Systematic Review and Meta-Analysis

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Tiam1 high expression is associated with poor prognosis in solid cancers: a meta-analysis

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Abstract

Background: A number of studies have attempted to determine the prognostic value of T-cell lymphoma invasion and metastasis-inducing factor 1 (Tiam1) in patients with solid cancers, but the reported results were of inconsistency. Thus, we performed a systematic review and meta-analysis to exhaustively evaluate the prognostic role of Tiam1 expression in patients with solid cancers.

Methods: We retrieved literature published in between 1994 and April 22th, 2019 through searching PubMed, Web of Science and China national knowledge infrastructure (CNKI). Hazard ratios (HRs) coupled with 95% confidence intervals (95% CIs) were used to assess the relationship of Tiam1 expression and overall survival (OS), and disease-free survival (DFS).

Results: A total of 2647 patients with solid cancers in 20 studies were enrolled in our meta-analysis eventually. The pooled results showed that Tiam1 high expression was closely correlated with poor OS (HR = 2.17, 95% CI: 1.80–2.61, $P = .000$) and DFS (pooled HR = 1.95, 95% CI = 1.58–2.40, $P = .000$). Moreover, our subgroup analysis and sensitivity analysis demonstrated the reliability and stability of our pooled results.

Conclusion: In conclusion, this meta-analysis confirmed that Tiam1 higher expression positively correlated with OS and DFS, suggesting that Tiam1 may act as a valuable prognostic predictor and therapeutic target for patients with solid cancers. Nevertheless, in future more homogeneous and prospective studies should be performed to further support our findings.

Abbreviations: CI = confidence interval, DFS = disease-free survival, EMT = epithelial-mesenchymal transition; HR = hazard ratio, NOS = Newcastle-Ottawa Scale, OS = overall survival, Tiam1 = T-cell lymphoma invasion and metastasis-inducing factor 1.

Keywords: cancer, meta-analysis, Tiam1, prognosis

1. Introduction

Cancer, as a severe public health problem, results in enormous economic burden worldwide.[1] It is very urgent to comprehensively elucidate its pathogenesis and develop effective therapeutic strategies. Growing evidence shows that the imbalance between oncogenes and tumor suppressor genes plays a pivotal role in transferring normal cells into malignant cells.[2–6] Hence, it is of great significance to identify these genes, clarify their functions in disease progression, and assess their prognostic role in cancer, for optimizing individualized therapy of cancer.

T-cell lymphoma invasion and metastasis factor 1(Tiam1) was found in mice T lymphoma cells at the very start and then identified as a metastasis-associated-gene.[7–9] As a guanine nucleotide exchange factor, Tiam1 has been identified a specific activator of Rho-like GTPases Rac1.[8,9] Moreover, numerous studies demonstrated that the activation Tiam1-Rac signaling plays a crucial role in enhancing invasion and metastasis of various cancers.[10] Additionally, a recent study suggested that Tiam1 could activate Wnt/β-catenin signaling to facilitate thyroid cancer epithelial-mesenchymal transition (EMT)-mediated metastasis.[11] Metastasis is an essential hallmark of cancer that always confers poor oncologic outcomes.[12] In accordance with this, a large body of evidence supported that an increased Tiam1 expression predicted poor prognosis in patients with solid cancers.[13–18] Nevertheless, 2 early studies reported the inverse result that the increased Tiam1 expression correlated with a better prognosis.[17,19]Therefore, in the current study we performed a systematic review and meta-analysis to exhaustively assess the prognostic role of Tiam1 expression in solid cancers, aiming to provide evidence for the improved individualized therapy.

2. Materials and methods

The Institutional Review Board of 3201 Hospital, Xi'an Jiaotong University Health Science center approved this study. The current meta-analysis was conducted according to the Preferred Reporting Items for Systematics Reviews and Meta-Analyses guidelines.[20]

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2.1. Search strategy

We retrieved literature published in between 1994 and April 22th, 2019 through searching PubMed, Web of Science and China national knowledge infrastructure (CNKI) using a search algorithm based on a combination of the following keywords

(1) "Tiam1" OR "T-cell lymphoma invasion and metastasis-inducing factor 1"OR"T lymphoma invasion and metastasis 1" AND
(2) "tumor or tumor or cancer or carcinoma or adenocarcinoma or neoplasm or sarcoma or osteosarcoma or fibrosarcoma or rhabdomyosarcoma or glioma or glioblastoma or melanoma or retinoblastoma or choriocarcinoma or cholangiocarcinoma or teratoma or hepatoblastoma or nephroblastoma".

The search strategy we used when searching PubMed was illustrated in Supplement 1. Reference lists from identified original studies and review articles were also carefully screened to identify additional eligible studies, which might be missed by electronic search strategies.

