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REVIEW

Correlation Between Tumor Vasculogenic Mimicry and Poor Prognosis of Human Digestive Cancer Patients: A Systematic Review and Meta-Analysis

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Abstract

Vasculogenic mimicry (VM) is a new pattern of blood supplement independent of endothelial vessels, which is related with tumor invasion, metastasis and prognosis. However, the role of VM in the prognosis of cancer patients is controversial. This study aimed to perform a meta-analysis of the published data to attempt to clarify the prognostic value of VM in the digestive cancer. Relevant studies were retrieved from the PubMed, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure and VIP databases published before March 29, 2018. Studies were included if they detected VM in the digestive cancer and analyzed the overall survival (OS) or disease-free survival (DFS) according to VM status. Two independent reviewers screened the studies, extracted data, and evaluated the quality of included studies with the Newcastle-Ottawa scale. Meta-analysis was performed using STATA 12.0 software. A total of 22 studies with 2411 patients were included in this meta-analysis. Meta-analysis showed that VM was related with the poor OS (HR = 2.30, 95% CI: 2.06–2.56, $P < 0.001$) and DFS (HR = 2.60, 95% CI: 2.07–3.27, $P < 0.001$) of patients with digestive cancer. Subgroup analysis showed VM was related with tumor differentiation, lymph node metastasis and TNM stage. Moreover, the present meta-analysis was reliable, and there was no obvious publication bias. This meta-analysis suggested that VM was a poor prognosis of digestive cancer patients. Further large and well-designed studies are required.

Keywords Vasculogenic mimicry · digestive cancer · prognosis · meta-analysis

Introduction

Digestive cancer is well known as the most common malignant tumors in the world [1], and mainly contains esophageal squamous cell carcinoma (ESCC), gallbladder carcinoma (GBC), gastric carcinoma (GC), hepatocellular carcinoma (HCC), pancreatic cancer (PaCa) and colorectal carcinoma (CRC). Despite of the advances in surgery and chemotherapy, digestive cancer remains the leading cause of cancer-related death. More importantly, the 5-year survival rate of digestive cancer still remains low [2].

Vasculogenic mimicry (VM) is an alternative type of blood supply system independent of endothelial vessels in malignant tumor cells [3]. VM was first reported in highly aggressive melanoma cells by Maniotis et al. in 1999 [4]. At present, VM has been observed in various solid tumor types including respiratory [5], digestive [6, 7] and genital system tumors [8, 9]. Many evidences indicate that VM can reflect the plasticity of aggressive tumor cells and express vascular cell markers. Therefore, VM is positive for PAS staining, while is negative for CD31 or CD34

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staining which are the markers of vascular endothelial cell [4]. In the meantime, red blood cells can be seen in VM channels. Moreover, VM is associated with tumor differentiation, invasion, metastasis and late clinical stage. Simultaneously, patients with tumor-related VM have poor prognosis [10]. However, some studies indicated that there were no significance between VM and the prognosis of tumor [11, 12]. Therefore, the results of different studies are controversial, and the prognostic value of VM in digestive cancer remains unclear.

To provide comprehensive and reliable conclusions, a meta-analysis was performed to make an objective evaluation of the prognostic significance of VM in the patients with digestive cancer.

Materials and Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement [13].

Search Strategy

The current study was limited to evaluate the prognostic implication of VM in human digestive cancer patients. Relevant studies were screened by an electronic search in PubMed, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) and VIP databases with the following keywords: ('digestive system neoplasm' or 'cancer of digestive system' or 'digestive cancer' or 'esophageal cancer' or 'gastric cancer' or 'colorectal cancer' or 'intestinal cancer' or 'liver cancer' or 'pancreatic cancer' or 'gallbladder cancer') and ('vasculogenic mimicry' or 'vascular mimicry' or 'VM' or 'tumor cell-lined vessels') and ('prognosis' or 'survival' or 'outcome'). The most recent studies were performed on March 29, 2018, and there were no language restrictions or the minimum number of patients. Titles and abstracts were used to identify related studies, and then full texts were read carefully.

Selection Criteria

Studies included in the analysis must to meet the following criteria: (1) case control studies focus on the relation between VM and digestive cancer risk; (2) studies on patients should be digestive cancer, including ESCC, GBC, GC, HCC, PaCa and CRC; (3) assessment of VM-positive primary tumor tissues must be used by the immunohistochemical or histochemical double staining method. The exclusion criteria were as follows: (1) literature reviews, comments, editorials, case report or duplicated publications; (2) no sufficient data to estimate the HR and 95% CI; (3) studies referring to VM but not to humans with VM with digestive cancer; (4) studies whose language was not Chinese or English.

