Clinical and prognostic role of Vasohibin-1 expression in solid tumors: An evidence from a meta-analysis

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Abstract

Background

The role of Vasohibin-1 (VASH1) expression in solid tumors remains controversial. We thus performed this meta-analysis to elucidate the associations between VASH1 expression and the prognosis of solid tumors.

Methods

We searched relevant literature in PubMed, Web of Science and EMBASE. The hazard ratio (HR) or odds ratio (OR) and 95% confidence intervals (CIs) were measured by fixed-effects or random-effects models. Publication bias was assessed using funnel plots and Egger's regression test.

Results

The results showed that VASH1 expression exhibited a significantly decreased overall survival (OS) time (HR = 1.85; 95% CI = 1.27–2.69) and disease-free survival (DFS) (HR = 1.80; 95% CI = 1.41–2.29) time. Meanwhile, VASH1 expression was found significantly associated with TNM stage (OR = 1.96; 95% CI = 1.57–2.46), tumor stage (OR = 2.35; 95% CI = 1.88–2.93), lymph node metastasis (OR = 2.02; 95% CI = 1.37–2.98), venous invasion (OR = 1.63; 95% CI = 1.00-2.65), tumor grade (OR = 1.74; 95% CI = 1.13–2.67) and microvessel density (MVD) (OR = 4.30; 95% CI = 2.31–8.03). However, no significant association was found between the VASH1 expression and distant metastasis (OR = 1.81; 95% CI = 0.74–1.41).

Conclusion

This study demonstrated that VASH1 expression was relevant to more aggressive clinicopathological parameters and might predict inferior DFS and OS in solid tumor patients.

Background

Cancer is a deadly disease that has plagued mankind for centuries and is still growing at a terrifying rate with an estimated more than 14,400,000 new cases all over the world, partly owing to the change of lifestyle and increased life expectancy [1]. The occurrence of cancer is due to many factors, such as dietary factors, carcinogen exposure, radiation, individual difference, et al [2]. Even though the exact mechanism is not entirely clear, the subtle correlation between some biological behaviors and cancer is being investigated, for example, angiogenesis [3]. Tumor angiogenesis, normally regulated by a relative balance between stimulatory and inhibitory factors, has been regarded as a

key catalyst for tumor progression, metastasis and poor prognosis in most cases [4, 5].

VASH1, a member of vasohibin protein family, has been identified as an endogenous inhibitor of angiogenesis and expressed in endothelial cells (ECs) [6]. Consisting of eight exons and seven introns, its genes localize at chromosome 14q24.3, which could be induced by vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF-2) [4]. Considering that angiogenic disorder is one of the hallmarks of cancer, as an important vascular regulator, VASH1 may accelerate or inhibit the genesis and progression of cancer in some ways [7]. In reality, to explore the role of VASH1 on cancers, scholars have carried out many experiments (or researches) and achieved preliminary results. For example, Wang et al. retrospected 117 patients with primary hepatocellular carcinoma (HCC), which manifested that high expression of VASH1 could result in more adverse clinical and prognostic outcomes [8]. Furthermore, from a study conducted by Miyazaki et al, a negative correlation was found between VASH1 and tumor grade, microvessel density (MVD) and five-years survival rate [9]. But reversely, another experiment conducted by Li et al., which based on rodent model, stated that VASH1 might inhibit the proliferation and metastasis of HCC and therefore prolong the life of experimental mice [10]. By retrospectively analysing the data from 118 consecutive renal cell carcinomaclear (RCC) patients, Kanomata et al. have yielded a similar conclusion - a higher VASH1 expression was observed with significantly shorter OS [11]. The discrepancies between these studies highlight the importance of evaluating the clinical and prognostic significance of VASH1 in human malignant neoplasms.

We, therefore, performed this study to provide a more rigorous assessment of existing clinical and prognostic data by systematically reviewing the studies reporting VASH1 and corresponding outcomes. We reviewed and conducted a meta-analysis of these studies which reported the relationship between VSAH1 expression and the following outcomes: TNM stage, tumor stage (T stage), lymph node metastasis (N stage), distant metastasis (M stage), venous invasion, tumor grade, MVD, OS, and DFS in solid tumors.

Methods

This meta-analysis followed the PRISMA guidelines [12].

Literature search and inclusion criteria

The literature retrieval was performed by two independent members of the author team (Ye Tian and Chenkui Miao) in electronic databases including PubMed, Web of Science and EMBASE databases from inception until January 2020. The search strategy in PubMed included the following domains: "Vasohibin-1", "Vasohibin 1", "VASH1", "cancer", "carcinoma", "neoplasm", "tumor ", and "malignancy". These terms were combined with "AND" or "OR". Web of Science and EMBASE searches were completed with the authors' terminology. Also, the reference lists of included studies and related comments were manually filtered for new studies that may be relevant.

Studies were included if they: (1) were studies on malignant tumor; (2) evaluated the relationship between VASH1 expression and clinical outcomes; (3) reported the clinicopathological parameters in study patients; (4) included the control group. To supplement our literature searching, the reference lists of relevant articles were reviewed for eligibility.

Data Extraction

All records were independently evaluated by three investigators (Ye Tian, Chenkui Miao, Xiaohan Ren) through title, abstract and full-text screening. Any discrepancies about record eligibility were resolved by a discussion between two members as well as a fourth author (Qi Gu). All studies meeting inclusion criteria were retained in the analysis.