2.2. Selection and exclusion criteria

Studies included in this meta-analysis must met the following requirements:

(1) patients were diagnosed with solid cancer by pathological confirmation;
(2) The expression of Tiam1 expression must be quantitatively detected using quantitative real-time polymerase chain reaction (q-PCR) or immunohistochemistry (IHC);
(3) The relationship between Tiam1 expression and survival was explored;
(4) The Hazard Ratios (HRs) and their 95% confidence intervals (CIs) for survival prediction based on Tiam1 expression level were readily available or could be calculated indirectly;
(5) The most representative and most accurate study was considered to avert cohort overlapping when the same sample source was analyzed in multiple studies.

Studies satisfying the abovementioned inclusion criteria were further excluded if they had any of the following flaws:

(1) duplicated publications or data;
(2) animal or cell studies;
(3) erratum, conference, review articles, comments or letters;
(4) insufficient data or information to obtain HR;
(5) publications not written in Chinese or English.

2.3. Data extraction

The following data from the full texts of eligible studies were extracted: the first author, publication year, recruitment time study design, type of cancer, the number of cases, gender ratio, median age, tumor stage, method of detecting Tiam1 expression, cut-off value of Taim1 overexpression, HRs of Tiam1 expression for OS and DFS, follow-up time and adjusted variables. If the HR for OS or DFS were calculated using both univariate and multivariate analyses, the latter was first chosen, considering that these results were adjusted for confounding factors. Besides, when a study did not provided the HRs, we estimated HRs and their corresponding 95% CIs from Kaplan-Meier curves using the Engauge Digitizer version 9.8 according to the method described by Parmar et al[21] and Tierney et al[22]. Any divergence in the extraction and explanation of all data was solved through discussion.

2.4. Quality assessment

The quality of the enrolled studies was independently assessed based on the Newcastle-Ottawa Scale (NOS) score.[23] In the NOS system, a score >6 was considered high quality.

2.5. Statistical analysis

HRs and their 95% CIs were pooled to estimate the effect of Tiam1 overexpression on survival. If the pooled HR exceeded 1 and its 95% CI did not intersect with the invalid line in the forest plot, the high expression of Tiam1 predicted a poor OS or DFS. Once the 95% CI intersect with the invalid line, the pooled HR was regarded of no significance. Inversely, the pooled HR less than 1 signified a better OS or DFS. The heterogeneity was examined using Cochrane Q test and Higgins' I-squared, in which $P<.05$ or $I^2 \geq 25\%$ was considered significant heterogeneity. We chose the random effects model to pool data when there was statistically significant heterogeneity. Otherwise, the heterogeneity could be neglected for its subtle influence, and the pooling analysis was conducted using a fixed effects model. Based on race, cancer type, the number of cases, detection method, adjusted TNM stage, and adjusted tumor differentiation, we conducted meta-regression analyses and subgroup analyses to determine the sources of heterogeneity and the reliability and stability of our pooled results. Additionally, sensitivity analysis was done by sequentially deleting single study to further verify the reliability and stability of our pooled results. The potential publication bias was evaluated by the funnel plot and Egger test.[24] $P<.05$ was regarded significant. Statistical analysis was fulfilled using STATA version 12.0 (StataCorp, College Station, TX).

3. Results

3.1. Study search and selection

We identified 324 records in PubMed, 247 records in Web of Science, 82 records in CNKI. We had a sum of 397 records after ruling out 256 duplicated publications. We then excluded 320 records which were review articles, letters, studies only with laboratory data, without survival analysis, or focusing irrelevant themes. We further removed 57 full-text articles based on the inclusion and exclusion criteria of this meta-analysis. The remaining 20 articles were ultimately identified as eligible ones and enrolled into in this meta-analysis[13–19,25–37] (Fig. 1).

3.2. Study demographics

The main demographics of the 20 included studies are shown in Table 1. Fifteen different kinds of cancers were explored in our meta-analysis. All included studies were retrospective. Except 2 studies from Germany and USA, all studies were conducted in China. The sample size ranged from 76 to 217 across the included studies. A total of 20 included studies with 2647 patients reported HRs for OS, and 16 studies calculated HR using multivariate analysis. HRs for DFS were reported in 7 studies with 1048 patients and 4 studies provided HRs calculated using multivariate

