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REVIEW

High Tiam1 expression predicts positive lymphatic metastasis and worse survival in patients with malignant solid tumors: a systematic review and meta-analysis

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Background: Many studies have explored the prognostic value of T-cell lymphoma invasion and metastasis inducing factor 1 (Tiam1) and its association with lymphatic metastasis in malignant solid tumors, but the conclusions remain controversial. Therefore, we performed a meta-analysis to systematically assess the prognostic value of Tiam1 expression and its association with lymphatic metastasis in malignant solid tumors.

Methods: We searched eligible studies in PubMed, Web of Science and EMBASE databases (from inception up to October 2018). The combined HR with 95% CI was used to estimate the prognostic value of Tiam1 expression. The correlation between Tiam1 expression and lymphatic metastasis was assessed using the combined odds ratio (OR) with 95% CI.

Results: A total of 17 studies with 2,228 patients with solid tumors were included in this meta-analysis. The overall estimated results showed that high Tiam1 expression was significantly associated with shorter overall survival (HR= 2.08, 95% CI: 1.62–2.68, $P<0.01$), and disease-free survival (HR = 1.86, 95% CI: 1.49–2.32, $P<0.01$). Besides, we also found that there was a close relationship between high Tiam1 expression and positive lymphatic metastasis (OR=2.63; 95% CI: 1.79–3.84, $P<0.01$).

Conclusion: High Tiam1 expression was significantly associated with shorter survival and positive lymphatic metastasis in patients with malignant solid tumors. Therefore, Tiam1 may be a promising prognostic biomarker and an effective therapeutic target for malignant solid tumors.

Keywords: tumor, Tiam1, survival, meta-analysis

Introduction

Cancer has become a leading cause of death and major public health problem worldwide due to its high incidence and mortality1 Although the methods of diagnosis and treatment of cancers have been greatly improved in recent years, long-term survival in some types of cancers remains unsatisfied as a whole1 Tumor biomarkers have values of early detection, prognosis evaluation and drug discovery of cancers, so as to identify specific biomarkers have been attracting many researchers.[2] A great plenty of tumor biomarkers have been discovered in recent years, but only a handful of biomarkers could be applied for clinical practice.[3] Accordingly, it remains imperative to explore novel sensitive biomarkers that exhibit excellent performances in predicting prognosis in cancers.

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T-cell lymphoma invasion and metastasis-inducing factor 1 (Tiam1), a specific guanine nucleotide exchange factor, a member of the Rho GTPase family, was first discovered by Habets et al and identified as an invasion and metastasis-related gene in mice with aggressive T-cell lymphoma.[4,5] The *TIAM1* gene is located in the q22 band of chromosome 21 and the centromeric end of the *AML* 21 gene and contains 2 exons (~7.3 kb) separated by 1 intron (14 kb)[6] Tiam1 is mainly expressed in normal brain and testis tissues with only minimal or no expressions detected in other normal tissues[7] Additionally, Tiam1 is highly expressed in various cancers as well,[6,8–23] and its overexpression in cancer cells could contribute to proliferation,[24–27] invasion and metastasis,[28–31] angiogenesis[32] and chemo-resistance of cancer cells[33] Of note, Tiam1 expressed in tumor stromal microenvironment also plays a role in regulating tumor invasion, metastasis and chemo-resistance. Cancer-associated fibroblast (CAF) is a major stromal cell in cancer stromal microenvironment.[34,35] A recent study by Izumi et al[33] showed that CAFs isolated from colorectal cancer (CRC) tissues could induce chemo-resistance of CRC cells when the two kinds of cells were co-cultured, but surprisingly the direct inhibition of Tiam1 in CAFs could result in enhanced chemo-sensitivity of CRC cells[33] Considering the multiple functions of Tiam1 in cancer progression, many researchers focused on exploring the prognostic value of Tiam1. However, the conclusions about the prognostic value of Tiam1 in malignant solid tumors remain controversial. Most of studies suggested that high Tiam1 expression was related to shorter survival in many tumors, including hepatocellular carcinoma, pancreatic cancer, gallbladder cancer, prostate cancer, ovarian cancer and breast cancer. On the contrast, a few of studies indicated that low Tiam1 expression was associated with poor prognosis in patients with gastric cancer[18] and papillary thyroid cancer[12] Considering that most of the single-center studies had the limitations of sample size and methodology, we herein performed a meta-analysis to systematically evaluate the prognostic significance of Tiam1 expression in patients with solid tumor. In addition, *Tiam1* is an invasion and metastasis-related gene, so in this meta-analysis, we also performed a pooling analysis to assess the association between Tiam1 expression and lymphatic metastasis.

Materials and methods

This systematic review and meta-analysis were performed according to PRISMA statement issued in 2009[36] Besides, this study was approved by Ethics Committee of Qinghai province people's Hospital.

Literature search strategy

We searched eligible studies in PubMed, Web of Science and EMBASE databases (from inception up to October 2018). The search terms included "cancer," "tumor," "carcinoma," "adenocarcinoma," "neoplasm," "malignant," "malignancy," "Tiam1," "T lymphoma invasion and metastasis 1" "T-cell lymphoma invasion and metastasis inducing factor 1", "survival," "prognosis," and "prognostic." The search strategy used in PubMed was as follows: (((((((((cancer[Title/Abstract]) OR tumor[Title/Abstract]) OR carcinoma[Title/Abstract]) OR adenocarcinoma[Title/Abstract]) OR neoplasm[Title/Abstract]) OR malignant[Title/Abstract]) OR malignancy [Title/Abstract])) AND (((Tiam1[Title/Abstract]) OR (T lymphoma invasion[Title/Abstract] AND metastasis 1[Title/Abstract])) OR (T-cell lymphoma invasion[Title/Abstract] AND metastasis inducing factor 1[Title/Abstract]))) AND (((survival[Title/Abstract]) OR prognosis[Title/Abstract]) OR prognostic[Title/Abstract]). Additionally, we also manually searched eligible studies from the references of the identified articles.