Data Collection

Two of the authors who were responsible for study selection extracted all data independently according to the selection criteria. The following items were collected: first author's last name, year of publication, region, type of digestive cancer, VM assay methods, type of survival, the total case, the number and the percentage of VM positive [14]. The quality of included studies were assessed using the Newcastle –Ottawa scale [15], which consists of eight items assessing three aspects of a study including patient selection, comparability of study groups and ascertainment of outcome. Studies with scores of five to nine were regarded as high quality; otherwise those with scores of zero to four were regarded as low quality.

Statistical Analysis

Statistical analyses were performed using STATA 12 software (STATA Corp., College Station, TX). Hazard ratios (HRs) and 95% CIs were used to assess the effect of VM on overall survival (OS) or disease-free survival (DFS). The Chi-square-based Cochrane's Q test and I^2 index were used to evaluate the study of heterogeneity. If there was mild heterogeneity among studies ($P > 0.10$, $I^2 < 50\%$), the fixed effects model was used; otherwise, the random-effects model was applied to pooled data ($P < 0.10$, $I^2 > 50\%$). Moreover, subgroup analysis was used to evaluated the source of heterogeneity on the basis of type of digestive cancer. The sensitivity analysis was identified by reanalyzing the data using different statistical approaches. Publication bias was evaluated by the Egger's test. All statistical tests were two-sided, and a P value of <0.05 was considered to be statistically significant.

Results

Characteristics of Studies

Initially, 389 studies were retrieved using the above search strategy. After primary screening titles and abstracts, 50 full-text papers were retrieved for further assessment of eligibility. Eventually, a total of 22 independent studies were involved in this present meta-analysis [7, 16–36]. The procedure for study selection was illustrated in Fig. 1. The main characteristics of these studies were shown in Table 1. Six types of digestive cancer were investigated including ESCC, GBC, GC, HCC, PaCa and

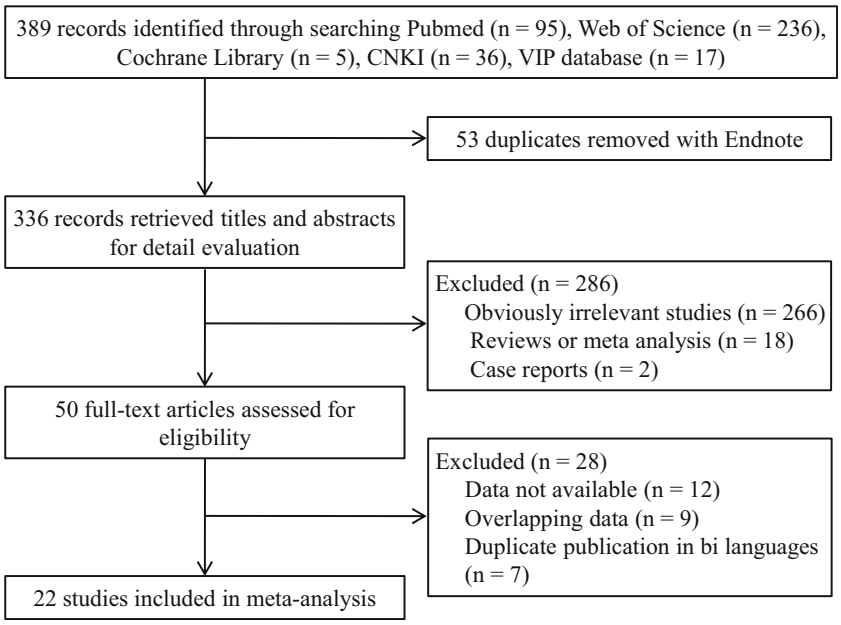

Fig. 1 Flow chart of the literature search process

CRC. Among these, two studies were conducted in the non-Asia, and twenty studies were in the Asia. Moreover, nine studies were performed using CD34+/PAS staining, twelve studies were using CD31+/PAS staining, and one studies were using CD31+/CD34+ staining. Of the 22 studies, 877 out of 2411 patients were