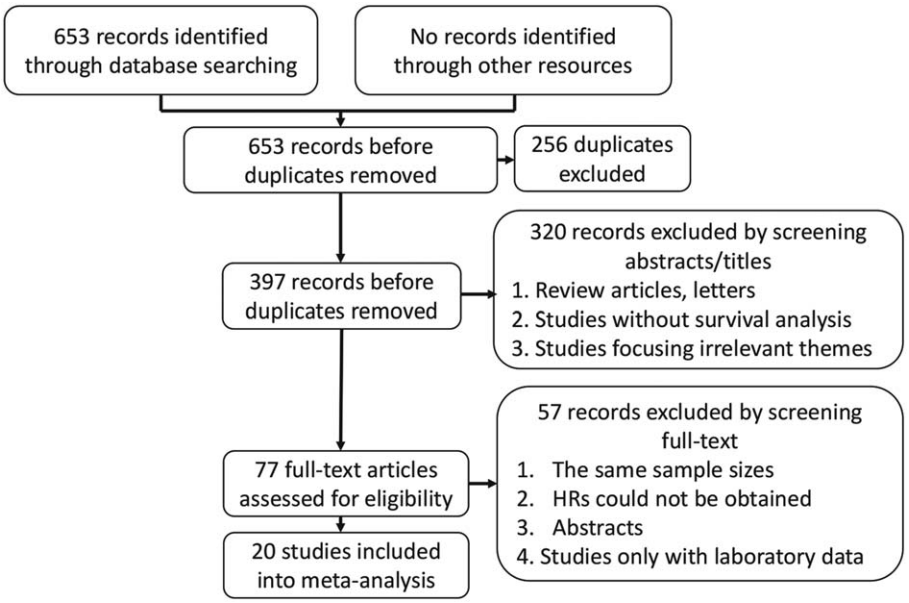

Figure 1. Flowchart of study selection.

analysis. Of all included studies, 18 studies assessed the Tiam1 expression using immunohistochemical staining method, while 2 studies did use polymerase chain reaction method. The Cut-off values of Taim1 overexpression were not consistent across included studies. Each of the included studies was given less than 6 scores, suggesting all studies were high-quality enough for pooling analysis.

3.3. The prognostic significance of Tiam1 high expression in overall survival (OS) and disease-free survival (DFS) of cancer patients

HRs for OS were available in all 20 studies with 2647 patients. Because there was statistical heterogeneity in all the 20 datasets ($I^2 = 52.3\%$, $P = .003$), the overall pooled HR was calculated with the random-effects model. The forest plot results were shown in Figure 2, which suggested that Tiam1 high expression was linked with poor OS (HR = 2.17, 95% CI: 1.80–2.61, $P = .000$).

HRs for DFS were available in 7 studies with 1048 patients.[18,26,28,30–33] Because there was no statistical heterogeneity in all the 7 datasets ($I^2 = 41.9\%$, $P = .111$), the fixed-effects model was chosen to calculate the overall pooled HR. As shown in Figure 3, the overall pooled HR was 1.95 (95% CI: 1.58–2.40; $P = .000$), suggesting that Tiam1 high expression was linked with poor DFS as well.

3.4. Meta-regression and subgroup analysis of heterogeneity for overall survival

We performed meta-regression analyses and subgroup analyses based on race, cancer type, the number of cases, detection method, adjusted TNM stage, and adjusted tumor differentiation, to investigate the sources of heterogeneity and determine whether the heterogeneity significantly affected the reliability and stability of the pooled HR for OS. As the results of meta-regression analyses showed, all these potential factors could not significantly interpret the heterogeneity for the pooled HR for OS (Fig. 4). However, in subgroup analysis we found that the heterogeneity completely vanished in group with adjusted tumor differentiation (HR = 2.59, 95% CI: 2.145–3.127, $P = .000$; $I^2 = 0\%$, $P = .852$) (Fig. 4), hinting that tumor differentiation might account for a degree of heterogeneity, and Tiam1 higher expression had stronger efficacy in predicting prognosis in cancer patients with unanimous tumor differentiation. Additionally, our subgroup analysis showed that Tiam1 high expression was linked with poor OS in all groups, which verified the robustness of our overall pooled HR for OS.

3.5. Sensitivity analysis and publication bias

Sensitivity analysis by sequentially deleting single study was done to further verify the reliability of our synthesized results for OS and DFS. We found that no single study significantly changed the pooled HRs for OS (Supplement 2) and DFS (Supplement 3), further verifying the reliability of our pooled results. In addition, we applied Begg funnel plot and Egger test to evaluate the publication bias for OS. As shown in Figure 5, the shape of the funnel plots for OS was of symmetry. Moreover, the Egger test showed no statistical significance ($P = .752$). Thus, no publication bias for OS existed in this meta-analysis.

4. Discussion

A large number of studies indicated that an increased Tiam1 expression correlated with unfavorable oncologic outcomes in a wide range of solid cancers,[13–16,18,27,29,30] but some other studies reported a superior survival duration in cancer patients with an increased Tiam1 expression.[17,19] Therefore, in the current study we performed a systematic review and meta-analysis to exhaustively evaluate the prognostic role of Tiam1 expression in solid cancers, aiming to providing evidence for the improved individualized therapy.