For each included record, two investigators independently extracted relevant data to rule out any discrepancies. Disagreements were resolved by a discussion between two investigators. The following data were recorded from all eligible studies: (1) the first author's name and year of publication, (2) the study nationality, (3) cancer types, (4) sample and pathology type, (5) the cut-off value and assay method, (6) following-up months, (7) the case number of VASH1 relatively-high expression and prognostic outcomes. Those indirectly reported HRs and 95% CIs were extracted from graphical survival plots using Engauge Digitizer version 4.1 (markmitch, Boston, USA) [13].

Quality Assessment

We used the Newcastle-Ottawa scale (NOS) score to independently evaluated the study quality, which allows for the evaluation of methods of patient selection, comparability of study groups, and reporting

of essential outcomes [14]. With the score ranging from 0 to 9, studies with scores ≥ 6 were graded as high quality. Details are available in Table 1.

Table 1
Newcastle-Ottawa scale (NOS)

Reference	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Total Scores
Yu et al. [17]	★	★	★	★	★☆	★	★	☆	7
Yu et al. [18]	★	★	★	★	★★	★	☆	★	8
Ninomiya et al. [19]	★	★	★	★	★★	★	★	☆	8
Wu et al. [20]	★	★	☆	☆	★★	★	★	★	7
Ma et al. [21]	★	☆	★	★	★★	★	★	☆	7
Sano et al. [22]	★	★	☆	★	★★	☆	★	☆	6
Torii et al. [23]	★	★	☆	★	★★	☆	★	☆	6
Mikami et al. [24]	★	★	☆	★	★★	★	★	☆	7
Shen et al. [25]	★	★	☆	★	★★	★	★	☆	7
Liu et al. [26]	★	★	☆	★	★★	☆	★	★	7
Murakami et al. [27]	★	★	★	★	★★	☆	★	☆	7
Yan et al. [28]	★	★	★	★	★★	★	★	☆	8
Zhang et al. [29]	★	★	★	★	★☆	☆	★	☆	6
Kitajima et al. [30]	★	★	☆	★	★☆	★	★	☆	7
Kosaka et al. [31]	★	★	★	★	★☆	★	★	☆	7
Kanomata et al. [32]	★	☆	★	★	★★	☆	★	☆	6
Miyazaki et al. [33]	★	★	☆	★	★☆	★	★	★	7
Wang et al. [34]	★	★	★	☆	★★	☆	★	☆	6
Notes: ★,score; ☆, not score									

Statistical analysis

Stata version 16.0 (Stata Corporation, College Station, TX, USA) was used to calculate all statistical analyses. All reported P-values were two-sided, with $p < 0.05$ defined as statistically significant. Testing for the heterogeneity of pooled effects (HR; OR), Cochrane Q-test [15] and the inconsistency index value (I2) [16] were performed in the meta-analysis. The fixed-effects model or random-effects model was selected following the heterogeneity of included studies. The funnel plot and Egger's test were used to judge the publication bias.

Results

Characteristics of included studies

The flowchart shows the literature retrieval and selection process (Fig. 1). Using the search strategy in PubMed, Web of Science, EMBASE and the Cochrane Register of Controlled Trials databases, we initially collected a total of 132 studies, but 63 of them were excluded after screening the titles and abstracts. By further reviewing assessing the remaining studies, 30 studies were excluded for review articles, letters, research with non-human or not relevant to the current analysis. Eventually, 18 studies were identified as meeting our inclusion criteria [17–34], whose detailed information was shown in Table 2. The VASH1 relatively-low expression group (1225 individuals; 52.8%) was regarded as the control group. The main assay method of all studies was immunohistochemistry (IHC).

Table 2
Characteristics of enrolled studies

Reference	year	Tumor Histology	Case nationality	Detected sample	Technique	Cut-off value	Follow-up time	Quality score
Yu et al. [17]	2019a	Ovary serous carcinoma	China	Tissue	IHC	Final scores ≥ 3	6-105 months	7
Yu et al. [18]	2019b	Epithelial ovarian cancer	China	Tissue	IHC	Final scores ≥ 3	6-105 months	8
Ninomiya et al. [19]	2018	Squamous cell carcinoma of the esophagus	Japan	Tissue	IHC	> Average MVD/VASH1	5 years	8
Wu et al. [20]	2017	Lung squamous cell carcinoma	China	Tissue	IHC	Final scores ≥ 3	8–71 months	7
Ma et al. [21]	2017	Esophageal carcinoma	China	Tissue	IHC	Mean value > 4	N.R	7
Sano et al. [22]	2017	Ovarian carcinoma	Japan	Tissue	IHC	> Median immunostained vessels	0-143 months	6
Torii et al. [23]	2017	Head and neck squamous cell carcinoma	Japan	Tissue	IHC	VASH1 expression ≥ 1.11%	14–194 months	6
Mikami et al. [24]	2017	Renal cell carcinoma	Japan	Tissue	IHC	VASH1 density ≥ 268.8	N.R	7
Shen et al. [25]	2015	Gastric carcinoma	China	Tissue	IHC	Combined staining score ≥ 5	N.R	7
Liu et al. [26]	2015	Colorectal carcinoma	China	Tissue	IHC	N.R	N.R	7
Murakami et al. [27]	2014	Hepatocellular carcinoma	Japan	Tissue	IHC	VASH1/CD34 > 0.459	median 36 months	7
Yan et al. [28]	2014	Colorectal carcinoma	China	Tissue	IHC	Combined staining score ≥ 5 s	4–83 months	8
Zhang et al. [29]	2014	Non-small cell lung carcinoma	China	Tissue	IHC	Immunohistochemical expression level ≥ 150%	52 months	6
Kitajima et al. [30]	2014	Colorectal carcinoma	Japan	Tissue	IHC	IHC score ≥ 6	0.13–118.4 months	7
Kosaka et al. [31]	2013	Prostate carcinoma	Japan	Tissue	IHC	VASH1 density ≥ 12 per mm2	4.9 years	7
Kanomata et al. [32]	2013	Renal cell carcinoma	Japan	Tissue	IHC	N.R	3026 days	6
Miyazaki et al. [33]	2012	Urothelial carcinoma	Japan	Tissue	IHC	> median value	0.7–20 years	7
Wang et al. [34]	2011	Hepatocellular carcinoma	China	Tissue	IHC	Immunohistochemical score (H-score) ≥ 6	5–62 months	6