Table 1 Main characteristics of studies included in the meta-analysis

References	Year	Region of China	Tumor type	VM assay methods	Case (n)	VM+ (n)	VM+ (%)	Survival	Follow-up (months)	NOS score	Quality
Baeten [7]	2009	Non-Asian	CRC	CD31+/CD34+	117	23	19.7	OS	150	3	Low
Chai [16]	2013	Asian	ESCC	CD34+/PAS	160	78	48.8	OS	108	7	High
Guzman [17]	2007	Non-Asian	HCC	CD31+/PAS	20	11	55.0	OS	40	3	Low
Li [18]	2010	Asian	GC	CD31+/PAS	173	40	23.1	OS	120	4	Low
Li [19]	2014	Asian	HCC	CD31+/PAS	161	61	37.9	OS	60	4	Low
Li [20]	2016	Asian	GC	CD31+/PAS	100	35	35.0	OS	120	4	Low
Liao [21]	2013	Asian	GC	CD34+/PAS	110	35	31.8	OS	90	4	Low
Liu [22]	2011	Asian	HCC	CD34+/PAS	151	31	20.5	OS/DFS	86	7	High
Lv [23]	2017	Asian	GC	CD34+/PAS	89	24	27.0	OS/DFS	111	7	High
Shao [24]	2016	Asian	HCC	CD31+/PAS	106	47	44.3	OS/DFS	80	7	High
Song [25]	2013	Asian	ESCC	CD34+/PAS	100	47	47.0	OS	56	5	High
Song [26]	2014	Asian	GC	CD31+/PAS	60	19	31.7	OS	72	6	High
Sun [27]	2006	Asian	HCC	CD31+/PAS	100	12	12.0	OS	80	4	Low
Sun [28]	2012	Asian	GBC	CD31+/PAS	71	18	25.4	OS	60	6	High
Wang [29]	2015	Asian	GC	CD31+/PAS	88	38	43.2	OS	47	4	Low
Yang [30]	2011	Asian	GC	CD31+/PAS	84	21	25.0	OS	60	5	High
Yang [31]	2015	Asian	HCC	CD31+/PAS	17	92	541.2	OS	70	4	Low
Yang [32]	2017	Asian	PaCa	CD34+/PAS	70	36	51.4	OS	72	6	High
Zhang [33]	2017	Asian	ESCC	CD34+/PAS	117	56	47.9	OS/DFS	80	6	High
Zheng [34]	2012	Asian	GBC	CD31+/PAS	52	8	15.4	OS	30	4	Low
Zhou [35]	2015	Asian	GC	CD34+/PAS	261	70	26.8	OS	120	6	High
Zhu [36]	2017	Asian	CRC	CD34+/PAS	204	75	36.8	OS	96	6	High

Annotation: *ESCC*, esophageal squamous cell carcinoma; *GBC*, gallbladder carcinoma; *GC*, gastric carcinoma; *HCC*, hepatocellular carcinoma; *PaCa*, pancreatic cancer; *CRC*, colorectal carcinoma; *OS*, overall survival; *DFS*, disease-free survival; *PAS*, periodic acid-Schiff; *VM+*, vasculogenic mimicry positivity; *NOS*, Newcastle –Ottawa scale

positive VM. Overall, the OS or DFS of these studies were ranged from 47 to 150 months, and twelve studies (54.5%) were high-quality. HRs with 95% CIs were extracted directly from 22 references for further study.

Association Between VM and Prognosis in Patients with Digestive Cancer

Overall, a significant relation was observed between VM-positive and OS. This present meta-analysis revealed that VM-positive may represent a poor prognostic factor for patients with digestive cancer (HR = 2.30, 95% CI: 2.06–2.56, $P < 0.001$; fixed-effect model: $Chi^2 = 31.22$, $I^2 = 32.7$, $P = 0.070$) (Fig. 2). Among all the studies, four studies have analyzed the association between the positive VM and DFS in patients with digestive cancer. As shown in Fig. 2, the VM-positive was also related with the DFS of patients with digestive cancer (HR = 2.60, 95% CI: 2.07–3.27, $P < 0.001$; fixed-effect model: $Chi^2 = 5.58$, $I^2 = 46.3$, $P = 0.134$).