In this meta-analysis, we scientifically pooled survival data of 2647 solid cancer patients enrolled in 20 clinical studies.

Table 1

Demographic information of included studies.

Reference	SD	RT	Country	Type of Cancer	Case (No.)	M/F	Median age (years)	TNM Stage	Detection method	Cut-off value of Taim1 overexpression	Survival end points	Follow-up (months)	NOS score	Adjusted variables
Liu 2014	R	2002–2006	China	LC	98	53/45	57	I-IV	IHCS	Stained extent score × stained intensity score ≥ 4	OS^M	NA	7	Sex, age, tumor size, tumor differentiation, TNM stage, lymph node status
Zhu 2019	R	2008–2011	China	LC	92	51/41	NA	I-IV	IHCS	Stained extent score = 2	OS^M	NA	7	Sex, age, tumor size, tumor differentiation, TNM stage, lymph node status, EGFR expression, ALK expression
Liu 2011	R	2005–2009	China	ESCC	173	95/78	NA	I-IV	IHCS	Stained extent score × stained intensity score ≥ 2	OS^K	Mean: 45	6	NA
Liu 2013	R	2003–2006	China	NPC	217	163/54	NA	I-IV	IHCS	Stained extent score × stained intensity score ≥ 4	OS^M	NA	8	NA
Qi 2009	R	NA	China	NPC	102	76/26	NA	II-IV	IHCS	Stained extent score = 2/3	DFS^M OS^M	Median: > 60	7	Sex, age, TNM stage, Rac1 expression
Ding 2014	R	1998–2000	China	NPC	140	104/36	NA	I-IV	IHCS	Stained extent score × stained intensity score ≥ 3	DFS^M OS^M	Median: 41.2	8	Sex, age, tumor size, differentiation, T classification, lymph node status, distant metastasis
Wang 2015	R	2003–2006	China	LSCC	98	NA	NA	I-IV	IHCS	Stained extent score × stained intensity score ≥ 4	OS^K	NA	6	NA
Hsueh 2011	R	1994–1999	China	PTC	106	23/83	43.5	I-IV	IHCS	Stained extent score × stained intensity score ≥ 180	DFS^K OS^M	Mean: 115.2	7	Sex, age, tumor size, tumor multi-centricity, histological type, loco-regional recurrence
Yang 2015	R	2001–2008	China	HNSCC	194	150/44	54.0	I-IV	IHCS	Stained extent score × stained intensity score ≥ 5	OS^M	Median: 79	8	Sex, age, tumor differentiation, TNM stage, chronic illness, tobacco use, alcohol use, without neck dissection, adjuvant radiotherapy, oral cavity cancer
Li 2016a	R	NA	China	BC	153	0/153	NA	NA	IHCS	Stained extent score = 3	DFS^M OS^M	NA	8	Age, menopausal status, molecular type, TNM stage, lymph node status, ER, Ki-67, PR and Her2 expression
Li 2016b	R	2006–2010	China	OC	182	0/182	NA	NA	IHCS	Stained extent score = 2/3	DFS^M OS^M	Median: > 60	8	Age, menopausal status, histological grade, metastasis, tumor stage
Yang 2018	R	2004–2008	China	CC	174	0/174	NA	0-IV	IHCS	Stained extent score = 3	OS^M	Median: 40	8	Age, tumor differentiation, TNM stage, lymph node status, HPV infection
Wang 2018	R	2010–2012	China	CC	84	0/84	41.3	I- II	IHCS	Stained extent score × stained intensity score ≥ 4	DFS^K OS^M	NA	7	Age, tumor size, histological grade and type, TNM stage, lymph node status, tumor depth
Walch 2008	R	1990–2000	Germany	GC	76	56/20	69.0	I-IV	IHCS	Stained extent score = 2/3	OS^K	NA	6	NA
Li 2017	R	2010–2011	China	CRC	193	111/82	NA	I-IV	PCR	NA	OS^M	NA	7	Age, gender, tumor size, location, miR-22
Izumi 2019	R	2005–2012	USA	CRC	110	NA	NA	II-III	PCR	NA	OS^M	NA	7	Age, sex, lymphatic invasion, venous invasion
Ding 2009	R	1999–2002	China	HCC	152	NA	NA	I-IV	IHCS	Stained extent score × stained intensity score ≥ 4	DFS^M OS^M	NA	8	Age, gender, tumor size, tumor grade, liver cirrhosis, HBsAg status, metastasis, recurrence, serum AFP
Du 2012	R	2000–2004	China	GBC	86	28/58	NA	I-II	IHCS	Stained extent score × stained intensity score ≥ 5	OS^K	Mean: 36	7	Lymph node metastasis, lymphovascular invasion, recurrence, tumor depth, TNM stage, Rac1 expression
Ding 2018	R	NA	China	PDAC	81	48/33	59	I-III	IHCS	Stained extent score × stained intensity score ≥ 4	OS^M	NA	7	Sex, age, tumor size, tumor location, pathological status, T classification, lymph node status
Zhao 2011	R	2000–2003	China	RCC	136	87/49	NA	I-IV	IHCS	Intensity score of, 2 with at least 50% of malignant cells with positiveTiam1 staining	OS^M	NA	7	Sex, age, tumor size, tumor location, T classification, lymph node status