Notes: IHC, immunohistochemistry

Clinicopathological Parameters And VASH1 Expression

The pooled OR from 18 studies, including 1092 high VASH1 and 1225 low VASH1 individuals, shown in Fig. 2–4 and Table 3. With the study of Liu et al. removed for sensitivity analysis, 10 studies estimated the association between VASH1 expression and TNM stage, indicating that a higher VASH1 expression

in malignancy tissue may lead to worse TNM stage (3/4) (OR = 2.35; 95% CI = 1.88–2.93; I2 = 31.4%). Conceivably, as with the TNM stage, a significant adverse effect was found in the analysis of tumor stage (OR = 1.96; 95% CI = 1.57–2.46; I2 = 37.9%) and lymph node metastasis (OR = 2.02; 95% CI = 1.37–2.98; I2 = 52.9%). However, no sufficient correlation was observed in distant metastasis (OR = 1.81; 95% CI = 0.74–4.41; I2 = 66.0%).

Table 3
Meta-analysis results of enrolled studies

	N[a]	VASH1 + [b]	VASH1-[c]	OR (95%CI)*	P[d]	HR (95%CI)*	P[d]
TNM stage (3/4)							
Total	10	723	854	1.96(1.57–2.46)	0.106	—	—
Tumor stage (T3/T4)							
Total	10	723	854	2.35(1.88–2.93)	0.157	—	—
Lymph node metastasis (N1-N3)							
Total	9	668	703	2.02(1.37–2.98)	0.030	—	—
Distant metastasis (M1)							
Total	5	385	474	1.81(0.74–4.41)	0.019	—	—
Venous invasion							
Total	5	430	522	1.63(1.00-2.65)	0.036	—	—
Tumor grade							
Total	11	900	979	1.74(1.13–2.67)	< 0.001	—	—
Microvessel density (MVD)							
Total	4	416	468	4.30(2.31–8.03)	0.006	—	—
Disease-free survival (DFS)							
Total	6	321	441	—	—	1.80(1.41–2.29)	0.302
Overall survival (OS)							
Total	13	761	922	—	—	1.85(1.27–2.69)	< 0.001
a Number of studies							
b Number of VASH1 positive (or high) patients							
c Number of VASH1 negative (or high) patients							
d Random-effects model was used when p value for heterogeneity test < 0.1; otherwise, fixed-effects model was used							

Moreover, the result reveled that high VASH1 expression exhibited a significant increased venous invasion (OR = 1.63; 95% CI = 1.00-2.65; I2 = 61.0%) and MVD (OR = 4.30; 95% CI = 2.31–8.03; I2 = 75.8%). And interestingly, VASH1 expression may be related with poorly-differentiated tumor cells (OR = 1.74; 95% CI = 1.13–2.67; I2 = 69.1%).

Prognostic Value Of VASH1 Expression For DFS And OS

The correlation of VASH1 expression and survival outcomes is shown in Fig. 4 and Table 3. A total of 14 studies comprising 1744 patients reported the effect of VASH-1 on DFS or OS in multiple tumors. For DFS, since no significant heterogeneity was observed among these studies (p = 0.302, I2 = 17.2%), a fixed-effect model was utilized. The pooled HR with 95% CI suggested that high VASH-1

expression in tumor tissues was significantly associated with poor DFS (pooled HR = 1.80, 95% CI: 1.41–2.29). Moreover, a higher VASH1 expression was observed with significantly shorter OS time (pooled HR = 1.87, 95% CI: 1.27–2.69; I2 = 80.0%), same as the conclusion of DFS.

Test Of Heterogeneity

For the comparison of the lymph node metastasis, distant metastasis, venous invasion, AJCC stage, tumor grade, MVD and OS, moderate heterogeneity was observed. However, no heterogeneity was observed in TNM stage, tumor, and DFS.

Sensitivity Analysis

Sensitivity analysis aimed at assessing whether the exclusion of any individual study influenced the overall results. Figure S1 revealed that the results were reliable, indicating that no individual study affected the pooled HR significantly.

