Vasculogenic mimicry as a poor diagnostic and prognostic indicator in patients with malignant melanoma: A systematic review and meta-analysis

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Abstract
Background: Vasculogenic mimicry (VM), a brand-new tumor microvascular model of non-endothelial cells, has been proposed as an important therapeutic target in malignant melanoma (MM). We performed a systematic review to evaluate the diagnostic and prognostic accuracy of VM for overall survival of MM patients. Methods: Using QUADAS-2 tool, the quality of the included studies was evaluated. Diagnostic capacity of VM variables were pooled by Meta-Disc software in term of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and the area under summary receiver operating characteristic (SROC). Results: A retrospective observational study was conducted based on ten studies including 978 clinically melanoma patients with proportion (P). VM+ melanoma cells were associated with poor prognosis in 38% of MM group (P = 0.35, 95% confidence intervals (CI): 0.27-0.42, p-value < 0.001). The pooled sensitivity and specificity were 0.82 (95% CI: 0.79-0.84) and 0.69 (95% CI: 0.66-0.71), respectively. Furthermore, the pooled PLR, NLR, and DOR were 2.56 (95% CI: 1.94-3.93), 0.17 (95% CI: 0.07-0.42), and 17.75 (95% CI: 5.30-59.44), respectively. Also, the AUC of SROC was 0.63, indicating high conserving of VM as a biomarker. Importantly, subgroup results suggested that VM+ tumor was a significantly accurate prognostic biomarker when diagnosed by CD31-/PAS+ staining methods in Asian MM samples (p-value < 0.001). Conclusions: Our findings support the potential of VM+ tumor as a promising prognostic biomarker and emphasize on an effective adjuvant therapeutic strategy in prognosis of Asian MM patients.

Background
Malignant melanoma (MM) is the most aggressive skin cancer and the most common skin disorder in Caucasians with an estimated global incidence of about 200,000 new cases per year and 50,000 cancer-related deaths in 2018 [1, 2]. Moreover, the incidence of MM has been rapidly increased over the last 10 years in Asian and Mediterranean population, and it is diagnosed as the seventh and the eighth most common cancer among men and women in Singapore, respectively [3-6]. Although the Asian population has a notably lower risk of MM than Caucasians due to ethnic differences, anatomic distribution, histologic subtypes, and stage at diagnosis [6, 7]. Interestingly, the Caucasians
melanoma patients are characterized by aggressive and progressive disease state, leading to major cancer-related morbidity and mortality of skin disorder [3]. Ultraviolet (UV) radiation, race, lifestyle, and genetic differences are the most important reasons for the higher mortality of melanoma [8-12], which can be decreased via early-stage detection and prevention [12, 13]. Dermoscopy and intrinsic molecular subtyping of melanoma have been widely accepted as an accurate diagnostic method with more than 50% accuracy compared to the clinical diagnosis in patients from Asian-Pacific and Central European countries [14, 15].

Recent investigations introduced a new non-angiogenesis dependent pathway entitled vasculogenic mimicry (VM), which refers to the extremely aggressive tumor cells that imitate endothelial cells and form a vessel-like structure [16, 17]. Eventually, VM has been considered as a cancer hallmark that can independently facilitate tumor neovascularization by formation of fluid-conducting and vascular endothelial cells [18-20]. VM was dedifferentiated into numerous cellular phenotypes and obtained endothelial-like features, resulting in the formation of the de novo matrix-rich vascular-like network, such as plasma and red blood cells [21, 22]. The co-generation of endothelial cells, channels, laminar structures, and heparin sulfate proteoglycans are the main pathophysiological characteristics of VM in human melanoma patients [23-25]. Aggressive VM+ tumor cells are characterized by a higher expression of the basement membrane extracellular matrix (ECM) component laminin5γ2 and metalloproteinases (MMPs)-1, -2, -9, and -14 [21, 22, 26]. In highly aggressive melanoma cells, downregulation of vascular endothelial cadherin and upregulation of ECM components promotes the perfusion of the VM pathway [19, 21]. Ultimately, the VM+ melanoma cells are associated with more aggressive and metastatic tumor biology.

