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ORIGINAL PAPER

Tumor vasculogenic mimicry predicts poor prognosis in cancer patients: a meta-analysis

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Abstract

Background Vasculogenic mimicry (VM) is the formation of vascular channels by tumor cells or tumor cell-derived, trans-differentiated cells in highly aggressive, solid tumors. However, the disease features and prognostic value of VM for overall survival of cancer patients remain controversial.

Method To systematically investigate the roles of VM in cancer progression and its prognostic values, we performed a meta-analysis based on 36 studies (33 eligible articles) including 3609 patients. The pooled hazard ratios (HRs) with 95 % confidence intervals (95 % CIs) were used to assess the relationship between VM and overall survival in cancer patients.

Results Vasculogenic mimicry was significantly associated with cancer differentiation, lymph node metastasis, distant metastasis, and TNM stage. The prognostic value of VM was significant in overall survival (HR 2.16; 95 % CI 1.98–2.38; $P < 0.001$). Analyses stratified by confounders, such as cancer type, ethnicity, VM detection methods, sample size, and Newcastle–Ottawa quality score, found similar significant results.

Conclusions The presence of VM predicts poorer survival outcomes in cancer patients.

Keywords Vasculogenic mimicry · Solid tumor · Angiogenesis · Survival · Meta-analysis

Introduction

The tumor vasculature system supplies blood for tumor growth and hematogenous dissemination, which have long been regarded as hallmarks of tumorigenesis [1, 2]. The well-known theory of vascularization in tumors is a complex process that involves angiogenesis (sprouting new vessels from existing vessels), vasculogenesis (recruiting circulating endothelial progenitor cells), co-option (hijacking of the existing vasculature) [3–6], and tumor cell-derived vasculature development known as vasculogenic mimicry (VM) [6–9].

Tumor VM refers to the plasticity of highly aggressive cancer cells that imitate endothelial cells and form vessel-like structure with the characteristic of positive PAS and negative endothelial cell markers, including CD31 or CD34 [8]. VM has been identified in many malignancies, such as melanoma [7, 10–13], gastric cancer [14–17], sarcoma [10, 18], ovarian tumor [19–21], hepatocellular carcinoma [22, 23], breast cancer [24, 25], head and neck cancer [26, 27], colorectal cancer [28, 29], glioma [30–33], lung cancer [34, 35], testicular germ cell malignant tumors [36], gallbladder

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cancer [37], prostate cancer [38], esophageal cancer [39], renal carcinoma [40], and osteosarcoma [41].

Vasculogenic mimicry may be important in the biological behavior of various tumors because it can establish an adequate vascular supply to enhance tumor growth and metastasis [8]. Growing evidence supports the notion of VM as a prognostic factor for poor clinical outcomes in various types of cancer, such as melanoma [7, 10, 42], sarcoma [10], ovarian tumor [20, 21], hepatocellular carcinoma [22, 23], and breast cancer [24, 25]. Nonetheless, some of these studies have not confirmed the association between VM and cancer survival [10, 12, 18, 19, 38, 43]. As a result, the prognostic value of VM in tumors is still inconclusive.

Therefore, we conducted a meta-analysis to determine the prognostic value of VM on overall survival in cancer patients.

Methods

Search strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [44–46]. Relevant articles were identified from PubMed, EMBASE, and the Web of Science databases with the following keywords: "cancer," "tumor," "neoplasm," "vasculogenic mimicry," "vascular mimicry," "VM," "tumor cell-lined vessels," "tumor derived endothelial cells," "prognosis," "survival," and "outcome." The last search was performed up to March 10, 2015, without restriction on language. All relevant publications in reference lists were also searched manually to find the additional eligible articles.

Selection criteria

To be included, studies had to have met several criteria: (1) the diagnosis of cancer must have been confirmed histologically or pathologically; (2) the association between VM and overall survival (OS) or disease features, such as tumor differentiation, TNM stages, lymph node metastasis, and distant metastasis, had to be evaluated; and (3) data had to be sufficient to estimate hazard ratios (HRs) for overall survival and risk ratios (RRs) for disease features. In case of duplicated articles [10, 47], only the most complete ones were included [10]. Narrative reviews, abstracts, letters, comments, editorials, and case reports were excluded.