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) the prognostic value of Tiam1 expression in malignant solid tumor in terms of overall survival (OS), recurrence-free survival (RFS) or disease-free survival (DFS) was explored; 2) the Tiam1 expression was divided into high/positive and low/negative groups; 3) HRs and 95% CIs, which were used to estimate the prognostic value of Tiam1 expression, were reported directly or could be calculated from the Kaplan–Meier curves; 4) the studies were published in English; 5) the studies were published in full text and 6) the study was the most informative report, if the same patient population was enrolled into different studies.

The exclusion criteria were as follows: 1) the studies were duplicated publications, reviews, case reports, conference abstracts, editorials or case reports; 2) the studies were only involved in animal and cell experiments and 3) HRs and CIs could not be extracted.

Data extraction and quality assessment

Two independent authors (Caixia Yang and Chenlin Ma) extracted the information from the included literature using a predefined template based on the reporting checklists of PRISMA[36] The following items were extracted: tumor type, the first author's last name, country, publication year, country, sample number, age, gender,

antibody source detection methods, definition of high Tiam1 expression, T stage, TMN stage, distant metastasis, lymph node metastasis, survival outcomes, and HR and its corresponding 95% CI. Software Engauge Digitizer 4.1 (https://markummitchell.github.io/engauge-digitizer/) was used to extract HR and its corresponding 95% CI from Kaplan–Meier curve, if HR and its corresponding 95% CI was not directly reported. The methodological quality of included studies was evaluated using the Newcastle Ottawa scale,[37] in which the quality score ranges from 0 to 9. Usually, a study with 6 or more scores is considered to be methodologically sound. With respect to data extraction and quality assessment, any inconsistencies were removed by discussion among all authors.

Statistical analysis

HR with its corresponding 95% CI was used to estimate the prognostic value of Tiam1 expression in patients with malignant solid tumors. HR >1 (low expression as reference) suggested that patients with high Tiam1 expression had shorter survival than those with low expression. The correlation between Tiam1 expression and lymphatic metastasis was assessed using the combined OR with 95% CI, and OR >1 (low expression as reference) indicated that high Tiam1 expression was closely associated with positive lymphatic metastasis. Heterogeneity among the included studies was assessed using Higgin's I^2 statistic. I^2>50% signified statistically significant heterogeneity. A fixed-effects or random-effects model was applied to evaluate the prognostic value of Tiam1 expression and its association with lymphatic metastasis. A fixed-effects model was chosen when there was no obvious heterogeneity among studies[38] Otherwise, a random-effects model was used. Begg's test[39] and Egger's test[40] were employed to assess the publication bias. Subgroup analysis and meta-regression analysis were performed according to sample size, tumor type, antibody source and quality score to explore the sources of heterogeneity. Sensitivity analysis was conducted by sequentially omitting one study to explore the robustness and reliability of the overall estimated results. All statistical processes were fulfilled using STATA, version 12.0 (Stata Corporation, College Station, TX, USA). All statistical tests were 2-sided, and P p<0.05 was considered as the statistical significance.

Results

Literature selection

The flowchart of literature search and selection is shown in Figure 1. A total of 161 publications were

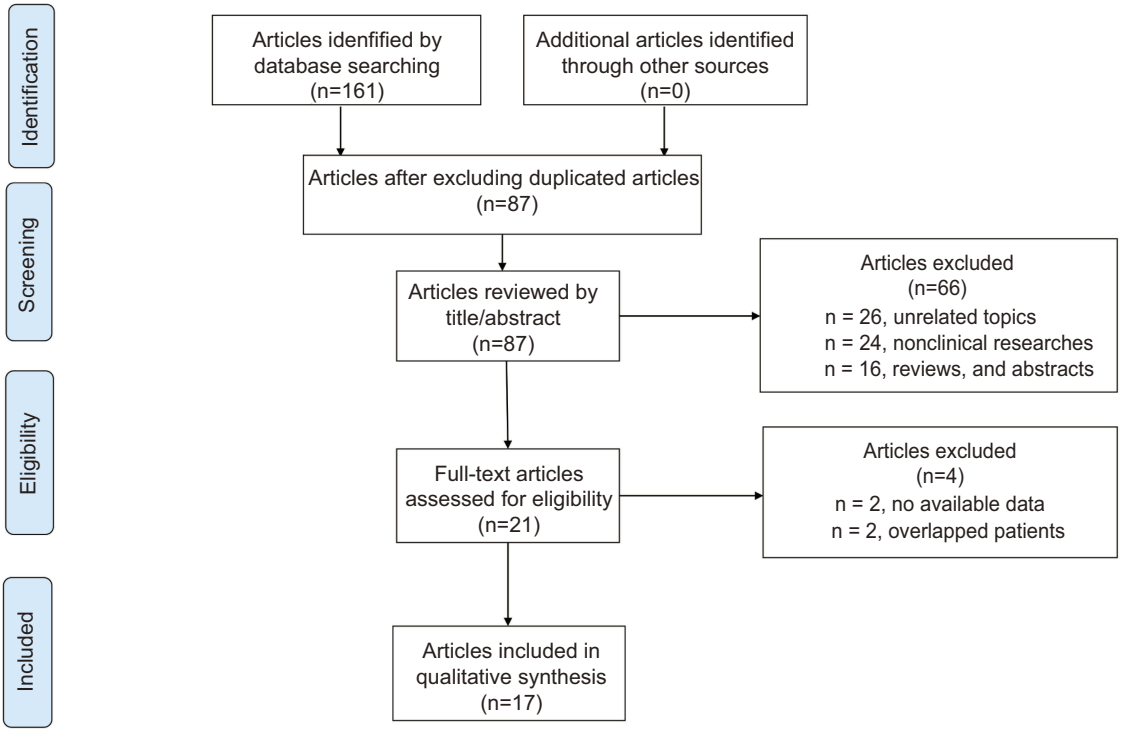

Figure 1 Flow diagram of selecting eligible studies.