Accumulated evidence suggests that VM is related to a poor prognosis in various malignant human tumors, including breast [27], colorectal [28], prostate [29], hepatocellular carcinoma [30], lung [29], ovarian [31], gastric [32], and bladder cancers [33]. Despite numerous experimental studies, the prognostic value of VM for survival in MM patients is still controversial and inconclusive. Certainly, understanding the role of VM in MM pathogenesis can help to develop effective treatments for tumor invasion and drug resistance in MM [34].
Hence, we conducted a quantitative systematic review along with a comprehensive meta-analysis investigation based on eligible studies to resolve inconsistent and often ambiguous findings. Furthermore, we planned to identify the prognostic accuracy of VM+ cancer patients to predict other clinical pathological feature outcomes of MM.

Methods
This systematic review and meta-analysis were performed according to recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines [35].

Search strategy and study selection
MEDLINE electronic databases of Pubmed, Embase, Wiley Online Library, Web of Science, Science Direct, Cochrane library, and VIP-Google Scholar were searched without using language restrictions to assess the prognostic value of VM in melanoma patients prior to April 18, 2019. Definitely, different spelling and synonyms were combined applying Boolean “OR” and main terms were linked applying Boolean “AND” to identify all the relevant studies. The search string was conducted using MeSH terms and following main headline terms or free word based on the research question (both the UK and US spellings), such as: “vascular mimicry OR vasculogenic mimicry OR tumor cell-lined vessels OR tumor-derived endothelial cells” AND “prognosis OR survival OR outcome” AND “melanoma OR basal cell carcinoma OR squamous cell carcinoma OR cancer OR neoplasms OR malignant melanoma OR basal-cell skin OR squamous-cell skin OR skin”. The comprehensive literature search strategies were detailed in Table S1 (Additional file 1: Table S1), which were retrieved and screened by three researchers separately (ZZ, SI, HH, and MDS).

Inclusion/exclusion criteria
The current meta-analysis covered all prospective and randomized controlled trials (RCTs) studies that were considered eligible if they met the following criteria: (i) Melanoma patients were confirmed by immunohistochemical or histochemical tests. (ii) VM+ tumor tissues samples were assessed by
classical staining in the tissue specimens, positive Periodic Acid-Schiff (PAS) and/or negative endothelial cell markers, CD34 or CD31; (iii) No previously received systemic treatment for metastatic disease. Likewise, we excluded all non-comparative, review, case-control, conference abstracts, meeting, comments, and unrelated articles, as well as family-based, in vitro, and animal studies. Moreover, we excluded duplicate studies, continued work of previous publications, and poor quality studies, as well as those with incomplete and/or missing data such as sample size and VM frequency.

**Data extraction and quality assessment**

All selected articles were reviewed independently by three researchers (ZZ, SI, and MDS) according to PICO (population, intervention, control, and outcomes) principle [36] and any disagreements or inconsistencies in a search process were addressed through consultations and debate. If an acceptable consensus was not reached, a third partner (QW) would resolve these disagreements based on the original data. The key demographics and clinicopathological information of all the qualified data collections were summarized in Table 1 and Table 2; including the first author’s name, publication year, total cases, gender, country of origin population, age, follow up time, VM+ or VM-rate, analyzing methods of VM, Clark level, and location of sampling. Besides, we e-mailed corresponding authors to obtain any missing and additional information, as well as original data needed for the meta-analysis. If the above data were not cited in the original study or no reply was received by email, the item was reported as “not reported (NR)”. All eligible studies were assessed based on the Newcastle-Ottawa scale (NOS) [37] and Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) [38] protocols. Also, the probability of bias was calculated based on the criteria from the Cochrane Collaboration’s tool (Cochrane handbook for systematic reviews of interventions version 5.1.0.).

**Statistical analysis**

The current systematic meta-analysis was carried out applying Comprehensive Meta-Analysis (CMA) software (the USA, version 2.2.064). The diagnostic accuracy and ROC curves were conducted on
MetaDiSc (version 1.4). Besides, the quality of study was calculated by RevMan version 5.2 [39, 40]. Pooled specificity, pooled sensitivity, negative likelihood ratio (NLR), positive likelihood ratio (PLR), and diagnostic odds ratio (DOR) were calculated by corresponding 95% CIs to evaluate the diagnostic value of VM. Furthermore, the summary receiver operating characteristic (SROC) curve was calculated for the involved studies with an overall area under the curve (AUC). Results of the meta-analysis were reported as a proportion (P) with 95% confidence intervals (CIs). All data were reported as means ± STD, standard deviation (SD) or median (range), as well as a description of qualitative variables as number and percentage. The chi square-based Q-test was applied to testify between-study heterogeneity. Subgroup analysis was performed to identify the source of existing heterogeneity between the VM+ and available sub analyses such as sample size, race, and VM detestation methods. Publication bias was assessed using Begg’s funnel plots [41] and Egger’s regression test [42]. A value of “Pr > |z|” less than 0.05 was considered to be potential publication bias. All reported p values were two-sided and p-value < 0.05 was considered statistically significant.