BC = breast carcinoma, CC = cervical cancer, CRC = colorectal cancer, ESCC = esophageal squamous cell carcinoma, GBC = gallbladder carcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, Her2 = receptor tyrosine-protein kinase erbB-2, HNSCC = head and neck squamous cell carcinoma, IHCS = immunohistochemical staining, K = survival data was calculated from Kaplan-Meier survival curve, LC = lung cancer, LSCC = laryngeal squamous cell carcinoma, M = multivariable analysis; NA = not available, NOS = Newcastle-Ottawa Scale, NPC = nasopharyngeal carcinoma, OC = ovarian carcinoma, PDAC = pancreatic ductal adenocarcinoma, PCR = polymerase chain reaction, PR = progesterone receptor, PTC = papillary thyroid carcinoma, RCC = renal cell carcinoma, RT = recruitment time, SD = study design.

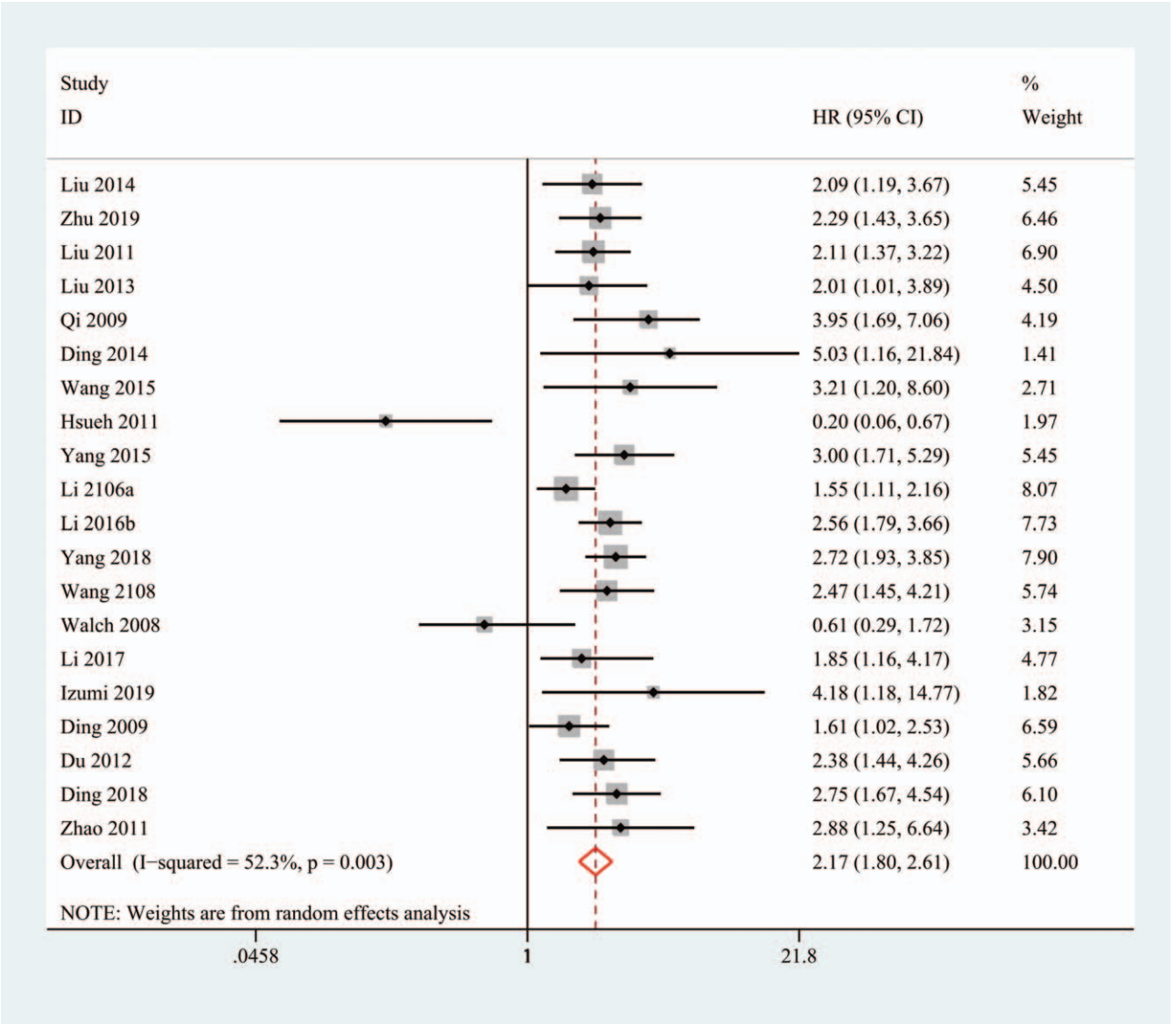

Figure 2. Forest plot diagrams of hazard ratios for the prognostic value of Tiam1 in OS. A HR > 1implied a worse OS for the group with Tiam1 high expression. The center of the lozenge gave the combined HR for the meta-analysis, and its extremities gave the 95% CI. CI = confidence interval, HR = hazard ratio, OS = overall survival, Tiam1 = T-cell lymphoma invasion and metastasis-inducing factor 1.

Altogether, our overall pooled results showed that Tiam1 high expression was significantly associated with poor OS (HR = 2.17, 95% CI: 1.80–2.61, $P = .000$) and DFS (pooled HR = 1.95, 95% CI = 1.58–2.40, $P = .000$), verifying the value of Tiam1 high expression as an adverse prognostic factor in solid cancers. The overall pooled results may be challenged with the significant