Publication Bias

The funnel plot (Fig. 5) and Egger's test were used to assess publication bias. The funnel plot indicates that no significant publication bias for TNM stage, tumor, lymph node metastasis, distant metastasis, which were confirmed by Egger's test respectively (P = 0.219, P = 0.113, P = 0.784, P = 0.535). Similarly, no publication bias was found in venous invasion (Egger's test : P = 0.915), tumor grade (Egger's test : P = 0.120), OS (Egger's test : P = 0.693) and DFS (Egger's test : P = 0.353). However, we found publication bias in the analysis of MVD (Egger's test: P = 0.013).

Discussion

As an endogenous inhibitor of angiogenesis, VASH1 may play a pivotal role in maintaining vascular homeostasis, preventing pathological angiogenesis [35]. VASH1 may possess the duality functions - an experiment based on the mice model stated that the decrease of VASH1 resulted in a long lifespan, which contrary to the prime expectation of the experimenters [36]. Meanwhile, the feasible suppression and facilitation of VASH1 on tumors have of late years investigated by scholars and the results remain controversial [37, 38].

Meta-analysis can provide more reliable results compared with a single study and serves as a powerful tool to explain controversial conclusions. For this reason, we performed a meta-analysis to clarify whether VASH1 expression has a significant impact on the clinical and prognostic outcomes of

cancer. To our knowledge, this is the first complete meta-analysis concerning the role of VASH1 in solid tumors. In our analysis, we found that VASH expression was relevant to more aggressive clinicopathological parameters and might predict inferior DFS and OS in cancer patients.

The result of our analysis showed that high expression of VASH1 might be associated with more inferior TNM stage, tumor stage, lymph node metastasis, distant metastasis and tumor grade, same as the conclusion with many studies, for example, Cao et al. and Zhang et al. [39, 40]. Despite the concrete mechanism not being clearly understood, an accountable explanation is that - in the process of tumor angiogenesis, the out-off-balance between VASH1 and VEGF may lead to the formation of numerous new blood vessels with fragmentary structure or lack of basement membrane, although the inhibition role of VASH1 in tumor vascularization. And the noteworthy increase of vascular permeability caused by this imbalance could further accelerate the proliferation and metastasis of cancer cells [41]. Put another way, VASH1 suppresses tumor angiogenesis but not the tumor cells. MVD, as an independent predictor of poor prognosis, is generally regarded connected with clinical outcome, for instance, tumor grade, pathologic stage et al. [42, 43]. Additionally, from the present analysis, an advanced relevance between venous invasion, MVD, and VASH1 expression was found, which was opposite to our expectations. Interestingly, considering that the indispensable effect of VASH1 on maintaining vascular health and inhibiting angiogenesis, this unexpected result is worth a thorough discussion. Firstly, as we know, VASH1 is induced by angiogenic factors, to illustrate, VEGF and FGF-2 [4]. There is a positive relevance between the intensity of VASH1 and VEGFA in tumor cells [31, 44]. Nevertheless, with VASH1 degraded and inactivated after its secretion in the tumor microenvironment, the IHC staining of VASH1 in vascular ECs may not demonstrate its anti-angiogenic activity, but only reflect the response of ECs to angiogenic stimulation [45]. Secondly, as a feedback regulator of angiogenesis, VASH1 is up-regulated with VEGFA expression. Yet this endogenous up-regulation is not enough to inhibit neovascularization. Researchers found that in tumor tissue, not only MVD expression increased but also the more ripe microvasculature where the VASH1 mainly expressed [46]. These mature vasculature may supply more nutrition for tumors, and therefore facilitate tumor growth and distant metastasis. Consequently, the increase of VASH1 expression may

be associated with the enhancement of tumor invasiveness [25, 27]. Thirdly, VASH1 might be an activator or inhibitor of angiogenic factor mRNA translation, and this dual functional role may be the reason for VASH1 to inhibit angiogenesis and to profit ECs survival [47, 48].

Finally, our results showed that the higher expression of VASH1 associated with shorter DFS and OS time, which was in line with conclusions from most studies [33, 34]. From our perspective, the high expression of VASH1 is related to worse clinicopathological features and thus shorten survival time. However, the results of the OS time showed high heterogeneity, which might be caused by different types of solid tumors.

Furthermore, despite the overall robust statistical evidence generated through this analysis, some limitations have been identified. Firstly, owing to the limited quantity of the studies included, further subgroup analysis is unavailable, for example, cancer types. Secondly, IHC based VASH1 detection has limitations for its subjectivity in determining a clear definition of "positive (or high)" tumor VASH1 staining. Meanwhile, different studies had different definitions of positive expression of VASH1 (final scores, VASH1 density, IHC expression level, et al.), and thus more uniform standards need to be established. Thirdly, only the Asian population was applicable in this meta-analysis, which might minimize the analyzing value to some level. Moreover, the difference in samples from different institutions might reduce the credibility of our conclusion, which serves as an unavoidable factor in the study.

Conclusion

In conclusion, our meta-analysis suggested that high expression of VASH1 could act as a common maker to predict a high risk of clinical outcomes and poor OS or DFS in patients with a solid tumor. However, based on the limitations of this meta-analysis, large size, and better design studies are needed to validate the clinical role of VASH1.