Subgroup Analyses

In order to further explain the results of OS in digestive cancer, subgroup analyses were performed to stratify by region, tumor types, VM assay methods, the number of case, the follow-up time and the quality (Table 2 and Supplemental Fig. 1). The pooled data analysis of different regions in the world indicated a very obviously relation of VM with OS in both the non-Asian (HR = 4.17, 95% CI: 2.63–6.61, $P < 0.001$) and the Asian regions (HR = 2.22, 95% CI: 1.99–2.48, $P < 0.001$). After stratifying by the tumor types, a significantly poor OS was obtained in all types of VM-positive digestive cancer including ESCC ($P < 0.001$), GBC ($P = 0.002$), GC ($P < 0.001$), HCC ($P < 0.001$), PaCa ($P = 0.012$) and CRC ($P < 0.001$). In the subgroup analysis based on VM detection methods, the results showed that they existed poor OS in CD34/PAS staining (HR = 2.35, 95% CI: 2.00–2.75, $P < 0.001$), CD31/PAS staining (HR = 2.11, 95% CI: 1.81–2.45, $P < 0.001$) and CD31+/CD34 staining (HR = 4.29, 95% CI: 2.69–6.85, $P < 0.001$). VM-positive showed poor OS in the studies with smaller cases ($n < 100$) (HR = 2.23, 95% CI: 1.83–2.70, $P < 0.001$) and larger cases ($n \geq 100$) (HR = 2.33, 95% CI: 2.05–2.65, $P < 0.001$). The relation between VM-positive and the OS of patients with digestive cancer was also present in studies with less than or equal 60 months (HR = 1.92, 95% CI: 1.56–2.38, $P < 0.001$) as well as more than 60 months follow-up time (HR = 2.44, 95% CI: 2.16–2.77, $P < 0.001$). Moreover, VM-positive showed poor OS in the studies with high quality (HR = 2.51, 95% CI: 2.15–2.92, $P < 0.001$) and low quality (HR = 2.11, 95% CI: 1.81–2.45, $P < 0.001$).

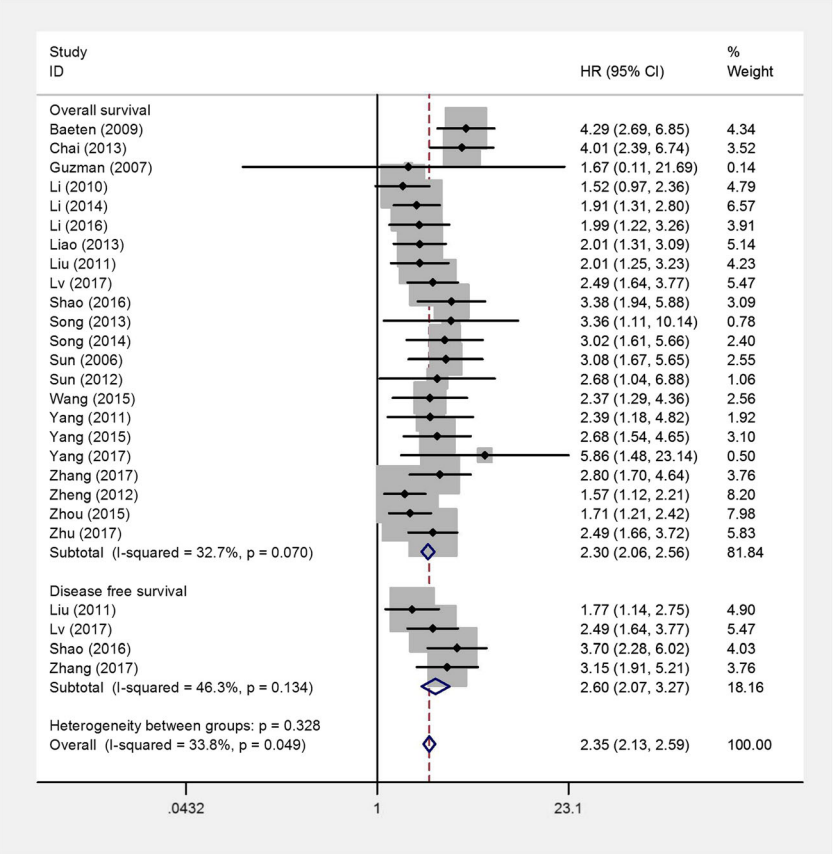

Fig. 2 Forest plot showing the combined relative HR for overall survival and disease free survival