Results

Description of studies

A detailed PRISMA flowchart of the study identification, screening, and exclusion process was shown in Fig. 1. The primary manual search yielded 426 potentially eligible literatures through searching of electronic databases and 1 record by manual search. After excluding duplicate studies (198 studies), 229 publications were kept for screening, of which 102 records were excluded according to the inclusion and exclusion criteria from database searching. Then, the remaining 127 articles were further assessed by abstract reviewing, and 67 studies were discarded either due to cell or animal studies data. Following careful review of titles and abstracts, 60 studies were considered in full-text articles and assessed for suitability. 20 studies were excluded for obvious irrelevance, 16 studies were precluded for other cancer studies, and 12 studies dismissed due to no related essay (Also see Additional file 1: Table S2). Finally, 12 studies were presented in this meta-analysis [43-53].
Characteristics of studies

The demographic information of all relevant studies was detailed in Table 1. According to this table, a total of 12 studies with 978 MM patients were included in this systematic review and meta-analysis, between 1999 and 2017. Most of the studies were conducted in people of the Asian race, tracked by 7 studies (58.4%) [47, 48, 50-54] and 4 studies (33.4%) in European countries [44, 46, 49, 55], one study in USA (8.2%) [43], and no study from African populations. Gender subgroups among 978 patients included 377 male and 307 female patients. The major clinicopathological features of the included studies are shown in Table 2. More than 80% of the MM patients were diagnosed by histopathological tests. PAS combined-staining with endothelial markers (CD31 or CD34) is a commonly used method for identification of tumor VM in paraffin-embedded tissue specimens (66.7%) in 8 studies [44, 48, 50-55] as well as PAS staining in 4 studies [43, 46, 47, 49]. Moreover, significant predictors of VM+ in both adjusted and unadjusted analyses were Clark level IV/V (84.4%). Finally, eleven studies reported the association between VM and clinicopathological parameters regarding OS [43-54], with the follow-up period ranged from 39-480 months.

Quality assessment

All 12 papers were methodologically essayed according to NOS and QUADAS-2 quality evaluation standards of the Cochrane Reviewer handbook. Both systems' tools focused on the study dependent on the methodology. Overall, the average NOS score was approximately 7.4 out of 12, which could be classified nearly in the high quality group. For each study, the NOS score is sorted in Table 1. Furthermore, QUADAS-2 results confirmed that significant bias was not detected in the present meta-analyses. Details of the quality evaluation of eligible studies according to the NOS score were summarized in the Additional file 1: Table S3. The reviewers' decisions about each risk of bias and applicability concerns graph were presented as percentages across selected studies. Figure S1 shows all parameters of QUADAS-2 assessment individually (Additional file 2: Figure S1). In this study, no significant bias and applicability concerns were found in all the selected studies.
Outcome of the meta-analysis

The relationship between VM+ and overall survival of MM patients was identified applying the pooled proportions test method. We used a random effect approach because the heterogeneity of the overall prognosis was relatively high, which is shown across the study ($I^2 = 79.8$, $p$-value < 0.001). Based on heterogeneous cross of 12 studies, VM was associated with poor prognosis in 38% of MM group compared to the VM-group ($P = 0.35$, 95% confidence intervals (95% CIs): 0.27-0.42, $p$-value < 0.001). Therefore, these results suggested that VM+ indicated a poorer prognosis for MM patients (Fig. 2).

Diagnostic accuracy

The effect of heterogeneity on the diagnostic threshold was evaluated based on the Spearman correlation coefficient. Fig. 3 presents the forest plots of pooled sensitivity and specificity, with their 95% CIs for individual studies. According to the results, the overall pooled sensitivity of VM+ tumor was 0.82 (95% CI: 0.79-0.84, Fig. 4a), while the specificity of VM+ tumor was 0.69 (95% CI: 0.66-0.71; Fig. 4b), among the 12 included studies. Furthermore, the overall pooled results for PLR, NLR, and DOR were 2.56 (95% CI: 1.94-3.93), 0.17 (95% CI: 0.07-0.42), and 17.75 (95% CI: 5.30-59.44), respectively.