Data extraction

Two investigators (JP Yang and YD Liao) separately extracted the data on authors, year of publication, races

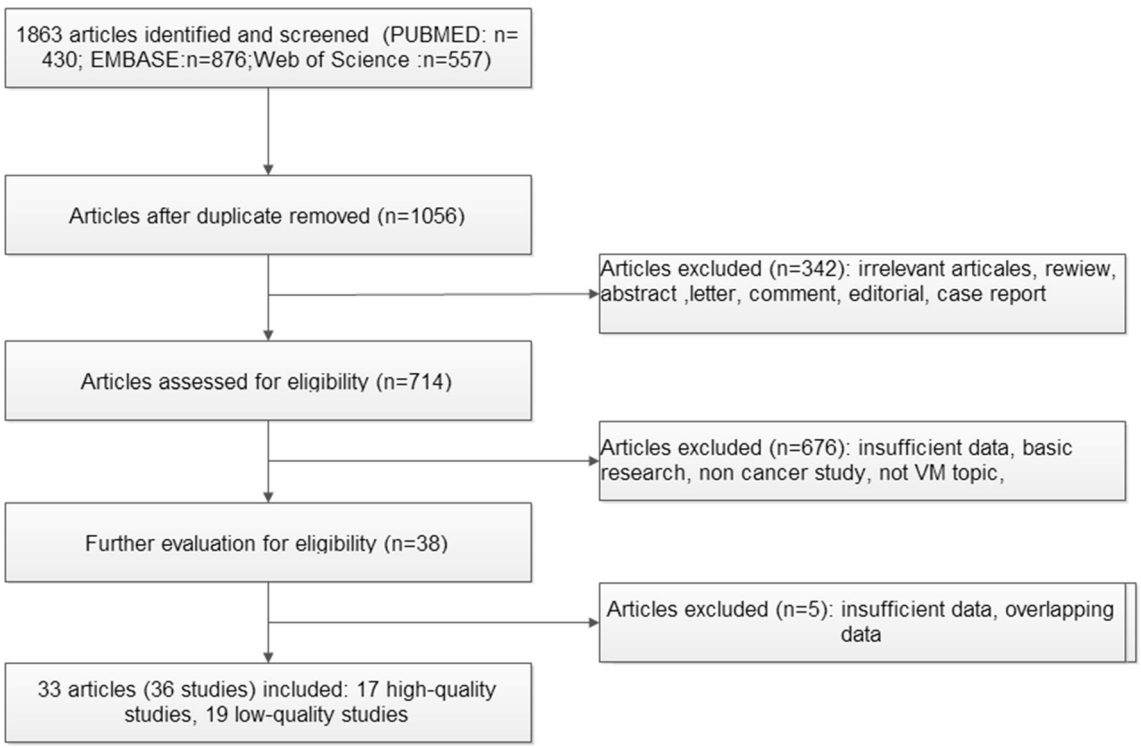

Fig. 1 Flow chart of study selection in the meta-analysis of the effects of vasculogenic mimicry on tumor features and survival in cancer patients

Table 1 Summary of 36 studies (from 33 articles) included in a meta-analysis of the association of vasculogenic mimicry with disease characteristics and overall survival in cancer patients