heterogeneity. Thus, to investigate the sources of heterogeneity and determine whether the heterogeneity significantly affected the reliability and stability of the overall pooled HR for OS, we performed meta-regression analyses and subgroup analyses based on race, cancer type, the number of cases, detection method, adjusted TNM stage, and adjusted tumor differentiation or grade. As the results of meta-regression analyses showed, all these potential factors could not significantly interpret the heterogeneity for the pooled HR for OS (Fig. 4). However, in subgroup analysis we found that the heterogeneity completely vanished in group with adjusted tumor differentiation (HR = 2.59, 95% CI: 2.145–3.127, $P = .000$; $I^2 = 0\%$, $P = .852$) (Fig. 4), hinting that tumor differentiation might account for a degree of heterogeneity, and Tiam1 high expression had stronger efficacy in predicting prognosis in cancer patients with unanimous tumor differentiation. Additionally, in general, our subgroup analysis showed that Tiam1 high expression was linked with poor OS in all groups, suggesting that the overall pooled HR for OS was reliable and stable. Furthermore, we also did sensitivity analysis by sequentially omitting single study and publication bias assessment to further verify the reliability and stability of our pooled results. From the results, we found that no single study significantly changed the overall pooled HRs for OS and DFS, and there was no significant publication bias, further demonstrating the robustness of our pooled results. Therefore, our comprehensive analyses strongly supported the notion that