retrieved from electronic databases. Further, 74 publications were excluded due to duplicates. Then, the remaining publications were reviewed by the title and abstract, in which 66 publications were excluded owing to unrelated topics, nonclinical studies, reviews and conference abstracts. Next, 4 publications were further excluded after full-text reviewing for lacking available data and enrolling overlapped patients. Finally, a total of 17 studies were included in our meta-analysis.[6,8–23]

Basic characteristics of included studies

A total of 17 studies enrolling 2,228 patients with malignant solid tumors were included in this meta-analysis. The included studies were published from 2006 to 2018. A total of 16 studies assessed the prognostic value of Tiam1 for OS[6,8–10,12–23] and 6 studies for DFS.[11,14,16,19,21,22] Besides, 15 studies reported the association between Tiam1 expression and lymph node metastasis.[6,8–10,12–15,17–23] All the included studies detected the Tiam1 expression in protein level. More details about the main characteristics of the included studies were presented in Tables 1 and 2.

Pooling analysis

A total of 16 studies with 2,168 patients explored the correlation between Tiam1 expression and OS. The random-effects model was employed to pool HRs and their 95% CIs due to the significant heterogeneity among these studies (I^2=68.2%, p<0.01). The result showed that patients with high Tiam1 expression had shorter OS than those with low expression (HR=2.08, 95% CI: 1.62–2.68, p<0.01; Figure 2). Six studies with 845 patients reported the relationship between Tiam1 expression and DFS. Because of no significant heterogeneity (I^2=48.2%, p=0.08), the fixed effect model was used to pooling data. The result showed that patients with high Tiam1 expression also had shorter OS than those with low expression (HR=1.86, 95% CI: 1.49–2.32, p<0.01; Figure 3).

Table 1 The main characteristics of the included studies

Study	Country	Tumor type	No. of patients	Age (years)	Male	T stage (≥ T3)	TNM stage (≥ III)	Distant metastasis	Lymphatic metastasis (high expression/total)	
					Percent in total cases				Negative	Positive
Ding et al 2009[9]	China	HCC	152	NR	78.9	NR	NR	5.8	78/128	19/24
Ding et al 2014[8]	China	NPC	140	Mean 48.3	74.3	40.7	57.1	10.7	57/91	42/49
Ding et al 2018[6]	China	PDAC	81	Median 59	59.3	12.3	NR	NR	15/47	15/34
Du et al 2012[10]	China	PGC	86	NR	32.6	NR	0	NR	50/62	22/24
Engers et al 2006[11]	Germany	PC	60	Mean 65.75	NR	38.3	NR	NA	NR	NR
Hsueh et al 2011[12]	China	PTC	106	Median 43.5	78	27.4	NR	16	51/94	6/12
Li et al 2016a[13]	China	OC	182	Mean 48.3	NR	NR	NR	53.3	37/85	71/97
Li et al 2016b[14]	China	BC	153	NR	NR	45.1	NR	NR	26/57	39/96
Liu et al 2011[15]	China	ESCC	173	NR	54.9	NR	59.5	NR	62/76	97/97
Liu et al 2013[16]	China	NPC	217	NR	75.1	48.4	66.8	11.1	NR	NR
Liu et al 2014[17]	China	LUAD	98	Median 57	54.1	NR	45.9	NR	15/39	45/59
Qi et al 2009[22]	China	NPC	102	Median 69	74.5	34.3	75.5	6.8	3/12	57/90
Walch et al 2008[18]	Germany	GC	55	NR	73.6	25	NR	NR	12/22	25/45
Wang et al 2014[21]	China	HNSCC	119	NR	NR	44.5	61.3	NR	18/82	27/37
Yang et al 2015[19]	China	HNSCC	194	Median 54	77.3	16	38.7	NR	66/131	46/63
Yang et al 2018[20]	China	CC	174	NR	NR	NR	48.9	NR	31/78	59/96
Zhao et al 2011[23]	China	RCC	136	NR	64	25.7	NR	NR	37/108	16/28

Abbreviations: NR, not reported; NOS, Newcastle Ottawa scale; OS, overall survival; DFS, disease-free survival; DM, distance metastasis; CST, cell signaling technology; HCC, hepatocellular carcinoma; NPC, nasopharyngeal carcinoma; PDAC, pancreatic ductal adenocarcinoma; PGC, primary gallbladder carcinoma; PC, prostate carcinoma; PTC, papillary thyroid carcinoma; OC, ovarian carcinoma; BC, breast carcinoma; ESCC, esophageal carcinoma; LUAD, lung adenocarcinoma; GC, gastric carcinoma; HNSCC, head and neck squamous cell carcinoma; CC, cervical carcinoma; RCC, renal cell carcinoma.