References	Population	Tumor type	VM assay methods	Cases	No. of cases		NOS score	Quality[a]
					VM+	VM−		
1. Maniotis [7]	Non-Asian	Melanoma	PAS	234	106	128	2	Low
2. Shirakawa [24]	Asian	Breast cancer	PAS	331	26	305	3	Low
3. Sun [10]	Asian	Sarcomas	CD31/PAS	37	10	27	3	Low
4. Sun [10]	Asian	Sarcomas	CD31/PAS	69	13	56	5	High
5. Sun [10]	Asian	Sarcomas	CD31/PAS	81	11	70	4	Low
6. Sun [10]	Asian	Melanoma	CD31/PAS	190	10	180	3	Low
7. Sun [22]	Asian	HCC	PAS	99	12	87	4	Low
8. Sun [14]	Asian	Gastric cancer	CD31/PAS	84	21	63	3	Low
9. Liu [26]	Asian	HNC	Pan-cytokeratin/CD34	112	41	71	2	Low
10. Hillen [43]	Non-Asian	Melanoma	PAS	58	22	36	2	Low
11. Gao [19]	Asian	Ovarian tumor	CD31/PAS	84	36	48	2	Low
12. Zhang [11]	Asian	Melanoma	PAS	124	54	70	3	Low
13. Baeten [28]	Non-Asian	Colorectal cancer	PAS	117	23	94	2	Low
14. Wang [18]	Asian	Sarcomas	CD34/PAS	45	25	20	2	Low
15. Wang [36]	Asian	TGCMT	CD34/PAS	40	22	18	4	Low
16. Li [15]	Asian	Gastric cancer	CD31/PAS	173	40	133	6	High
17. Wang [27]	Asian	HNC	CD31/PAS	203	44	159	7	High
18. Liu [23]	Asian	HCC	CD34/PAS	151	31	120	4	Low
19. Liu [30]	Asian	Glioma	CD34/PAS	101	13	88	5	High
20. Sun [37]	Asian	Gallbladder cancer	CD31/PAS	71	18	53	6	High
21. Liu [38]	Asian	Prostate cancer	CD31/PAS	96	24	72	6	High
22. Liu [29]	Asian	Colorectal cancer	CD34/PAS	203	39	164	4	Low
23. Van Beurden [12]	Non-Asian	Melanoma	PAS	123	42	81	5	High
24. Wu [34]	Asian	Lung cancer	CD34/PAS	305	109	196	6	High
25. Yu [20]	Asian	Ovarian tumor	CD31/PAS	87	50	37	5	High
26. Chai [39]	Asian	Esophageal cancer	CD34/PAS	188	78	110	7	High
27. Wang [31]	Asian	Glioma	CD34/PAS	86	23	63	6	High
28. Zhang [42]	Asian	HNC	CD34/PAS	42	18	24	2	Low
29. Zhang [40]	Asian	Renal carcinoma	CD34/PAS	110	30	80	7	High
30. Liu [25]	Asian	Breast cancer	CD31/PAS	90	26	64	6	High
31. Ren [41]	Asian	Osteosarcoma	CD34/PAS	66	15	51	6	High
32. Qi [57]	Asian	Gastric cancer	CD31/PAS	60	19	41	6	High
33. Song [16]	Asian	Gastric cancer	CD31/PAS	60	19	41	6	High
34. Sun [21]	Asian	Ovarian tumor	CD34/PAS	53	19	34	6	High
35. Li [35]	Asian	Lung cancer	CD34/PAS	51	17	34	3	Low
36. Zhou [17]	Asian	Gastric cancer	CD34/PAS	261	70	191	7	High

VM+ patients with positive vasculogenic mimicry, *VM−* patients without vasculogenic mimicry, *NOS score* score of Newcastle–Ottawa scale, *PAS* periodic acid–Schiff staining, *HCC* hepatocellular carcinoma, *HNC* head and neck cancer, *TGCMT* testicular germ cell malignant tumors

[a] Low-quality studies had NOS scores of zero to 4; high-quality studies had scores of 5–9

(Asian or non-Asian), tumor types, VM assay methods, disease information (including cancer differentiation, TNM stages, lymph node metastasis, and distant metastasis), sample sizes, and number of VM-positive or VM-negative patients. HRs with 95 % CIs were extracted from multivariable analyses. When HRs and 95 % CIs could not been directly extracted from the original studies, they were calculated using the method of Tierney et al. [45].

Two investigators assessed the quality of included studies using the Newcastle–Ottawa scale [48]. This scale consists of eight items assessing three aspects of a study: patient selection, comparability of study groups, and ascertainment of outcome. Each item could be awarded 1 point except for the item on comparability, which allowed 2 points. Studies with scores of five to nine were considered high quality; those with scores of zero to four were considered low quality.

Tumor differentiation grade was categorized as well (grade 1) or moderately/poorly differentiated (grades 2 and 3). TNM stage was dichotomized as I and II or III and IV. Lymph node metastasis and distant metastasis were both scored as positive or negative, respectively. Discrepancies were resolved by consensus.

Statistical methods

Hazard ratios (HRs) and 95 % CIs were used to evaluate the impact of VM on overall survival [49, 50]. In addition, risk ratios were used to summarize the association between VM and disease features: TNM stage, differentiation, lymphatic metastasis, and distant metastasis [49, 50]. The heterogeneity of pooled HRs and RRs was estimated using the Chi-square-based Cochrane's Q test ($P < 0.10$ was considered significant) and the I^2 index [51]. When heterogeneity was not so severe (I^2 values <50 %), a fixed-effect model was used. Otherwise, the random-effect model was applied to pooled data. A Galbraith plot was constructed to identify the main sources of heterogeneity [52].