Table 2 The subgroups analysis for VM and OS in patients with digestive cancer

Subgroups	Number of Studies	Case (n)	VM+ (n)	VM+ (%)	Pooled Data			Test for Heterogeneity	
					HR	95% CI	*P* value	*P* value	I^2 (%)
Region									
Non-Asian	2	137	34	24.8	4.17	2.63–6.61	< 0.001	0.491	0
Asian	20	2274	843	37.1	2.22	1.99–2.48	< 0.001	0.199	20.6
Tumor type									
ESCC	3	377	181	48.0	3.33	2.37–4.70	< 0.001	0.621	0
GBC	2	123	26	21.1	1.67	1.21–2.30	0.002	0.298	7.7
GC	8	965	282	29.2	2.03	1.71–2.39	< 0.001	0.600	0
HCC	6	555	254	45.8	2.37	1.90–2.95	< 0.001	0.514	0
PaCa	1	70	36	51	5.86	1.48–23.15	0.012	NA	NA
CRC	2	321	98	30.5	3.14	2.31–4.26	< 0.001	0.084	66.5
VM assay methods									
CD34+/PAS	9	1262	452	35.8	2.35	2.00–2.75	< 0.001	0.204	27.0
CD31+/PAS	12	1032	402	39.0	2.11	1.81–2.45	< 0.001	0.358	8.9
CD31+/CD34	1	117	23	19.7	4.29	2.69–6.85	< 0.001	NA	NA
Case (n)									
< 100	9	551	267	48.5	2.23	1.83–2.70	< 0.001	0.448	0
≥ 100	13	1860	610	32.8	2.33	2.05–2.65	< 0.001	0.026	48.3
Follow-up (months)									
≤ 60	7	576	204	35.4	1.92	1.56–2.38	< 0.001	0.070	32.7
> 60	15	1835	673	36.7	2.44	2.16–2.77	< 0.001	0.047	41.5
Quality									
High	12	1473	522	35.4	2.51	2.15–2.92	< 0.001	0.356	9.1
Low	10	938	355	37.8	2.11	1.81–2.45	< 0.001	0.056	45.7

Annotation: *OS*, overall survival; *ESCC*, esophageal squamous cell carcinoma; *GBC*, gallbladder carcinoma; *GC*, gastric carcinoma; *HCC*, hepatocellular carcinoma; *PaCa*, pancreatic cancer; *CRC*, colorectal carcinoma; *VM+*, vasculogenic mimicry positive; *PAS*, periodic acid-Schiff; *HR*, hazard ratio; *CI*, confidence interval; *NA*, Not available due to single study

Association Between VM positivity and the Clinicopathological Features

To investigate the relationship between VM and the clinicopathological features of patients with digestive cancer, subgroup analyses were performed to stratify by gender, age, tumor size, differentiation, lymph node metastasis and TNM stage. As shown in Table 3 and Supplemental Fig. 2, there was no statistically significant difference between VM and gender ($P = 0.983$), age ($P = 0.536$), tumor size ($P = 0.181$). However, VM was strongly associated with tumor differentiation (RR = 1.636, 95% CI: 1.427–1.875, $P < 0.001$), lymph node metastasis (RR = 1.410, 95% CI: 1.226–1.621, $P < 0.001$) and TNM stage (RR = 1.631, 95% CI: 1.430–1.860, $P < 0.001$).

Heterogeneity Analyses

In this present meta-analysis, a certain degree heterogeneity was detected in the relationship between VM and OS of patients with digestive cancer ($Chi^2 = 31.22$, $P = 0.070$, $I^2 = 32.7\%$) (Fig. 2). As shown in Table 2 and Supplemental Fig. 1, significant heterogeneity existed among the studies with region, tumor types, VM assay methods, the number of case, the follow-up time and the quality. However, subgroup analyses could not explain the source of heterogeneity at length. Hence, Galbraith graph was performed to further explore the heterogeneity source. As shown in Fig. 3a, the study conducted by Baeten et al. and Chai et al. might be the main source of heterogeneity. After removing the above study, essential change was not observed in the result of the meta-analysis, but the heterogeneity decreased significantly ($Chi^2 = 18.71$, $P = 0.475$, $I^2 = 0\%$) (Fig. 3b).

Sensitivity Analyses and Publication Bias

A sensitivity analysis was performed to determine whether modifying the meta-analysis inclusion criteria affected the final results. As shown Fig. 4, sensitivity analysis also

Table 3 The subgroups analysis for VM and the clinicopathological features of patients with digestive cancer

Clinicopathological features	Number of studies	Number of case (n)	Number of VM+ (n)	Pooled Data			Test for Heterogeneity		
				RR	95% CI	*P* value	Chi^2	*P* value	I^2 (%)
Gender (female vs. male)	16	1923	686	0.999	0.878–1.135	0.983	13.59	0.556	0
Age (year) (< 60 vs. ≥ 60)	8	1269	435	1.049	0.901–1.222	0.536	7.38	0.390	5.2
Size (cm) (≥ 5.0 vs. <5)	8	969	340	1.130	0.945–1.351	0.181	13.83	0.054	49.4
Differentiation (poor vs. well/moderate)	13	1511	559	1.636	1.427–1.875	< 0.001	56.56	< 0.001	78.78
Lymph node metastasis (yes vs. no)	12	1491	538	1.410	1.226–1.621	< 0.001	120.09	< 0.001	90.8
TNM stage (III/ IV vs. I/II)	15	1853	660	1.631	1.430–1.860	< 0.001	158.55	< 0.001	91.2