Table 2 The main characteristics of the included studies

Study	Tumor type	HR (95% CI)		Antibody source	Detection method	Definition of high expression	N-OS
		OS	DFS				
Ding et al 2009[9]	HCC	1.605 (1.018–2.529)	NR	Santa Cruz	IHC	Staining intensity: 2+-3+	8
Ding et al 2014[8]	NPC	5.029 (1.158–21.845)	NR	Santa Cruz	IHC	Staining index ≥3	7
Ding et al 2018[6]	PDAC	2.753 (1.670–4.536)	NR	Santa Cruz	IHC	Staining index ≥4	6
Du et al 2012[10]	PGC	2.5 (1.6–4.8)	NA	Santa Cruz	IHC	Multiplied score ≥4	6
Engers et al 2006[11]	PC	NR	3.75 (1.06–13.16)	Innogenex	IHC	Immunoreactive scores ≥3.5	6
Hsueh et al 2011[12]	PTC	0.2 (0.059–0.669)	NR	CST	IHC	H scores ≥180	7
Li et al 2016a[13]	OC	2.559 (1.788–3.663)	NR	Santa Cruz	IHC	Staining intensity: 2+-3+	8
Li et al 2016b[14]	BC	1.549 (1.112–2.157)	1.47 (1.056–2.047)	Santa Cruz	IHC	Staining intensity: 2+-3+	8
Liu et al 2011[15]	ESCC	2.11 (1.30–3.43)	NR	Santa Cruz	IHC	Staining intensity: 2+-3+	6
Liu et al 2013[16]	NPC	2.01 (1.01–3.89)	2.13 (1.16–3.93)	Abcam	IHC	Staining index ≥4	8
Liu et al 2014[17]	LUAD	2.085 (1.186–3.667)	NR	Santa Cruz	IHC	Staining index ≥4	7
Qi et al 2009[22]	NPC	3.95 (1.687–7.061)	3.525 (1.723–8.196)	Santa Cruz	IHC	Staining score: 2+-3+	7
Walch et al 2008[18]	GC	0.57 (0.26–0.97)	NR	Calbiochem	IHC	Staining intensity: 2+-3+	6
Wang et al 2014[21]	HNSCC	4.86 (1.39–16.97)	6.43 (1.78–23.21)	Santa Cruz	IHC	Staining index ≥4	6
Yang et al 2015[19]	HNSCC	3 (1.71–5.29)	1.709 (1.129–2.586)	Santa Cruz	IHC	Immunoreactive scores ≥6	8
Yang et al 2018[20]	CC	2.724 (1.930–3.846)	NR	Santa Cruz	IHC	Staining intensity: 2+-3+	7
Zhao et al 2011[23]	RCC	2.879 (1.247–6.645)	NR	Santa Cruz	IHC	Staining index ≥4	7

Notes: Staining index: The product of staining intensity: 0 (negative), 1 (weak), 2 (medium) and 3 (strong) and extent staining score: 1 (0%), 1 (1–25%), 2 (26–50%), 3 (51–75%) and 4 (76–100%). Multiplied score: the product of staining intensity:0 (negative), 1 (weak), 2 (medium) and 3 (strong) and extent staining score: 1 (0%), 1 (1–25%), 2 (26–50%), 3 (>50%). Immunoreactive scores: the product of staining intensity: 0 (negative), 1 (weak), 2 (medium) and 3 (strong) and extent staining score 1 (0%), 1 (1–25%), 2 (26–50%), 3 (51–80%) and 4 (>80%). H scores (Histoscore): the product of staining intensity: 0 (negative), 1 (weak), 2 (medium) and 3 (strong) and fraction score (percentage of positive tumor cells; range =0–100). Staining score: the numbers of positively staining cells were scored as 0% (–), 1–33% (+), 34–66% (++) or greater than 67% (+++).

Abbreviations: NR, not reported; NOS, Newcastle Ottawa scale; OS, overall survival; DFS, disease-free survival; HCC, hepatocellular carcinoma; NPC, nasopharyngeal carcinoma; PDAC, pancreatic ductal adenocarcinoma; PGC, primary gallbladder carcinoma; PC, prostate carcinoma; PTC, papillary thyroid carcinoma; OC, ovarian carcinoma; BC, breast carcinoma; ESCC, esophageal carcinoma; LUAD, lung adenocarcinoma; GC, gastric carcinoma; HNSCC, head and neck squamous cell carcinoma; CC, cervical carcinoma; RCC, renal cell carcinoma.

Besides, a total of 15 studies with 1,951 patients investigated the relationship between Tiam1 expression and lymph node metastasis. Because of significant heterogeneity (I^2=61.1%, p<0.01, we pool data on lymphatic metastasis using the random-effect model and found that high Tiam1 expression predicted a higher proportion of lymphatic metastasis (OR=2.63, 95% CI: 1.79–3.84, p<0.05; Figure 4).

Subgroup and meta-regression analyses

The subgroup and meta-regression analyses were conducted according to sample size, tumor type, antibody source, definition of high Tiam1 expression and quality score to explore the sources of the heterogeneity in the meta-analyses of the association of Tiam1 expression with OS and lymphatic metastasis. The results of subgroup analysis showed that the significant heterogeneity for OS and lymphatic metastasis still existed in subgroup analysis by any factor (Table 3). However, the results of meta-regression analysis showed that antibody source might explain the major heterogeneity in the meta-analyses of the association of Tiam1 expression with OS (p<0.01) (Table 4). Additionally, we found that high Tiam1 expression was associated with shorter OS and positive lymphatic metastasis in all subgroups, only with the exception of subgroup of the other antibody sources, suggesting that our overall estimated results were stable and reliable as a whole.

Sensitivity analysis and publication bias

We conducted sensitivity analysis by sequentially omitting one study to further explore the robustness and reliability of the overall estimated results about OS and lymphatic metastasis. The results showed that our pooled results about OS (Figure 5A) and lymphatic metastasis (Figure 5B) did not change