Abbreviations

VASH1: Vasohibin-1

HR: hazard ratio

OR: odds ratio

CIs: confidence intervals

DFS: disease-free survival

ECs: endothelial cells

VEGF: vascular endothelial growth factor

FGD-2: fibroblast growth factor 2

HCC: hepatocellular carcinoma

MVD: microvessel density

RCC: renal cell carcinomaclear

T stage: tumor stage

N stage: lymph node metastasis

M stage: distant metastasis

NOS: Newcastle-Ottawa scale

IHC: immunohistochemistry

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional files.

Competing interests

The author declares that they have no competing interests.

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Authors' contributions

YT and MC collected the data and performed the meta-analysis. YT wrote the manuscript. All the authors participated in the data analysis and approved the final version of the manuscript.

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Figures

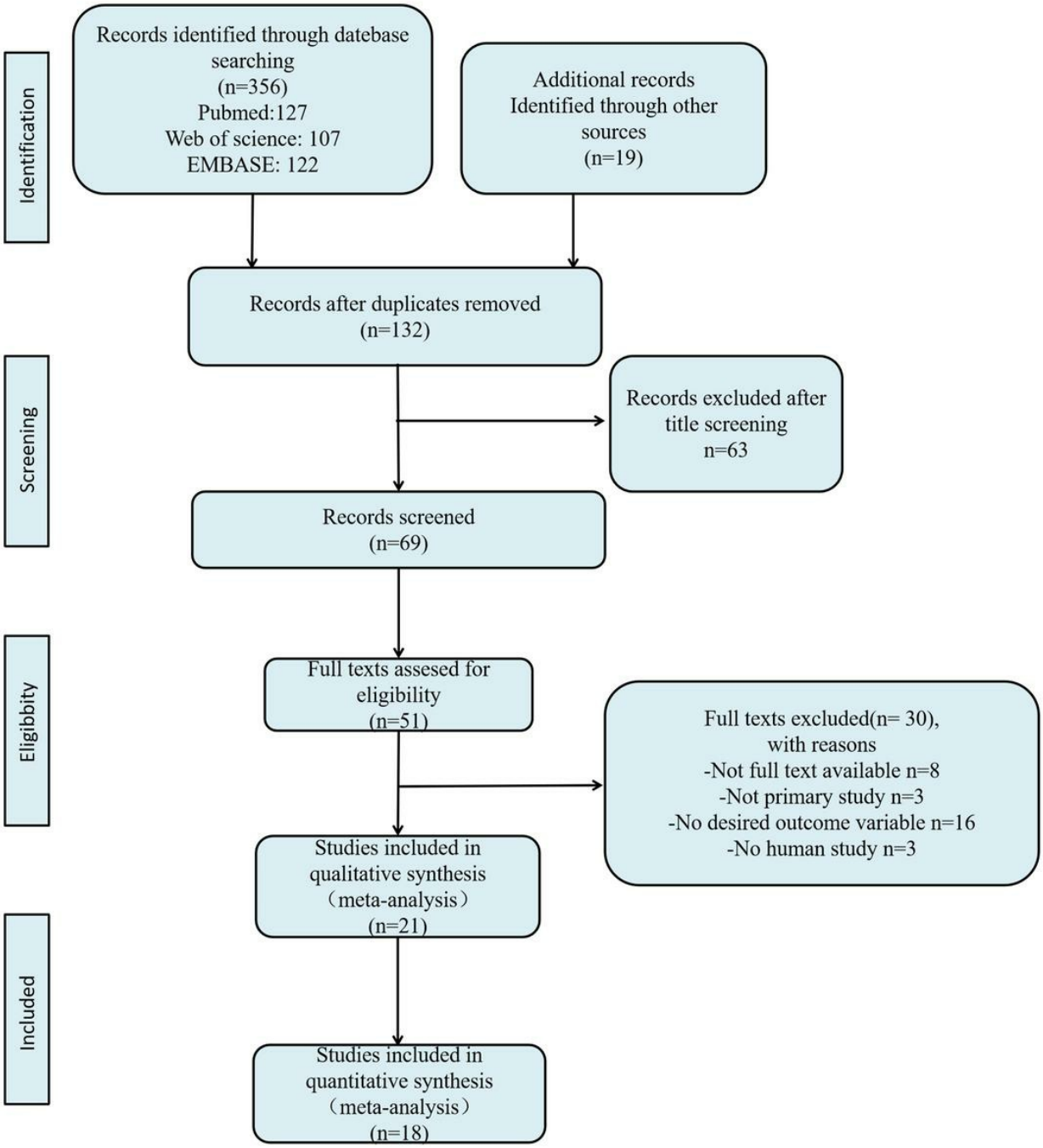


Figure 1

Flow diagram of literature search and selection process.