Subgroup analysis

Associations between VM+ and the possible demographic and clinicopathological features of MM patients are sorted in Table 3. According to the results, none of the above covariates contributed to the heterogeneity (all $p$-values > 0.05). Therefore, according to those covariates, the pooled sensitivity, specificity, PLR, NLR, DOR, and AUC were measured for significant sub-analysis parameters. We detected statistically significant relationships between VM and sample size, VM and
race, as well as between VM expression and staining method (Fig. 5). As shown in Fig. 5a and Table 3, VM+ is a potentially accurate prognostic biomarker in CD31-/PAS+ (P = 0.24, 95% CI: 0.15-0.35) compared to CD34-/PAS+ (P = 0.39, 95% CI: 0.27-0.42) and PAS+ staining subgroups (P = 0.40, 95% CI: 0.30-0.52). As a result, the CD31-/PAS+ staining methods are relatively accurate diagnostic methods for detection of the VM, with 75% sensitivity and 70% specificity. The subgroups analysis was performed based on sample size (≤100 vs. >100; Fig. 5b). The proportion of population with a high sample size (3 studies with more than 100 MM cases) was 0.41 (95% CI: 0.28-0.56; \( p\)-value = 0.12); while that of a sample size with less than 100 MM patients (9 studies) was 0.31 (95% CI: 0.23-0.41; \( p\)-value < 0.001). Meanwhile, the highest specificity, NLR, and AUC in sample sizes less than 100 suggested that VM is more accurate in diagnosis of smaller sample sizes. Interestingly, our results show that the overexpression of the VM was a high risk prognosis factor in Asia populations (7 studies with 503 cases; P = 0.32; 95% CI: 0.23-0.42; \( p\)-value < 0.001; Fig. 5c). As seen in Table 3 and Fig. 5C, the pooled sensitivity and specificity were higher in the Asian patients compared to Caucasian patients (85% vs. 69% and 78% vs. 68%, respectively). Moreover, we could not find any significant correlation between the VM+ melanoma samples with gender, age, Clark level, and location of sampling (Data not shown).

**Publication bias and sensitivity analysis**

The publication bias and sensitivity were analyzed using Funnel plots and empirically utilizing regression tests according to Begg’s test. The analysis was conducted by excluding a single study at a time. A symmetric inverted funnel shape in this study implies a ‘well-behaved’ data set, in which publication bias is improbable. Following exclusion of the ten studies, there was no obvious statistical evidence for publication bias in our meta-analysis (t = 1.41; \( p\)-value = 0.19) (Fig. 6). Hence, the results of the current meta-analysis were credible and stable, due to no noticeable publication bias influencing overall results.

**Discussion**
To the best of our knowledge, this is the first meta-analysis study to identify prognostic value of VM+ in advanced melanoma patients. Our results indicate that 38% MM patients with VM+ have a poor prognosis ($P = 0.35$, 95% CI: 0.27-0.42, $p$-value < 0.001). Moreover, significant association was identified in the pathologic features of the VM+ melanoma samples by race, sample size, and VM detection methods, which adversely influenced cancer survival. In current study, the AUC of SROC was 0.63, indicating the high accuracy of VM as a biomarker for MM. In addition, our pooled results provided convincing evidence for a significant positive relationship between VM and less sample size.

Accumulating evidences indicated that VM is a new model of tumor microcirculation in highly aggressive malignant tumor cells [16, 17]. Recently, in vivo and in vitro studies showed that twist-related protein 1 (Twist1), neurogenic locus notch homolog protein 4 (Notch4), hypoxia inducible factor (HIF)-1a, EPH receptor A2 (EphA2), matrix metalloproteinase (MMP)-1, 2, -9, -14, and vascular endothelial (VE)-cadherin are potential therapeutic targets and prognostic indicators in VM+ tumor samples [22, 56]. Moreover, these studies suggest that VM+ tumor samples were resistant to common antiangiogenic drugs, such as apatinib, bevacizumab, and sunitinib [23, 34, 57]. The high ratio of neovascularization in VM+ tumor promotes angiogenesis, metastasis, and tumor growth along with extensive hypoxia and necrosis as well as induced recruitment of various pro-angiogenic factors, such as bone marrow-derived CD45+ myeloid cells, pericyte progenitor cells, and mature F4/80+ tumor-associated macrophages [58, 59]. Location variety and heterogenic morphology of MM tumors have a close relationship with the VM formation, which represented a noteworthy challenge for dermatologists [16, 60].