Annotation: *VM+*, vasculogenic mimicry positive; *RR*, risk ratio; *CI*, confidence interval

confirmed the results of the present meta-analysis were reliable and stable due to no individual study affected the pooled results. Furthermore, Egger's test was conducted to assess publication bias. As shown Fig. 5a, the results demonstrated a certain degree publication bias in our meta-analysis ($P = 0.034$, $t = 2.27$, 95% CI = 0.13 to

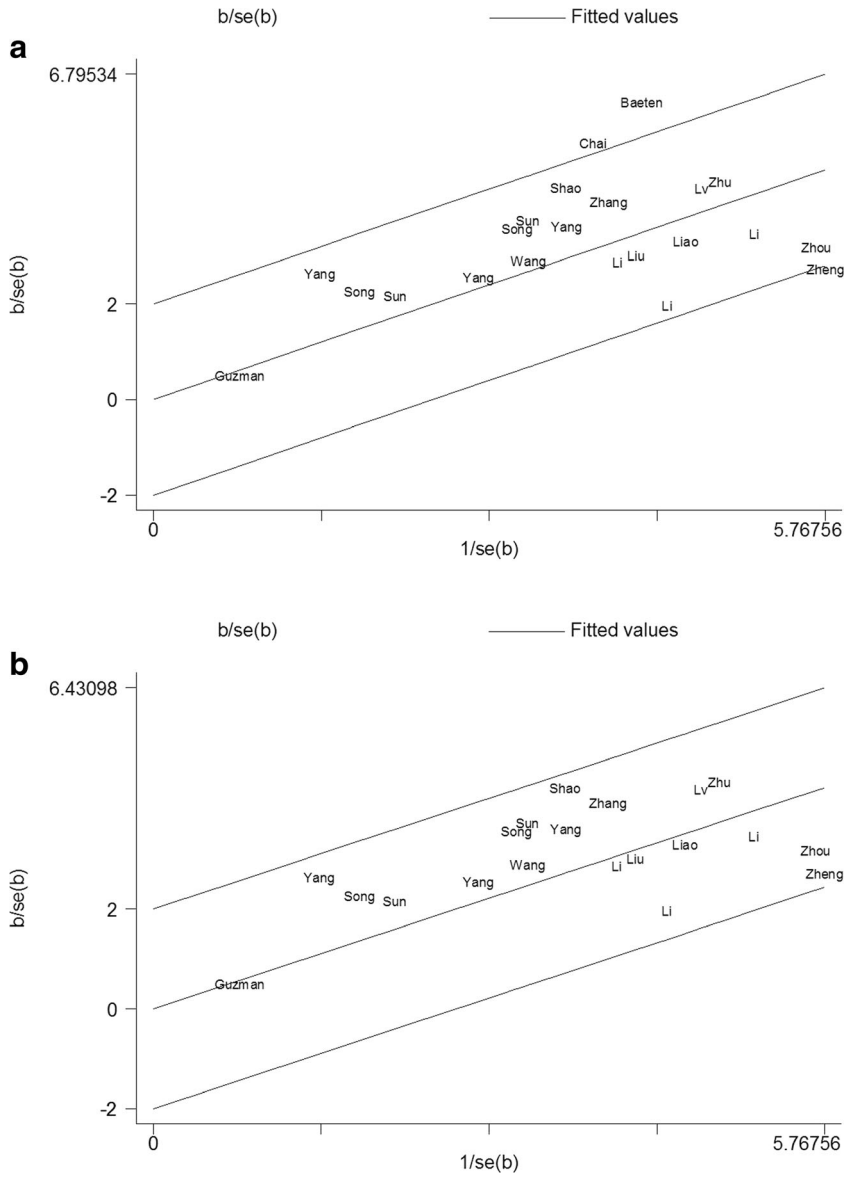

Fig. 3 Galbraith graph for the associations between VM and overall survival of patients with digestive cancer in the 22 studies (**a**) and after removing the two studies conducted by Baeten et al. and Chai et al. (**b**)