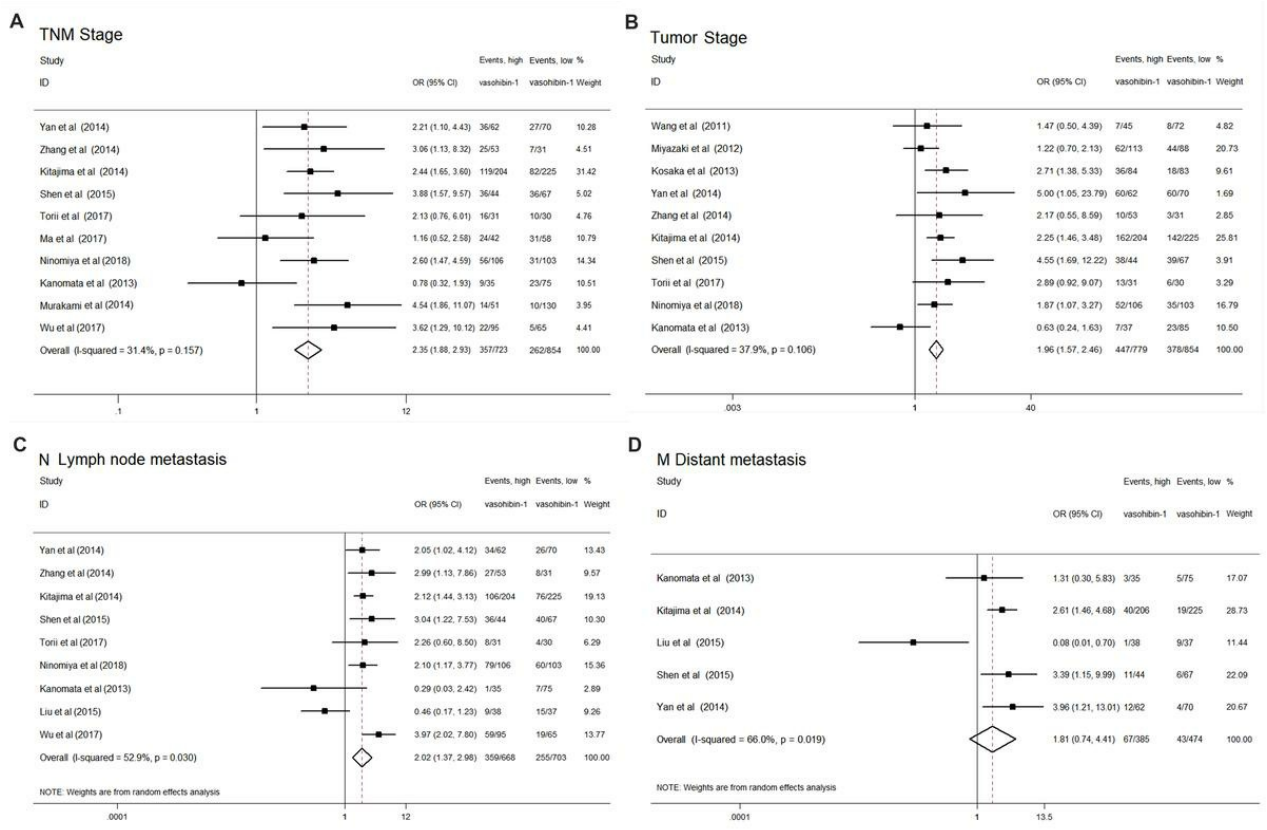


Figure 2

Forest plots of TNM stage, tumor stage (T stage), lymph node metastasis (N stage), distant metastasis (M stage). Notes: A : The forest plot of TNM stage; B : The forest plot of tumor stage; C : The forest plot of lymph node metastasis; D : The forest plot of distant metastasis.