Sensitivity analysis that assesses the stability of results was conducted by sequentially removing each individual study and recalculating the results [53]. Cumulative meta-analysis was conducted by publication times [54]. Publication bias was evaluated by the Begg's funnel plot and the Egger's test [55, 56].

All data were analyzed with the STATA software (version 12.0; STATA Corporation, College Station, TX). Unless otherwise stated, all P values were two-tailed and alpha was 0.05.

Results

Study characteristics

Of the 1056 articles identified in the literature search, 36 studies (described in 33 articles) representing 3609 patients were included in the meta-analysis (Fig. 1) [7, 10, 12, 14–31, 34–43, 57]. The most common cancers studied were melanoma and gastric cancers (Table 1). Vascular mimicry was detected in 8–56 % of patients. All but four studies were of Asian populations. Methods for detecting VM were PAS ($n = 7$), CD31/PAS ($n = 14$), CD34/PAS ($n = 14$), and pan-cytokeratin/CD34 ($n = 1$) staining. Of the 36 studies, 18 (50 %) were high-quality studies (Table 1) [12, 15–17, 20, 25, 27, 30, 31, 34, 37–41, 57]. Hazards ratios with 95 % CIs were extracted directly from 13 studies [14, 16, 17, 20, 23, 25, 34, 36, 37, 40, 41, 57] and calculated for the remaining 23.

Disease features associated with vascular mimicry

Several studies evaluated associations between VM and cancer differentiation status (14 studies [15, 17, 19, 21, 23, 25, 27, 29, 30, 34, 37, 39, 40, 42]; 2032 patients), lymph metastasis (10 studies [15, 17, 24, 25, 27, 34, 35, 37–39]; 1735 patients), distant metastasis (13 studies [14, 15, 18, 19, 21, 22, 24, 27, 36–38, 40, 42]; 1616 patients), and TNM stage (13 studies [15, 17, 19, 21, 23, 25, 27, 29, 34, 35, 37, 39, 40]; 1915 patients).

We found statistically significant associations between VM and cancer differentiation (well vs. moderate/poor: RR: 1.08; 95 % CI 1.04–1.12; $p < 0.001$), lymph node metastasis (N1 vs. N0: RR: 1.81; 95 % CI 1.43–2.29; $p < 0.001$), distant metastasis (M1 vs. M0: RR: 1.94; 95 % CI 1.56–2.41; $P < 0.001$), TNM stage (III/VI vs. I/II: RR: 1.81; 95 % CI: 1.48–2.23; $P < 0.001$) (Table 2, Figure S1).

Table 2 Subgroup differences in a meta-analysis of the association between vasculogenic mimicry and disease features in patients with cancer

Group	Studies (n)	Patients (n)		RR (95 % CI)	P	I^2 (%)	P^{a}_{het}
		VM+	VM−				
Sex (female vs. male)	17	592	1560	0.91 (0.74–1.12)	0.38	11.4	0.32
Differentiation (moderate/poor vs. well)	14	791	1241	1.08 (1.04–1.12)	<0.001	85.5	<0.001
Lymph metastasis (N1 vs. N0)	10	458	1277	1.81 (1.43–2.29)	<0.001	75.4	<0.001
Distant metastasis (M1 vs. M0)	13	356	1260	1.94 (1.56–2.41)	<0.001	44.2	0.04
TNM stage (III/VI vs. I/II)	13	557	1358	1.81 (1.48–2.23)	<0.001	79.0	<0.001

VM+ patients with positive vasculogenic mimicry, *VM−* patients without vasculogenic mimicry, *RR* risk ratio, P_{het} P values for heterogeneity from Q test

[a] A random-effect model was used when the P value for heterogeneity test was <0.05; otherwise, a fixed-effect model was used. I^2 the percentage of variability in RR attributable to heterogeneity

Vascular mimicry and overall survival

The meta-analysis revealed that the risk of mortality was significantly higher for cancer patients with VM than without VM (HR, 2.16; 95 %CI 1.95–2.38; $P < 0.001$) (Table 3, Fig. 2). There was moderate heterogeneity among studies ($P_{het} = 0.055$ and $I^2 = 29.4$ %) (Table 3), so we conducted subgroup analyses according to confounders, such as cancer types, ethnicity, VM detection methods, patient number, and quality score. After stratifying by cancer type, VM was still associated with statistically significantly poorer overall survival from melanoma, gastric cancer, sarcomas, ovarian tumor, hepatocellular carcinoma, breast cancer, head and neck cancer, colorectal cancer, glioma, lung cancer, and other types of cancer (Table 3). After stratifying by ethnicity, the pooled HRs of Asians and non-Asians were 2.13 and 3.45, respectively (Table 3). In the subgroup analysis based on VM detection methods, the pooled HR was 2.25 for PAS staining, 2.11 for CD31/PAS staining, 2.15 for CD34/PAS