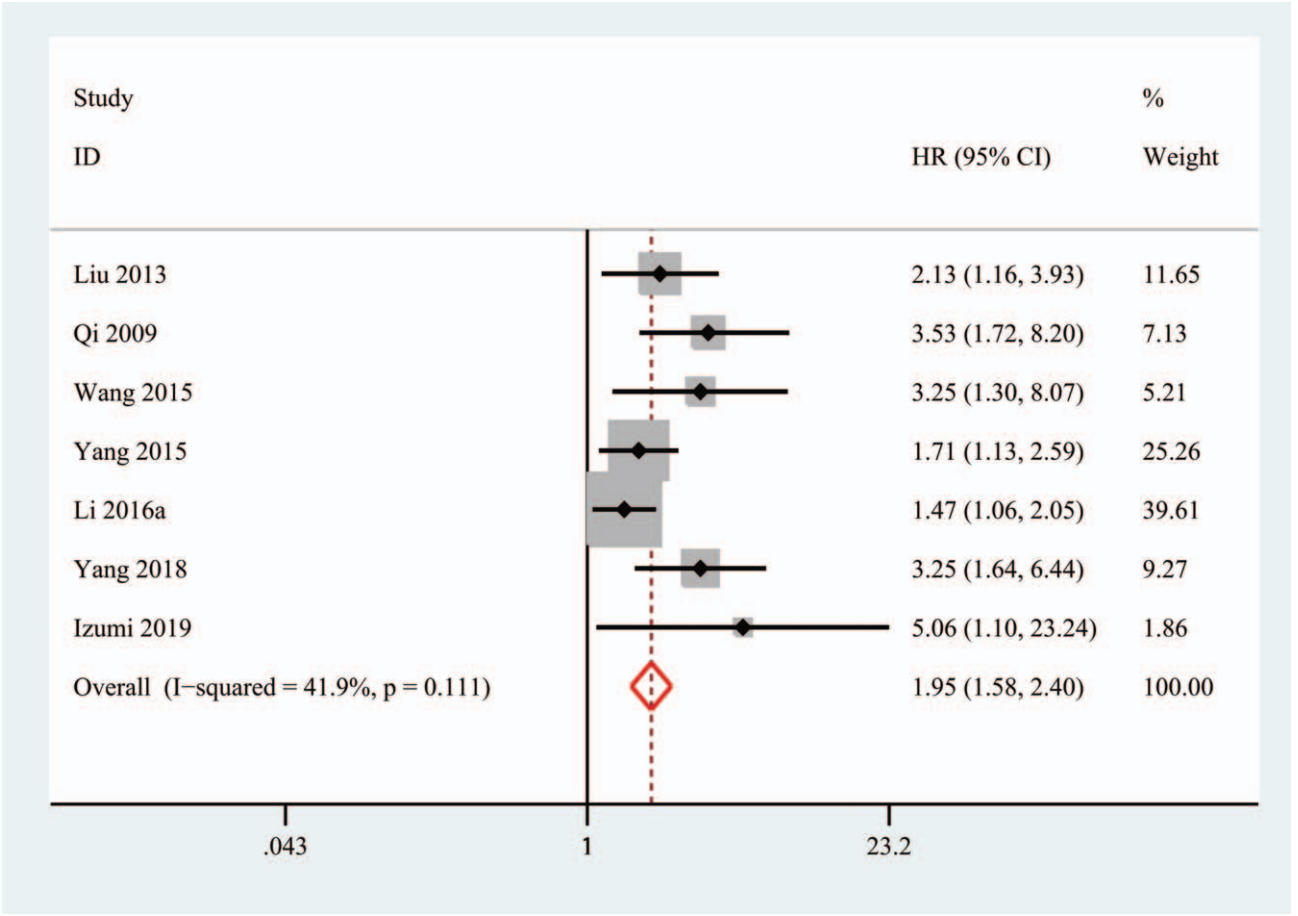

Figure 3. Forest plot diagrams of hazard ratios for the prognostic value of Tiam1 in disease-free survival.

Subgroup	No. of studies	Meta-regression		0.2 0.8 3.2 12.8	Harzard ratios(95% CI)	*p* value	Heterogeneity	
		tau^2	*p* -value				*p* -value	I^2
(1) Country		0.03	0.24					
China	18				2.233(1.876-2.659)	<0.01	0.021	44.90%
Other country	2				1.155(0.559-2.386)	0.665	0.015	83.20%
(2) Sample size		0.05	0.80					
≥150	12				2.172(1.537-3.07)	<0.01	<0.01	63%
<150	8				2.121(1.766-2.547)	<0.01	0.211	27%
(3) Detection methods		0.04	0.94					
IHCS	18				2.155(1.767-2.628)	<0.01	<0.01	56%
PCR	2				2.301(1.134-4.666)	0.021	0.259	21%
(4) Tumor type		0.04	0.47					
Digestive system tumor	9				2.024(1.616-2.536)	<0.01	0.18	30%
Head and neck carcinoma	7				2.157(1.07-4.347)	0.032	<0.01	75%
Gynecologic tumor	3				2.611(2.084-3.271)	<0.01	0.945	0%
Other tumor	2				1.866(1.069-3.256)	0.028	0.177	45.10%
(5) Adjusted factor(TNM stage)		0.02	0.14					
Yes	7				2.328(1.854-2.923)	<0.01	<0.01	57%
No	13				1.839(1.334-2.534)	<0.01	0.144	37%
(6) Adjusted factor(Differentiation)		0.03	0.36					
Yes	8				2.59(2.145-3.127)	<0.01	0.852	0%
No	12				1.896(1.428-2.518)	<0.01	<0.01	62%

Figure 4. Meta-regression and subgroup analysis exploring the sources of heterogeneity and assessing the stability of the pooled hazard ratio for overall survival.