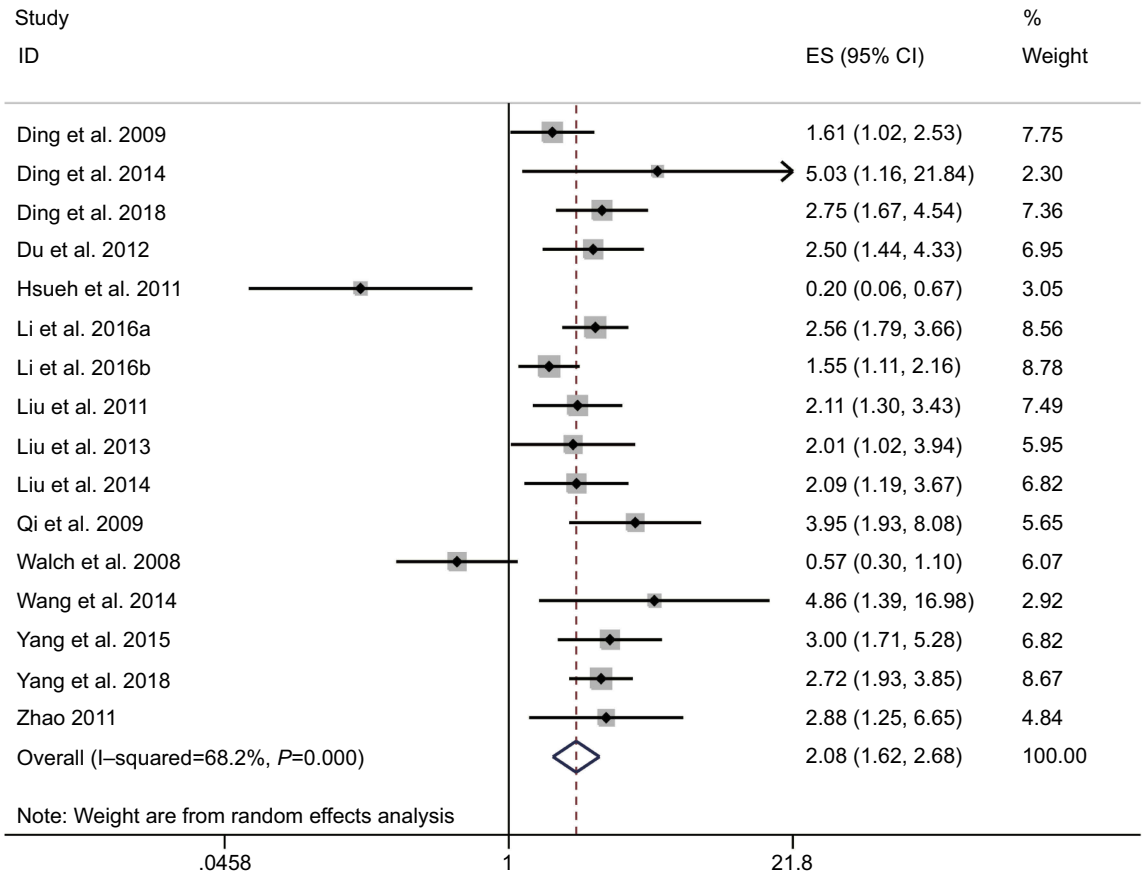

Figure 2 Forest plot of pooled HR for the association between high Tiam1 expression and poor overall survival (OS).

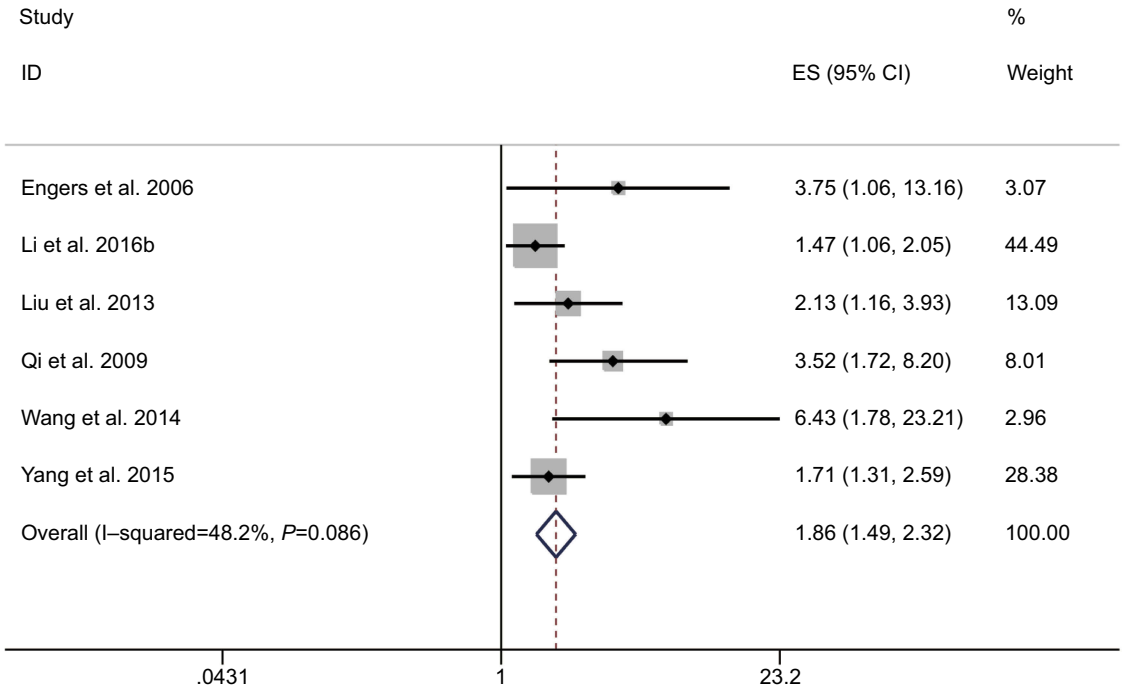

Figure 3 Forest plot of pooled HR for the association between high Tiam1 expression and poor disease-free survival (DFS).