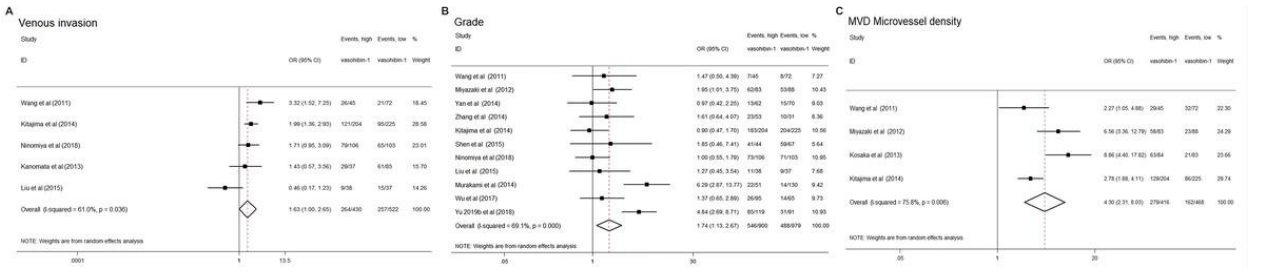
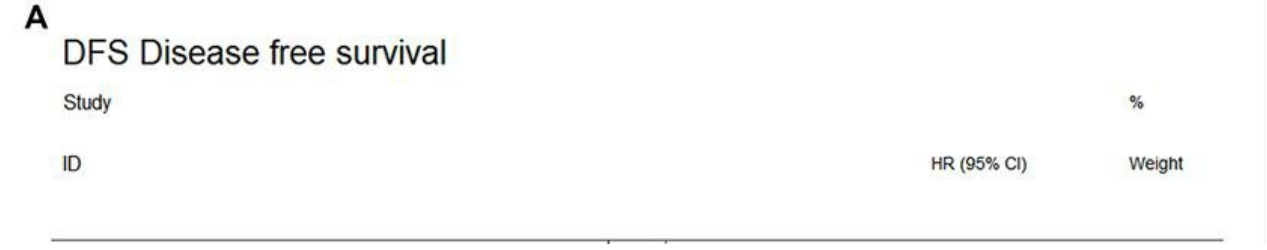
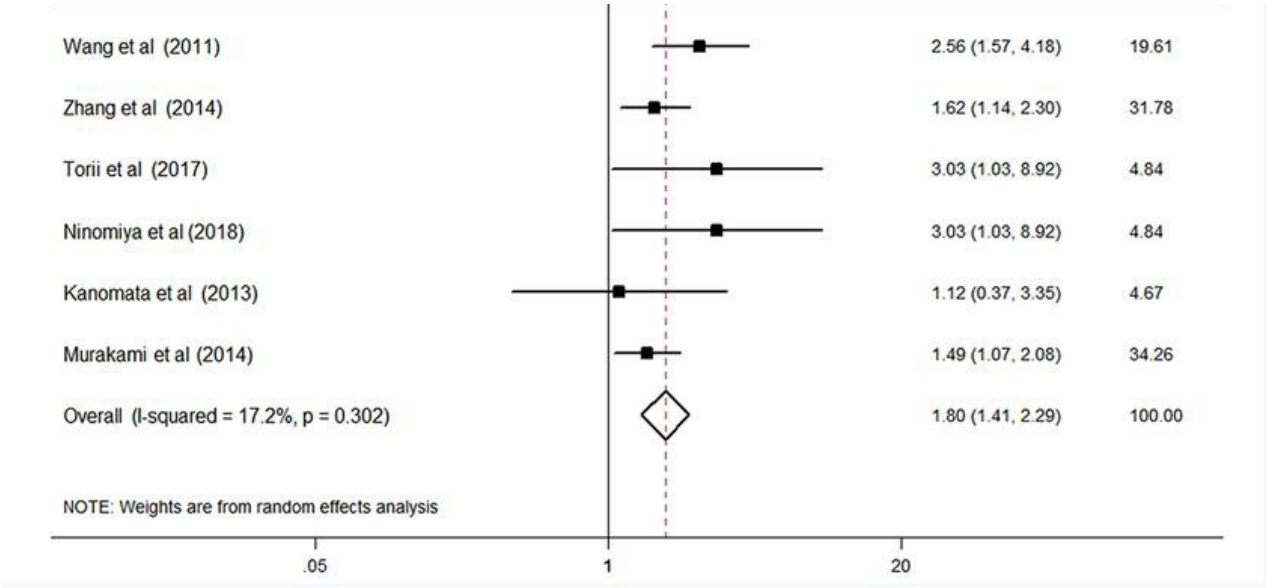


Figure 3

Forest plots of venous invasion, tumor grade, MVD Notes: A : The forest plot of venous invasion; B : The forest plot of tumor grade; C : The forest plot of MVD.





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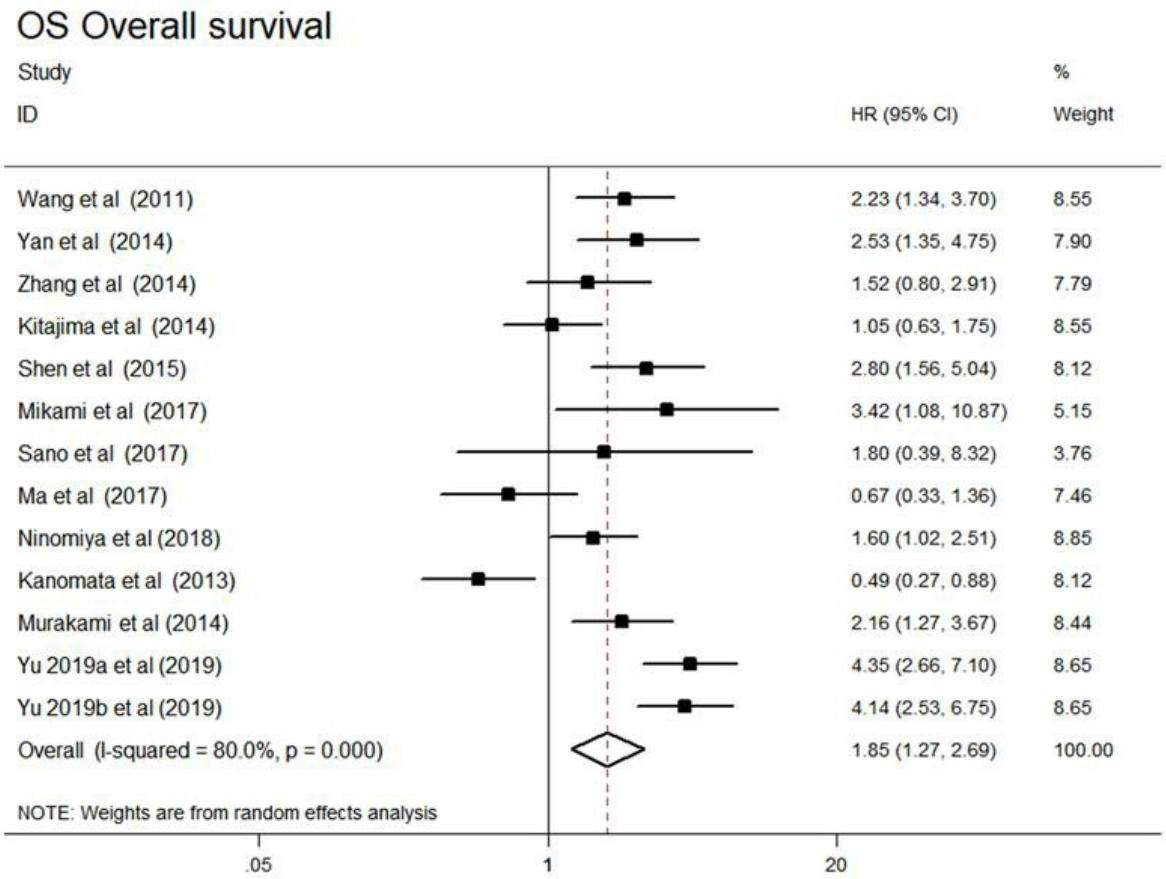