Table 3 Estimated effect of vasculogenic mimicry on overall survival in a meta-analysis of 36 studies of cancer patients by subgroup

Subgroup	Studies (*n*)	Patients (*n*)		Overall survival, HR (95 % CI)	P^a	I^2 (%)	P_{het}
		VM+	VM−				
Total	36	964	2645	2.16 (1.95–2.38)	<0.001	29.4	0.055
Cancer type							
Melanoma	5	234	495	2.14 (1.47–2.82)	<0.001	12.6	0.33
Gastric cancer	5	169	469	1.79 (1.37–2.20)	<0.001	31.3	0.21
Sarcomas	4	59	173	2.08 (1.23–2.94)	<0.001	0.0	0.59
Ovarian tumor	3	105	119	1.91 (0.63–3.18)	0.003	0.0	0.49
HCC	2	36	151	2.18 (1.36–3.00)	<0.001	0.0	0.55
Breast cancer	2	52	369	2.40 (0.85–3.95)	0.002	77.1	0.04
HNC	2	85	230	3.06 (1.85–4.27)	<0.001	0.0	0.73
Colorectal cancer	2	62	258	2.57 (1.72–3.42)	<0.001	61.8	0.11
Glioma	2	36	151	1.80 (1.22–2.39)	<0.001	0.0	0.36
Lung cancer	2	126	230	2.05 (1.26–2.85)	<0.001	0.0	0.46
Other[a]	6	187	384	3.05 (2.45–3.64)	<0.001	44.6	0.11
Ethnicity							
Asian	31	965	2746	2.13 (1.91–2.35)	<0.001	28.8	0.07
Non-Asian	4	193	339	3.45 (2.13–4.77)	<0.001	0.0	0.52
Assay methods							
PAS	7	285	801	2.25 (1.68–2.82)	<0.001	13.7	0.33
CD31/PAS	14	341	1044	2.11 (1.67–2.54)	<0.001	25.0	0.18
CD34/PAS	13	491	1169	2.15 (1.87–2.43)	<0.001	48.1	0.03
Pan-cytokeratin/CD34	1	41	71	2.84 (1.09–4.59)	0.002	NA	NA
Sample size (n)							
≤100	16	756	2170	2.01 (1.74–2.29)	<0.001	1.6	0.43
>100	19	402	915	2.43 (2.07–2.78)	<0.001	39.3	0.04
Study quality[c]							
Low quality	17	506	1535	2.47 (2.13–2.81)	<0.001	42.4	0.03
High quality	18	652	1550	1.95 (1.67–2.23)	<0.001	0.0	0.60

VM+ patients with positive vasculogenic mimicry, *VM−* patients without vasculogenic mimicry, *HR* hazard ratio, I^2 the percentage of variability in attributable to heterogeneity, P_{het} *P* values for heterogeneity from *Q* test, *HCC* hepatocellular carcinoma, *HNC* head and neck cancer, *PAS* Periodic acid–Schiff staining, *NA* not available

[a] A random-effect model was used when the *P* value for heterogeneity was <0.05; otherwise, a fixed-effect model was used

[b] Other included testicular germ cell malignant tumors, gallbladder cancer, prostate cancer, esophageal cancer, renal carcinoma, and osteosarcoma

[c] Low-quality studies had Newcastle–Ottawa quality scores of 0–4, and high-quality studies had scores of 5–9