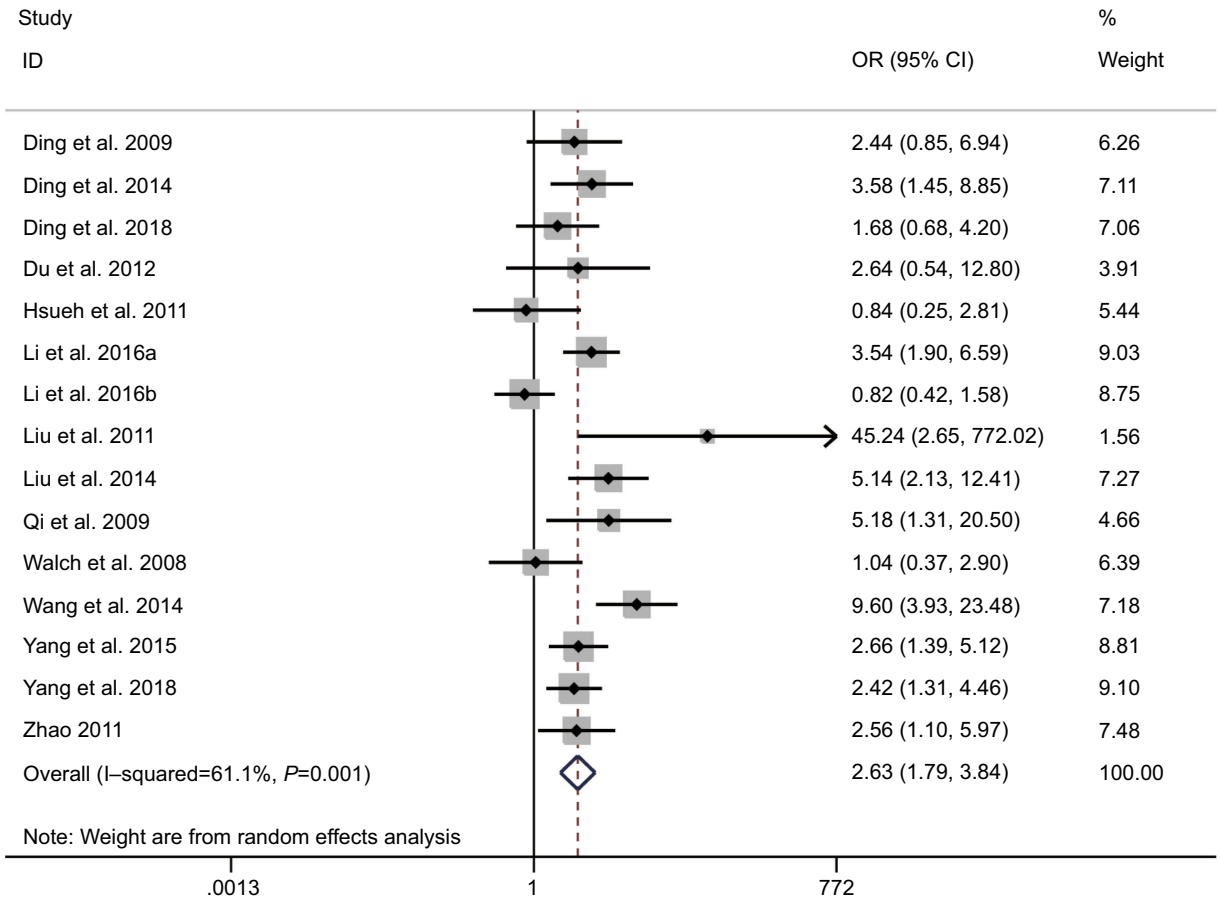

Figure 4 Forest plot of pooled HR for the association between high Tiam1 expression and positive lymph node metastasis.

significantly when any one of the included studies was omitted, thereby confirming the robustness of the overall estimated results.

The Begg's and Egger's tests were conducted to assess the publication bias for OS and lymphatic metastasis. The results showed that the Begg's funnel plots for OS (Figure 5C) and lymphatic metastasis (Figure 5D) were symmetric, and the *p*-values of Egger's tests for OS (p=0.804) and lymphatic metastasis (p=0.388) were >0.05, suggesting that there was no significant publication bias. Due to the limited number of eligible studies about DFS, publication bias assessment was not performed in this analysis.

Discussion

Many studies have explored the prognostic value of T-cell lymphoma invasion and metastasis inducing factor 1 (Tiam1) and its association with lymphatic metastasis in malignant solid tumors, but the conclusions remain controversial. Therefore, we performed a meta-analysis to systematically assess the prognostic value of Tiam1 expression and its association with lymphatic metastasis in malignant solid tumors.

To our best knowledge, this study is the first meta-analysis to systematically assess the prognostic value of Tiam1 expression and its association with lymphatic metastasis in patients with malignant solid tumors. A total of 17 studies with 2,228 patients with solid tumors were included in this meta-analysis. The combined results showed that high Tiam1 expression was significantly associated with shorter overall survival (OS; HR = 2.08, 95% CI: 1.62–2.68, P<0.01), and disease-free survival (DFS; HR = 1.86, 95% CI: 1.49–2.32, P<0.01). Besides, we also found that there was a close relationship between high Tiam1 expression and positive lymphatic metastasis (OR=2.63; 95% CI: 1.79–3.84, P<0.01). Furthermore, our subgroup, meta-regression, and sensitivity analyses showed that the overall estimated results were reliable and stable.

Multiple cellular functions of Tiam1 in tumor progression have been elaborated, which may account for the inverse association between Tiam1 expression and survival of cancer