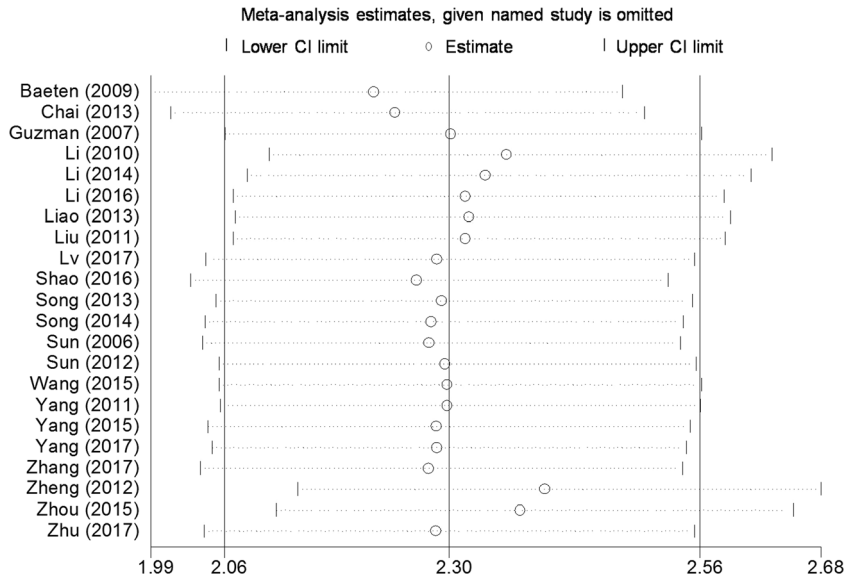

Fig. 4 Sensitivity analyses for the associations between VM and overall survival of patients with digestive cancer

3.12). However, after removing the study conducted by Yang et al. which was the only study about PaCa, there was no obvious publication bias in this meta-analysis ($P = 0.073$, $t = 1.90$, 95% CI = −0.16 to 3.23) (Fig. 5b), suggesting further large and well-designed studies about PaCa are required.

Discussion

It is widely accepted that tumor requires a blood supply for survival, growth and metastasis, which has been thought to be an angiogenesis dependent process. However, VM is the phenomenon where tumor cells mimic endothelial cells by forming blood vessels. The finding of VM explains why a variety of vascular targeting agents were less effective than expected [37]. Hence, the prognostic value of VM has been extensively explored in various cancers, but inconsistent results were obtained in different studies. Until now, there is no meta-analysis about the relation between VM and the prognosis of patients with digestive cancer. In consideration of these conflicting research results, we performed this meta-analysis to evaluate the association between VM and the prognostic value in digestive cancer.

Overall, this meta-analysis of 2411 patients involved in 22 independent studies indicated that VM was related with the worse OS and DFS of patients with digestive cancer. Subgroup analyses were performed to explore the source of heterogeneity based on region, tumor types, VM assay methods, the number of case the follow-up time and the quality. Furthermore, Our results showed that VM was related with tumor differentiation, lymph node metastasis and TNM stage. In our meta-analysis, Galbraith graph was performed to further explore the heterogeneity source, and this result indicated that the study conducted by Baeten et al. and Chai et al. might be the main source of heterogeneity. In addition, sensitivity analyses indicated that the results of the present meta-analysis were reliable. Egger's test confirmed there was no obvious publication bias in our meta-analysis after removing the study conducted by Yang et al. which was the only study about PaCa.

Many proteins and microenvironmental factors are involved in VM [38], but the mechanisms underlying its formation has not be identified. Hypoxia was the main induction of VM formation by promoting the plastic, transendothelial phenotype of tumor cells capable of VM [39–41]. Under condition of hypoxia, HIF-1α can induce the VM channel-forming cells by upregulating VM formation related molecules including vascular endothelial cadherin (VE-cadherin) [42], ephrin type-A receptor 2 (EphA2) [43], platelet endothelial cell adhesion molecule (PECAM) [44] and vascular endothelial growth factor (VEGF) [45]. VM formation can be induced by epithelial mesenchymal transition (EMT) [41], which is an evolutionarily conserved development process during that tumor cells lose epithelial characteristics and obtain mesenchymal properties. Moreover, cancer stem cells (CSCs) are by definition the tumor cell subpopulation with highest plasticity, which is an essential property for VM [46, 47]. Several studies have linked CSCs with VM capacity in different tumors including non-small cell lung cancer [48], breast cancer [49] and HCC. In addition, other factors are seems to be related to VM formation including extracellular matrix remodeling, autophagy and so on [46, 50].