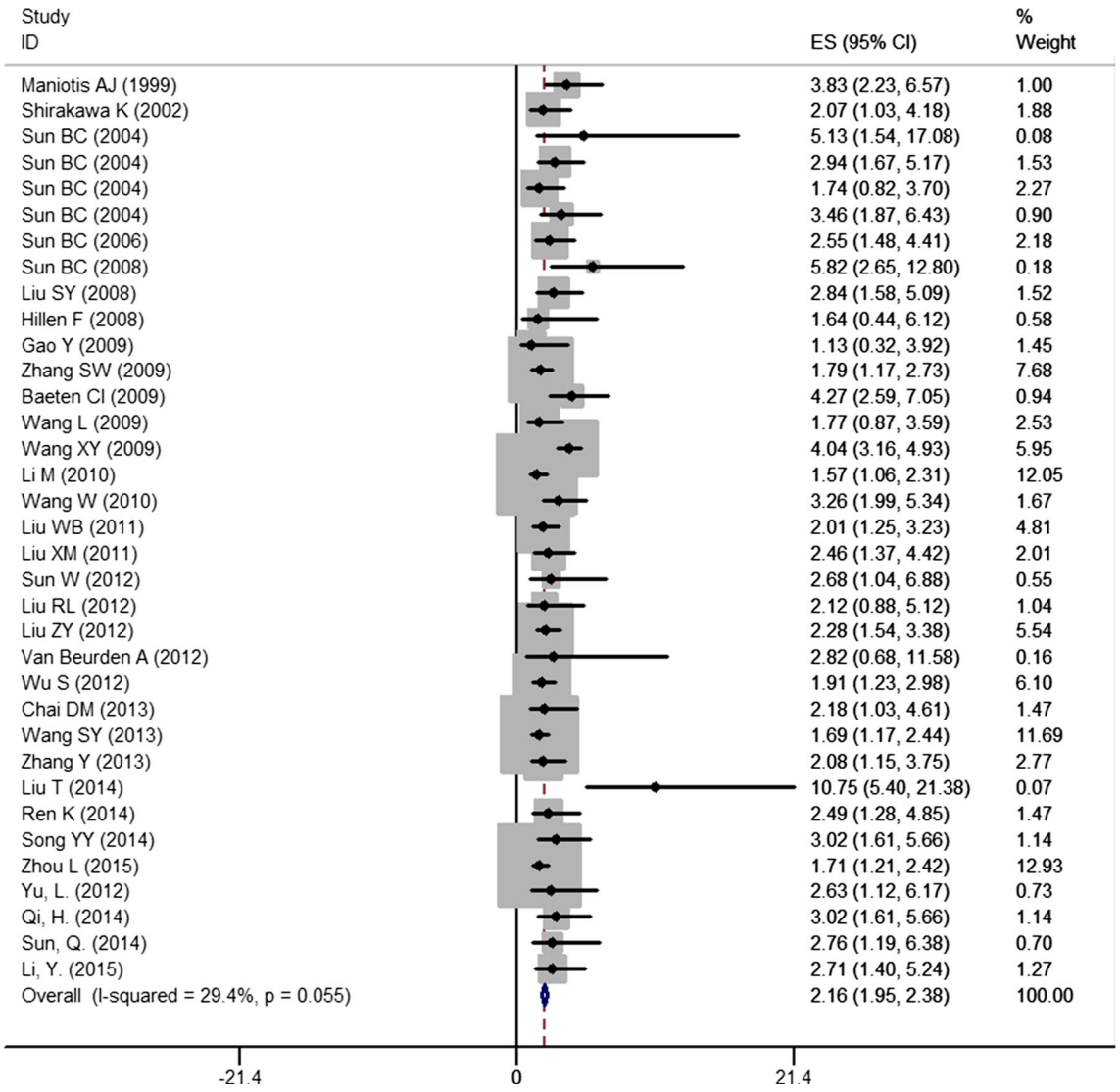

Fig. 2 Forest plots of the effects of vasculogenic mimicry on survival in patients with cancer

staining, and 2.84 for pan-cytokeratin/CD34 staining (Table 3). In studies with larger samples ($n \geq 100$) and smaller samples ($n < 100$), the pooled HRs were 2.01 and 2.43, respectively (Table 3). Stratification by quality scores revealed significant associations for both high- and low-quality studies (Table 3).

Test of heterogeneity

We created a Galbraith plot to identify potential sources of heterogeneity. The main contributors to heterogeneity were the studies by Liu and Wang [25, 36] (Fig. 3). When these two studies were omitted, I^2 % decreased from 29.4 to 0 %, and the statistical significance of the combined HRs in the overall and subgroup analyses was not substantially altered (data not shown.)

Sensitivity analysis, cumulative analyses, and publication bias

The pooled HRs remained the same in a sensitivity analysis in which each study was sequentially excluded (Figure S2). Moreover, cumulative meta-analyses suggested that the association has been significant since the first study was published in 1999 (Figure S3). These results indicate stabile and reliable findings. No indication of publication bias was found using Egger's test ($P = 0.82$), and the funnel plot seemed symmetrical (Fig. 4), indicating no marked publication bias.