Table 3 The prognostic role of Tiam1 expression in different subgroups

Variables	Overall survival			Lymphatic metastasis		
	Pooled HR (95% CI)	Heterogeneity		Pooled HR (95% CI)	Heterogeneity	
		I^2 (%)	*p*-Value		I^2 (%)	*p*-Value
Tumor type						
Digestive tumor	1.73 (1.07–2.78)[6,9,10,15,18]	75.8	<0.01	1.62 (0.87–3.03)[6,9,10,15,18]	68.8	0.01
Head and neck tumor	2.26 (1.08–4.72)[8,12,16,19,21,22]	76.1	<0.01	1.91 (0.99–3.66)[8,12,19,21,22]	87.9	<0.01
Gynecological tumor	2.64 (2.06–3.39)[13,20]	0	0.81	1.64 (1.31–2.05)[13,20]	4.7	0.31
The others	1.80 (1.34–2.44)[14,17,23]	10.9	0.33	1.52 (0.80–2.88)[14,17,23]	84.9	<0.01
Sample size						
≥131	2.21 (1.82–2.68)[8,9,13–16,19,20,23]	28.4	0.19	1.74 (1.24–2.44)[8,9,13–15,19,20,23]	74.5	<0.01
<131	1.72 (0.91–3.25)[6,10,12,17,18,21,22]	83	<0.01	1.56 (1.07–2.30)[6,10,12,17,18,21,22]	78.9	<0.01
Quality score						
8	2.02 (1.55–2.64)[9,13,14,16,19]	42.6	0.14	1.57 (0.95–2.59)[9,13,14,19]	82.5	<0.01
7	2.16 (1.20–3.89)[8,12,17,20,22,23]	74.8	<0.01	1.58 (1.18–2.13)[8,12,17,20,22,23]	65	0.01
6	1.98 (1.10–3.56)[6,10,15,18,21]	78	<0.01	2.16 (0.94–4.95)[6,10,15,18,21]	85.7	<0.01
Antibody source						
Santa Cruz	2.36 (2.00–2.79)[6,8–10,13–15,17,19–23]	23.8	0.2	1.78 (1.37–2.32)[6,8–10,13–15,17,19–23]	78	<0.01
The others	0.66(0.20–2.19)[12,16,18]	84.8	<0.01	1.00(0.72–1.38)[12,18]	0	0.75
Definition of high expression						
Staining intensity	1.75 (1.23–2.50)[9,13–15,18,20]	77.1	<0.01	1.39 (0.97–2.00)[9,13–15,18,20]	77.9	<0.01
Staining index	2.56 (1.92–3.42)[6,8,16,17,21,23]	0	0.7	2.23 (1.51–3.27)[6,8,17,21,23]	55.3	0.06
The others	1.81 (0.76–4.34)[10,12,19,22]	83.8	<0.01	1.43 (0.91–2.23)[10,12,19,22]	58.3	0.07

Table 4 The potential source of heterogeneity evaluated by meta-regression

Variables	Meta-regression for overall survival				Meta-regression for lymphatic metastasis			
	Tau2	Adj R^2 (%)	t-Value	*p*-Value	Tau^2	Adj R^2 (%)	t-Value	*p*-Value
Tumor type	0.25	−15.15	0.48	0.64	0.51	−10.13	−0.08	0.94
Sample size	0.24	−17.76	0.75	0.46	0.5	−7.87	−0.22	0.83
Quality score	0.25	−20.67	0.1	0.92	0.5	−8.27	−0.67	0.51
Antibody source	0.07	67.37	−3.39	<0.01	0.35	23.05	−2.16	0.05
Definition of high expression	0.21	−2.75	0.59	0.56	0.45	2.54	0.68	0.51

patients. First, metastasis is an essential hall marker of cancer and always leads to poor survival.[41–43] Numerous studies suggested that Tiam1 contributed to invasion and metastasis in various cancers, including osteosarcoma,[44] retinoblastoma,[45] gastric cancer,[46] CRC,[47–51] hepatocellular carcinoma,[25,52] breast cancer,[53] cholangiocarcinoma,[54] cervical cancer,[20] ovarian cancer,[55] nasopharyngeal cancer,[8,16] laryngeal cancer,[56] thyroid carcinoma,[57] nom-small cell lung cancer,[48] pancreatic cancer[6,58,59] and oral squamous cell carcinoma[27] Malliri et al reported that Tiam1 could facilitate E-cadherin-based adhesions between cancer cells in mouse intestinal tumors and human colon tumors, resulting in invasion and metastasis[60] Epithelial–mesenchymal transition (EMT) is a key process of enhancing cancer cell migration, invasion and metastasis.[28–31] Liu et al reported that Tiam1 overexpression could promote invasiveness and metastasis of thyroid carcinoma in vitro and in vivo by activating Wnt/EMT pathway[57] Similarly, Ding[6] and Yang et al[20] also demonstrated

