and performed by sequential omission of each individual study by using the “metaninf” STATA command. There was no significant change in the pooled HRs suggesting that our results were robust (data not shown).

Publication bias

We conducted a publication bias evaluation for the studies in terms of OS and DFS (Fig. 4A and 4B). The Begg’s funnel plot, which provides a visual assessment of the included studies and identifies any overt publication bias, was found to be symmetrical. An Egger’s test, which was applied for the formal evaluation of the studies, confirmed the absence of any significant publication bias ($P > 0.1$).

Fig. 4. Funnel plots of publication bias regarding the relationships between high Stathmin 1 expression and (A) OS and (B) DFS, inpatients with solid cancer types.

Discussion

Stathmin 1 is a microtubule-regulating protein that has an important role in the assembly and disassembly of the mitotic spindle [37]. At the molecular level, Stathmin 1 depolymerizes microtubules by either sequestering free tubulin dimers or directly inducing microtubule-catastrophe [31]. As mentioned before, Stathmin 1 is encoded by the human STMN1 gene, which has 4 serine phosphorylation sites. Phosphorylation at either Ser16 or Ser63 strongly reduces or abolishes the ability of STMN1 to bind to and sequester soluble tubulin [38]. STMN1 Ser16 can be phosphorylated by protein kinase C (PKC), PAK1, or Ca^{2+} /calmodulin-dependent kinase II/IV [39, 40], whereas Ser25 and Ser38 are targeted by mitogen-activated protein kinases (MAPKs) and cyclin-dependent kinases (CDKs) [41]. Overexpression of STMN1 in human cancer not only disrupts normal cell-cycle progression but, more importantly, facilitates polyploidy/aneuploidy of the targeted cells [15]. Stathmin 1 has been implicated in both G1-S and G2-M checkpoint control of cell-cycle progression by influencing the dynamics of microtubule formation and progression of the cell cycle [30]. Kang et al. [42] found that aberrant p53 immunoreactivity was associated with higher STMN1 expression in gastric adenocarcinoma, suggesting that overexpression of STMN1 might be partially due to inactivation of tumor-suppressor gene p53. Batsaikhan et al. [29] also demonstrated that activation-induced cytidine deaminase (AID) could be one of the activators of Stathmin 1 protein expression in gastric adenocarcinoma. P27 and STMN1 correlation was related either directly or by some other pathway. Matsumoto et al. [43] reported that aberrant AID reduces the copy number of CDKs inhibitors such as CDKN2A and CDKN2B, which are tumor suppressive genes and negatively controlled CDKs. AID could be an activator of the STMN1 protein via the AID/CDKN2A/CDKs/STMN1 pathway.

Recently, it was reported that high expression of Stathmin 1 was associated with poor tumor differentiation, large tumor size, advanced N stage, TNM clinical classification, tumor invasion, and distant metastasis in various human malignancies. In addition, it also demonstrated that inhibition of STMN1 expression can enhance the sensitivity of antimicrotubule chemotherapy drugs. Paclitaxel and vinblastine are the most effective chemotherapeutic agents against various cancers. Paclitaxel is a common cytotoxic agent that accelerates microtubule assembly from tubulin and blocks microtubule depolymerization, which leads to cell mitosis stagnation in the G2/M phase, and ultimately apoptosis. Vinblastine affects micro-tubule protein polymerization and stops mitosis. Although the two mechanisms of drug action are different, they both affect the dynamic balance of microtubules. Alli et al. [9] reported that overexpression of Stathmin 1 has been shown to decrease polymerization

of microtubules and markedly decrease the binding of, and sensitivity to, paclitaxel, but not affect the sensitivity to chemotherapeutic drugs that do not target microtubules in human breast cancer. Harada et al. [11] also demonstrated that high expression of Stathmin 1 might have poor therapeutic effects in OSCC treated with docetaxel-containing regimens. Meanwhile, a previous study reported that there was an increased STMN1 expression in the resistant A549 cell line [44], and the expression level of STMN1 was negatively correlated with the efficacy of vinorelbine plus cisplatin/carboplatin therapy in late NSCLC [45]. In addition, Rosell et al. [46] found that STMN1 levels could influence the time to progression of vinorelbine/cisplatin-treated patients. In addition, similar outcomes are also found in patients who treated with vinblastine [26]. It was speculated that STMN1 is critical in the anti-paclitaxel mechanism that blocks microtubule polymerization and reduces its binding to paclitaxel. It was also reported that the transcription factor forkhead box protein M1 (FOXM1) mediates resistance to docetaxel in gastric cancer via up-regulating Stathmin 1 [47]. Moreover, Stathmin 1 has stronger potential as a therapeutic target [10].

Our study provides a systematic analysis of the role of Stathmin 1 expression as a prognostic factor for solid tumors. We identified that high Stathmin 1 expression was associated with shorter OS, DFS, DSS and PFS/RFS, regardless of tumor type, ethnicity, method used to calculate HRs, detected method, and analysis type, except for HRs estimated indirectly by data extrapolated ($P = 0.083$), as well as analysis type not reported ($P = 0.083$). Actually, these were the same 2 studies analyzed in different subgroups. Considering the lower sample size of the only subgroup with different results (140 patients), we can ignore this inconsistent result to some extent.

However, this meta-analysis has several limitations. First, although 23 articles from 26 studies were included in this meta-analysis, the sample size (5335 patients) was relatively small. Second, we only considered studies that calculated, or allowed for the calculation of, HRs and 95% CIs. Other studies that provided odds ratios and relative risk estimates for survival were excluded. In addition, several HRs were calculated based on data extracted from the survival curve, bringing minor deviations. Third, due to the lack of a unified cut-off value in Stathmin 1 expression, different cut-off values were used in those studies. The inaccurate cut-off values may affect the availability of Stathmin 1 as a predictive biomarker in cancer prognosis. In view of this situation, a unified measuring method and cut-off value needs to be established. Fourth, although meta-analysis is now a widely used technique for summarizing evidence from multiple studies, it has its own limitations. All meta-analyses are affected by the quality of the included studies, and by the possibility of publication bias. Finally, owing to the lack of sufficient data, we could not explore the association between Stathmin 1 and other clinical parameters.

Conclusion

This meta-analysis demonstrated that high Stathmin 1 expression is associated with poor prognosis among study patients with solid tumors. Stathmin 1 could be used to substantially improve prognosis estimation and treatment decision-making. However, due to the limitation of the present analysis, this conclusion should be regarded cautiously. There is a need for further studies designed adequately with multicenter and larger sample size study designs to confirm our findings, as well as to explore more effective therapeutic strategies.

Disclosure Statement

The authors declare that no conflicts of interest exist.

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