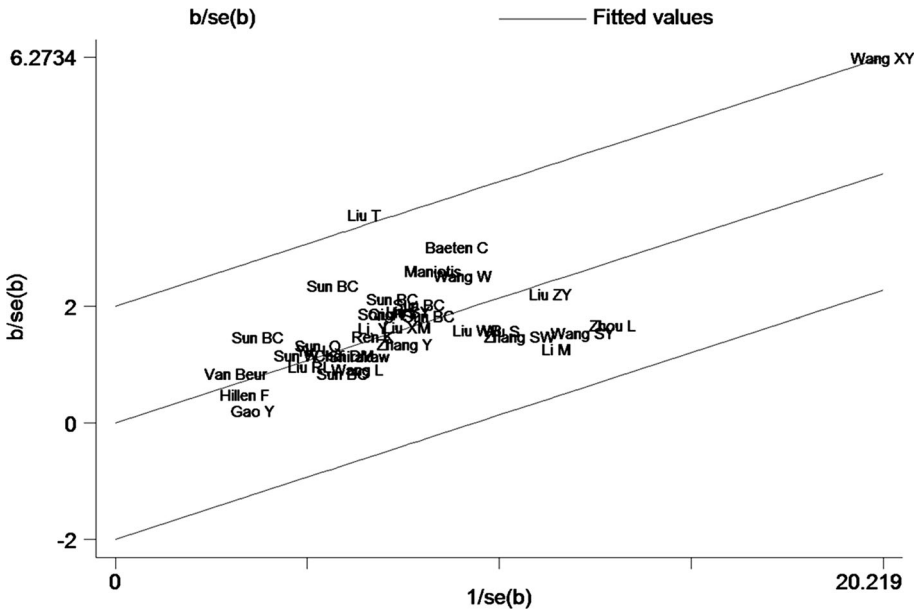

Fig. 3 Galbraith plot analysis of the amount of heterogeneity from all the included studies. The *Y*-axis shows the ratio of the log HR to its standard error (SE), and the *X*-axis shows the reciprocal of the SE. At a 2 standard deviation distance parallel to the regression line, the 2 lines create an interval. Studies lacking in heterogeneity would lie within the 95 % confidence interval. Studies by Liu and Wang were identified as potential sources of heterogeneity in a meta-analysis of the effects of vasculogenic mimicry on cancer survival

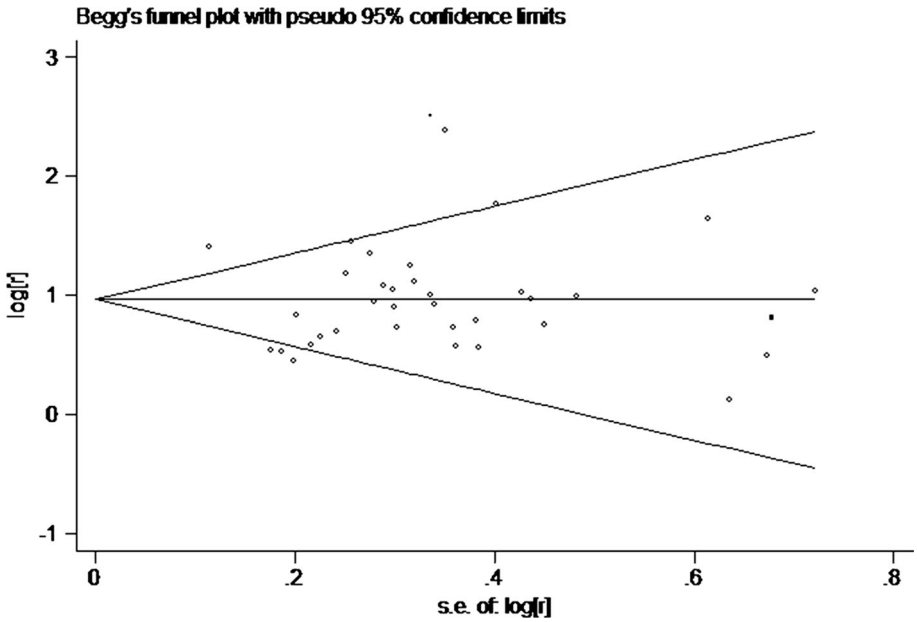

Fig. 4 Begg's funnel plot on the effects of vasculogenic mimicry on cancer survival indicated that publication bias was unlikely

Discussion

Our meta-analysis summarized the results of 36 clinical studies representing 3609 patients. Overall, positive VM status strongly predicted lower overall survival in patients with malignant cancers. Moreover, similar, significant results were found in the subgroup analyses by cancer types, ethnicity, VM detection methods, sample size, and study quality. Additionally, VM was also significantly associated with cancer differentiation, lymph node metastasis, distant metastasis, and TNM stage, which might adversely affect cancer survival.