Figure 4

Forest plots of DFS and OS time. Abbreviations: OS, overall survival; PFS, progression-free survival Notes: A: Forest plots of DFS; B: Forest plots of OS.

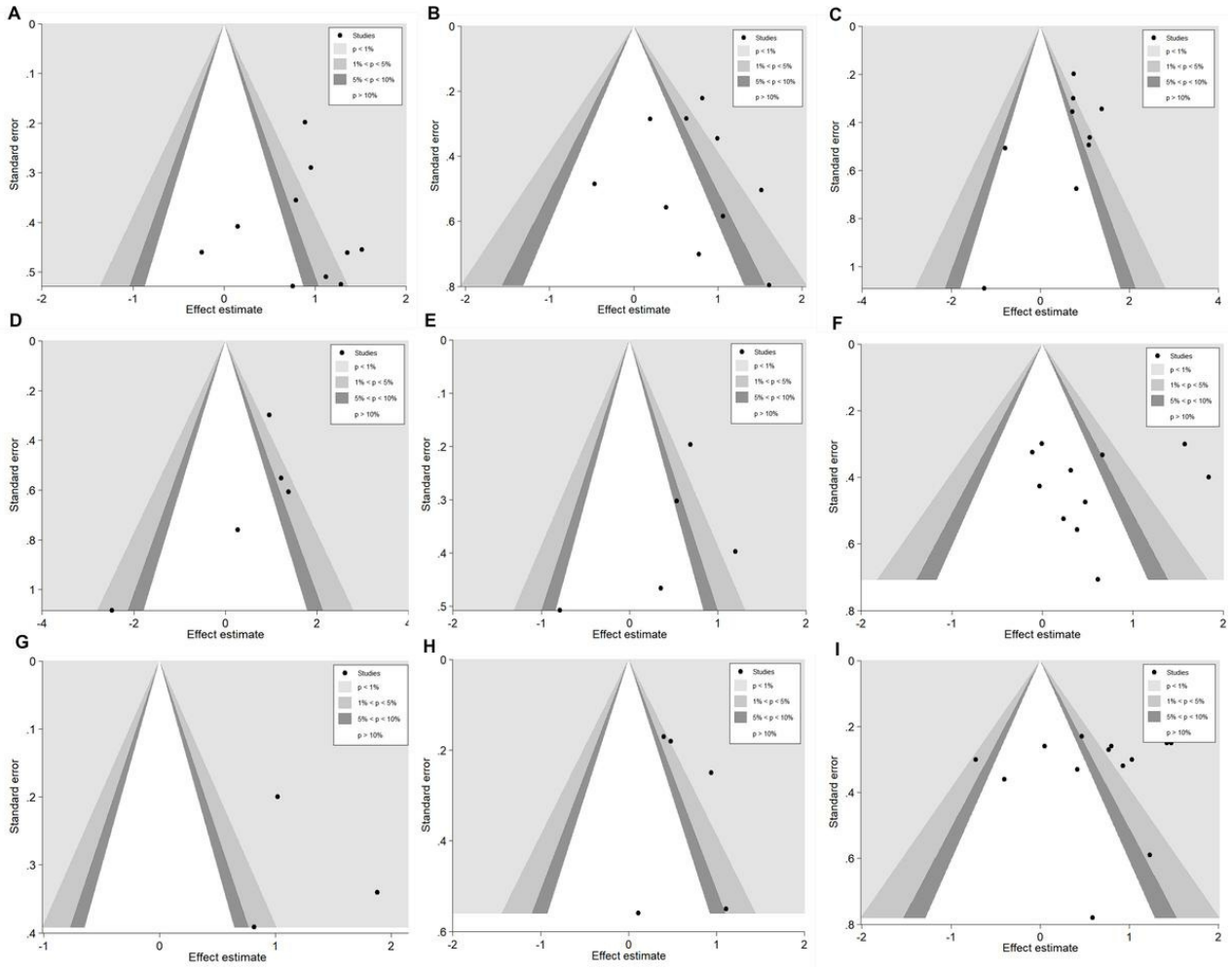

Figure 5

Funnel plots of TNM stage, tumor stage, lymph node metastasis, distant metastasis, venous invasion, tumor grade, MVD, DFS and OS time. Notes: A : The funnel plots of TNM stage; B : The funnel plot of tumor stage; C : The funnel plot of lymph node metastasis; D : The funnel plot of distant metastasis; E : The funnel plot of venous invasion; F : The funnel plot of tumor grade; G : The funnel plot of MVD; H : The funnel plot of DFS time; I : The funnel plot of OS time.

Supplementary Files

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