In digestive cancer, the mechanisms of VM formation are complex. Several studies have indicated that HIF-1α

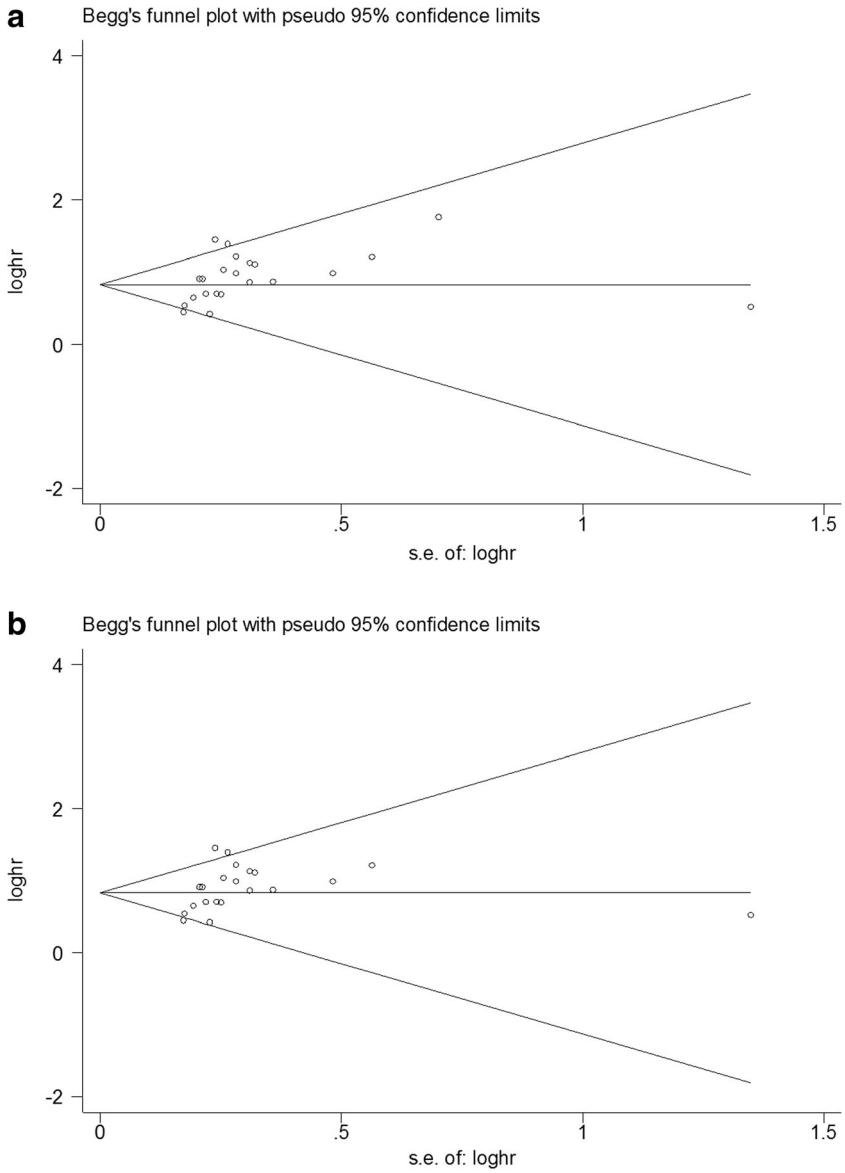

Fig. 5 Begg's funnel plot on the effects of VM on digestive cancer survival. **a** Begg's funnel plot demonstrated that there was a certain degree publication bias in the 22 studies. **b** Begg's funnel plot indicated that publication bias was unlikely after removing the study conducted by Yang et al. which was the only study about PaCa

was a critical mediator in VM formation, and VM as well as aberrant HIF-lα/E-cad expression were associated with the development of ESCC [16]. In addition, the abnormal expression of HIF-1α, VEGF, matrix metalloproteinase (MMP)-2 and MMP-9 were related with VM in GC [18]. In GBC, overexpressed HIF-1α was significantly associated with VM in GBC tissue samples [28], suggesting hypoxia may play a role in VM formation. Moreover, HIF-2α might regulate the binding of twist1 to VE-cadherin to promote VM formation in pancreatic cancer cells [32]. In HCC, Zinc finger E-box binding homeobox 2 (ZEB2), an EMT regulator, can promote VM formation through the EMT pathway [31]. Furthermore, the combined detection of VM and Aldehyde dehydrogenase 1 (ALDH1, a biomarker of CSCs) should be valuable as biomarkers for metastasis and thereby prognosis for CRC patients [36].

Although our meta-analysis has evaluated on the relation between VM and clinical outcomes of patients with digestive cancer, several limitations still exist. Firstly, the included studies were retrospective, and the randomised controlled trials (RCTs) had not been found. Secondly, we could not perform further subgroup analysis on DFS owing to limitations in the original studies. Finally, there was some publication bias among the eligible studies due to the quantitative limitation about the study on PaCa.

Taken together, the results of this meta-analysis collectively indicated that VM was a poor prognosis of digestive cancer patients, suggesting that VM-targeted therapies may hold the greatest promise in experimental and clinical cancer research.

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Compliance with Ethical Standards

Competing Interests The author(s) declare that they have no competing interests.

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