Tumor growth and hematogenous dissemination depend on adequate blood supply. Tumor vasculature is highly complex and possibly derived from a variety of sources, including angiogenesis [58], vasculogenesis [59–61], co-option [62], and vasculogenic mimicry [8, 63]. In VM, highly aggressive cancer cells form vessel-like structures by their high plasticity, which enables them to function as endothelial-like cells.

Several recent studies [7, 10, 12, 14–31, 34–43, 57] have reported that VM exists in various malignant tumors and is associated with tumor progression, metastasis, treatment failure, and increases death in many [6, 9, 18–23, 38].

Although one meta-analysis [64] has reported on the prognostic value of VM in cancer, it has some shortcomings. Data from one study were published in two articles [10], one of which should have been excluded from the analysis. Despite evidence of remarkable heterogeneity and publication bias, there was no attempt to explore the sources of heterogeneity, which might have compromised the interpretation. Time-to-event outcomes were assessed with relative risks, rather than with hazards ratios. Additionally, 12 new studies [12, 16, 17, 21, 25, 31, 35, 39–42, 57] evaluating the relationship between VM and survival outcomes have been published since September 2013. Thus, it was important to update the meta-analyses. The pooled results of our meta-analysis showed that VM was significantly associated with poor OS in cancer patients. What was more, the presence of VM was also significantly associated with cancer differentiation, lymph node metastasis, distant metastasis, and TNM stage.

We found an association of VM with a more aggressive tumor phenotype. Several underlying mechanisms are possible. First, VM could provide a functional perfusion pathway for rapidly growing tumors and possibly a metastatic escape route by transporting blood from leaky vessels or by connecting with the endothelial-lined vasculature [65]. Second, accumulating evidence [66] indicates that cancer stem cells are involved in VM formation, have been associated with tumor invasion and metastasis, and are therefore important in tumor progression. Third, the formation of VM involves signaling pathways and some factors related to tumor cell migration, invasion, and matrix remodeling, including Notch [67] and Nodal [68] signaling pathways, VE-cadherin [69, 70], EPH receptor A2(EphA2) [71, 72], matrix metalloproteinases [20, 22, 73], and hypoxia-inducible factor-1alpha (HIF-1(alpha)) [37, 39, 69, 74, 75]. Forth, hypoxia can modulate the expression of genes essential for cell viability, tumor growth, metastasis, and VM in cancer [76–78]. These hypoxia-induced VM and VM-associated genes highlight the critical importance of hypoxia in tumor progression. Finally, VM is lined with tumor-derived endothelial-like cells that differ from conventional endothelial cells. Therefore, VM might present with a native resistance to anti-angiogenic compounds, such as bevacizumab, sorafenib, and sunitinib.

Our study has some limitations. The moderate heterogeneity among the studies was a potential problem when interpreting the results, although when the studies by Liu et al. and Wang et al. [25, 36] were deleted from the analysis, our results remained the same. A more accurate pooled HRs analysis with sufficient data was required to adjust for covariates, such as age, sex, histological type, tumor differentiation, TNM stage, lymphatic metastasis, and distant metastasis, if these data were available. Finally, although publication bias was not detected using Begg's funnel plot and Egger's test, it always remains a possibility. However, several studies with contradictory results would be required to refute or reverse our findings. Our meta-analysis also has some strengths. Sensitivity analysis revealed no significant difference when any individual article was omitted. Moreover, cumulative meta-analyses demonstrated that inclinations toward the significant association have been evident since the first study in 1999. These analyses indicate that our results are stable and reliable.

We found that VM is associated with a worse prognosis in several different tumor types. Vasculogenic mimicry is also significantly associated with cancer differentiation, lymph metastasis, distant metastasis, and TNM stage. These results suggest that developing strategies against the VM would be a promising therapeutic approach to solid tumors.

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