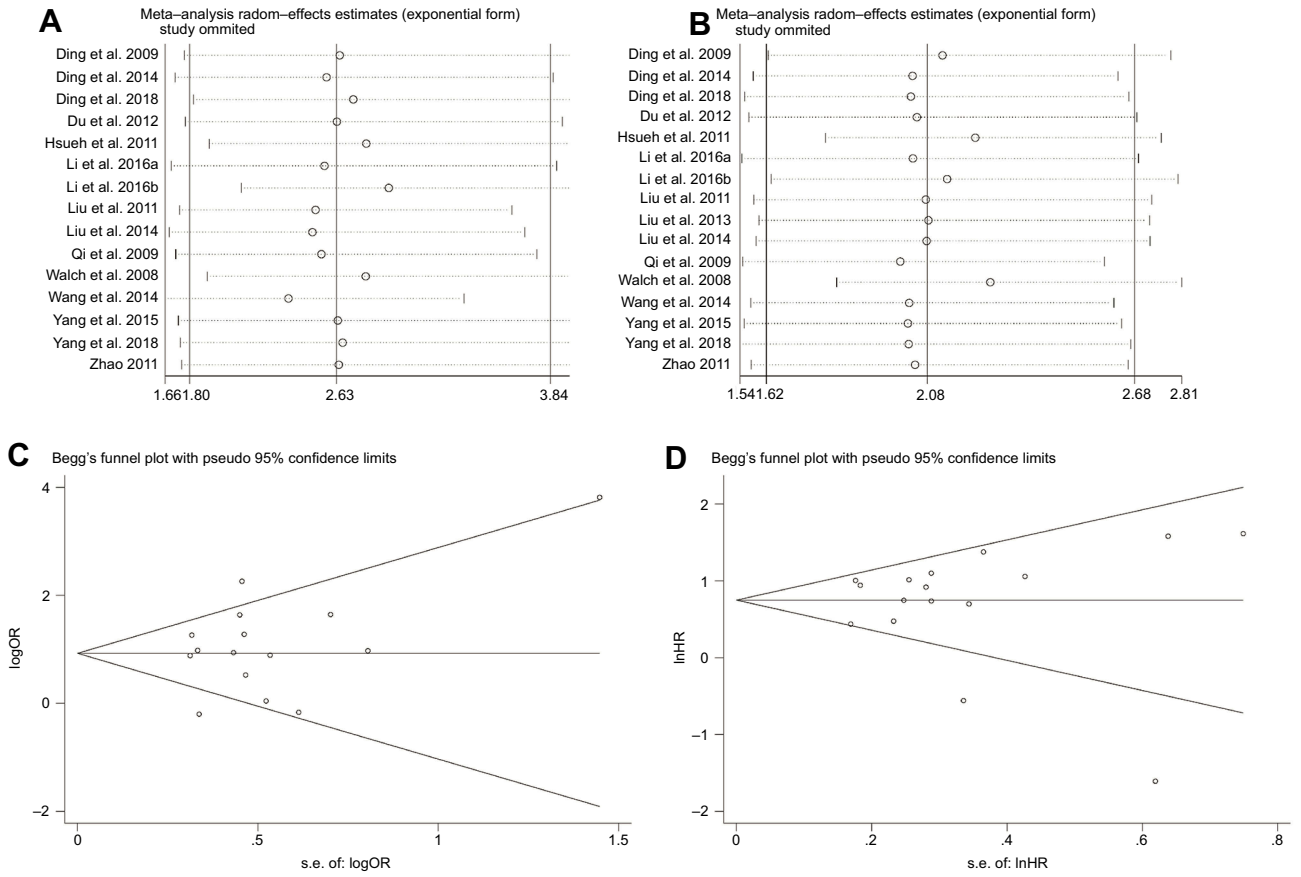

Figure 5 Sensitivity analysis for OS (**A**) and lymph node metastasis (**B**). Begg`s funnel plot of publication bias assessment for OS (**C**) and lymph node metastasis (**D**).

that Tiam1 overexpression could also boost invasion and metastasis of pancreatic cancer and cervical cancer by inducing EMT. Current evidence shows that angiogenesis is also involved in tumor metastasis.[61–63] A study by Yang et al suggested that depletion of Tiam1 could significantly suppress cervical cancer cell angiogenesis through inhibiting microtubule formation, blood vessels formation, as well as VEGF and VEGFA expression[20] Additionally, a recent study by Zhu et al also showed that Tiam1 overexpression could accelerate progression of lung adenocarcinoma by enhancing angiogenesis[32] Second, Tiam1 also has a role in regulating chemo-resistance of malignant cells. For instance, Hofbauer et al[24] reported that Tiam1/Rac1 signal transduction could contribute to chemoresistance of chronic lymphocytic leukemia cells. In a recent study, Izumi et al[33] found that Tiam1 was overexpressed in CRC patients who did not respond to chemotherapy and demonstrated that upregulation of Tiam1 could induce chemoresistance by enhancing stemness of CRC cells. Third, several studies also suggested that Tiam1 overexpression could promote the in vitro proliferation of malignant cells and in vivo growth of tumor.[24–27] As above, it can be easily deduced that Tiam1 expression in cancer cells is required for facilitating tumor growth, invasion, metastasis and chemo-resistance, which supports the prognostic value of Tiam1. Therefore, Tiam1 in tumor cells may be an attractive therapeutic target. Fourth, increasing evidence showed that the stromal microenvironment within cancers is a pivotal factor of regulating the growth, invasiveness, and metastasis and chemo-sensitivity of cancer cells,[64–68] and Tiam1 expressed in tumor stromal microenvironment also plays a role in regulating tumor invasion, metastasis and chemo-resistance. CAF is a major stromal cell in cancer stromal microenvironment.[34,35] Izumi et al[33] found that CAFs isolated from CRC tissues could induce chemoresistance of CRC cells when the two kinds of cells were cocultured, but surprisingly the direct inhibition of Tiam1 in CAFs could result in enhanced chemo-sensitivity of CRC cells[33] Thus, targeting Tiam1 in tumor stromal may be an ideal way to boost the effectiveness of chemotherapy. However, it was also reported that Tiam1 in tumor-associated fibroblasts had a role in modulating tumor invasion and metastasis, and knockout of Tiam1 in tumor-associated fibroblasts facilitated tumor invasion and metastasis.[69,70] Therefore, more

studies are warranted to fully elucidate the functions of Tiam1 in tumor stromal and to assess the integrated effects of Tiam1 in tumor epithelial cells and stromal.

There were some limitations in this meta-analysis. We should cautiously consider when interpreting the results of pooling analysis. First, only studies published in English were included in this meta-analysis, which probably introduced bias. Second, some of the included studies did not directly provide HRs and 95% CIs, and thereby we estimated HRs from the Kaplan–Meier curve using Engage Digitizer 4.1. Inevitably, manually extracting data from Kaplan–Meier curve will cause some calculation errors. Third, there was significant heterogeneity in this meta-analysis. We conducted subgroup and meta-regression analyses based on some factors and identified the antibody source as one of the main sources. In fact, many other factors including age, tumor size, gender, TNM stage, distant metastasis and follow-up time may also cause heterogeneity. However, we failed to conduct subgroup and meta-regression analyses based on these factors due to lacking relevant data in the included studies. Fourth, among all the 17 included studies, only 2 studies with a few patients were from Germany and the rest were all from China, and so it remains unclear whether our findings could be generalized to other populations, especially Caucasian and Africans.

Conclusion

High Tiam1 expression was significantly associated with poor survival and positive lymphatic metastasis in patients with solid tumors. Therefore, Tiam1 may be a promising prognostic biomarker and an effective therapeutic target for solid tumors.

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Disclosure

The authors report no conflicts of interest in this work.

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