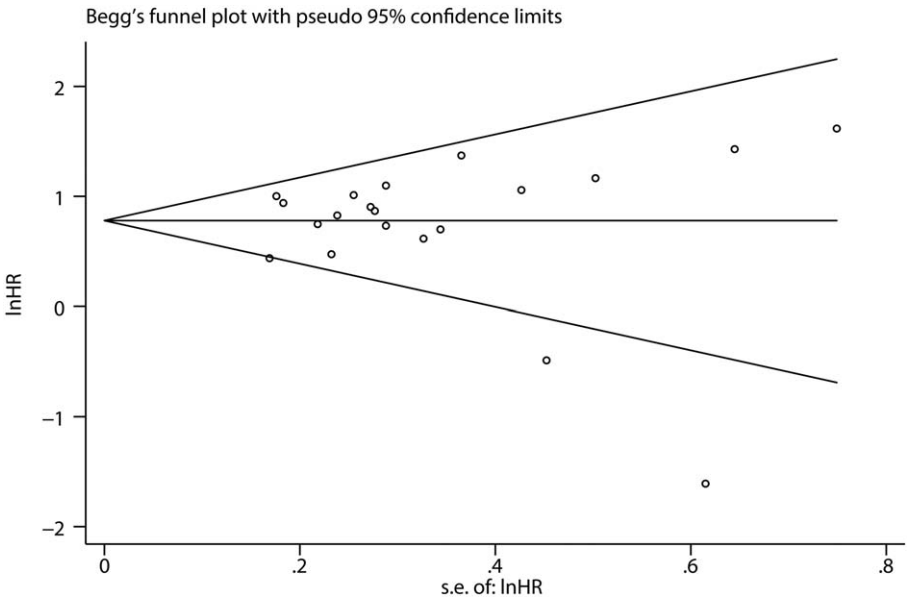

Figure 5. Begg funnel plot for publication bias assessment of the pooled hazard ratio for overall survival.

Tiam1 may be a useful prognostic biomarker for poor survival, suggesting Tiam1 could be explored as a promising therapeutic target for solid cancers.

The inverse association between Tiam1 expression and prognosis in patients with cancers may be interpreted by its roles in meditating tumor cell malignant phenotypes. First, as a metastasis-associated-gene, a large number of studies attested that Tiam1 could enhance tumor invasion and metastasis through activating Rac1. In addition, several recent studies also revealed that Tiam1 could facilitate epithelial-mesenchymal transition (EMT), a prerequisite for invasion and metastasis, of pancreatic,[13] lung,[35] cervical,[33] and thyroid[11] cancers. Second, Tiam1 has been reported to regulate tumor cell proliferation and apoptosis. Activation of Ras-MAP kinase signaling pathways play an important role in promoting tumor cell proliferation by facilitating cell cycle.[38–40] Tiam1-knockout mice were resistant to Ras-induced skin cancers, hinting that Tiam1 may be a responsive gene of Ras-MAP kinase signaling pathways and in implicated regulating tumor cell proliferation.[41] Consistently, many studies implied that Tiam1 overexpression exhibited an accelerative effect in regulating malignant cell proliferation in a wide range of cancers, including hepatocellular carcinoma,[42–44] oral cancer,[45] lung cancer,[35] esophageal cancer,[46,47] pancreatic cancer,[13,48] ovarian cancer,[49] cervical cancer,[33,50] colon cancer,[51–54] gastric cancer,[55] osteosarcoma,[56,57] nasopharyngeal cancer,[14] laryngeal cancer,[31] and cholangiocarcinoma.[58] Besides, lots of studies indicated that upregulation of Tiam1 could protect malignant cells from apoptotic death in esophageal cancer,[46,47] cervical cancer,[50] laryngeal cancer,[31] retinoblastoma,[59] and colon cancer.[54] Third, a few recent studies demonstrated that Tiam1 was able to promote of angiogenesis cervical[33] and lung cancer.[35] Fourthly, Tiam1 is involved in drug resistance of cancer cells. A most recent study showed that Tiam1 expression was significantly upregulated in colorectal cancer patients without positive response to chemotherapy and demonstrated that Tiam1 overexpression could induce drug resistance through promoting the stemness of colorectal cancer cells.[18] Similarly, it was also reported that Tiam1 participated in inducing resistance against doxorubicin in a 3D lymphoma model.[60] Taken together, all these evidence hold on to the notion that Tiam1 promote tumor progression by facilitating malignant cell invasion, metastasis, proliferation, angiogenesis, and drug resistance, as well as protecting malignant cells from apoptotic death, which could account for our findings in the current meta-analysis.

There are several limitations in our meta-analysis. First, all included studies were retrospective studies. In retrospective studies positive results were more likely to be reported than those with negative ones, which may cause bias. Second, most studies were conducted in China. Therefore, more clinical studies are required to further assess the prognostic value of Tiam1 in cancer patients from other countries. Thirdly, statistically substantial heterogeneity existed in the current meta-analysis. Accordingly, in future more homogeneous studies should be conducted to further validate our findings in this meta-analysis.

5. Conclusion

In summary, the current meta-analysis showed that Tiam1 higher expression positively correlated with shorter overall survival and disease-free survival, implying that Tiam1 may serve as a valuable prognostic indicator and treatment target for patients with solid cancers. However, more homogeneous and prospective studies should be conducted to further validate our conclusions in this meta-analysis.

Author contributions

Conceptualization: Fan Yang.
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Investigation: Jianlong Ding, WeiFeng Wu.

Methodology: Jianlong Ding.
Project administration: Fan Yang.
Resources: Fan Yang.
Software: Fan Yang.
Validation: Fan Yang.
Visualization: Jianlong Ding, Fan Yang.
Writing – original draft: Jianlong Ding.
Writing – review & editing: Jianlong Ding.

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