Our results clearly showed that VM is considered to have a negative effect on the overall survival of MM patients with a risk ratio of 0.35 (95% CI: 0.27-0.42, $p$-value < 0.001). Furthermore, our findings from sub-analyses underlined the status of VM formation in MM patients. We showed a stronger association between VM+ and sample size, VM+ and race, as well as VM+ and detection method of VM ($p$-value < 0.001). Our findings suggested that VM+ can be a significantly accurate prognostic biomarker when diagnosed by CD31-/PAS+ staining methods, with relatively accurate diagnostic value for VM detection (75% sensitivity and 70% specificity). Also, results of subgroup analyses
implied a better diagnosis of VM in less sample sizes compared to that in higher than 100 cases (P: 0.31, 95% CI: 0.23-0.41; \textit{p-value} < 0.001), with a pooled sensitivity of 85% and specificity of 78%.

Interestingly, our results proposed VM as a promising accurate biomarker and target for MM diagnosis and therapeutics in Asian patients than that in Caucasian patients, with a pooled sensitivity of 91% and specificity of 70.5%. Lifestyle factors such as UV radiation exposure and nutrition are synergistically effective on the prevalence of MM [61, 62]. Compared to Caucasians, Asian MM patients are diagnosed at older ages; hence, we face a large population of old MM patients [4, 12]. But considering that our study was limited to a small sample size of cases in the Caucasian group (475 cases), more large-size studies among Caucasian MM population should be performed to obtain a comprehensive result [61]. It is known that VM+ tumor samples profiling could be more accurate in the Asian population compared to the Caucasian population [62]. The meta-analysis showed that the CD31-/PAS+ staining is a more accurate detection method for VM+ tumor samples than CD34-/PAS+ and PAS+ staining. Meanwhile, this meta-analysis suggested that postoperative detection with CD34-and/or CD31- of VM+ tumor samples in MM would be useful in finding critical therapy targets as well as making better follow-up plans. Thus, we estimated OS in the meta-analysis, taking into account that the great majority of the studies do not report the information [62].

Several published meta-analyses have concerned to evaluate the dissimilarity of tumor VM relevant to the prognosis of cancers [27, 28, 30, 53, 63]. For example, Cao Z. et al. suggested that VM+ cancer patients have a poor 5-year overall survival rate compared to VM- cancer patients, particularly in metastatic diseases of sarcomas and lung, colon, liver, and melanoma cancers [19]. By contrast, Shen Y. et al. addressed the tumor VM formation as an unfavorable prognostic indicator in breast cancer patients (P = 0.23, 95% CI: 0.08-0.38, \textit{p-value} = 0.003) [64]. In line with our results, Yang JP. et al. findings showed that tumor VM is significantly associated with cancer differentiation, lymph node metastasis and distant metastasis, (P = 2.16; 95% CI: 1.98-2.38; \textit{p-value} < 0.001) [65]. With such foreground and assumptions, this current study allows us to reach a better understanding of the clinical role of VM formation in MM patients using the statistical approaches. Conversely, the correlation between VM and survival of cancer patients are controversial or inconclusive.
We would like to point out that there are some significant limitations in the current work: First, we only include papers published in English, but papers published in other languages, especially Chinese and Russian, were excluded, which certainly causes selection bias. Also, we did not consider the sensitivity analysis when reflecting on the significant difference among individual articles. Importantly, in most selected studies, the comments detection methods were IHC technique. The different primary antibodies with a wide range of the antibody dilution might also affect the IHC sensibility. Furthermore, the small sample size, short follow-up times, and no homogeneous distribution of the population (no studies upon the African publication) might also affect the precision of the estimate. Finally, the publication bias results showed that these limitations were not sufficiently enough to influence of the analysis of late-stage and fatal complications. It is clear that future clinical studies with larger sample sizes, standardized protocols, and more homogenizes populations would be required to fully understand the prognostics potential of tumor VM in melanoma patients.

Conclusions
The results of the present meta-analysis for the first time suggested that VM+ tumor is associated with a poor OS of MM patients, as well as it is a more accurate prognostic biomarker in less sample size groups of Asian patients. Therefore, the tumor VM status could be a promising prognostic biomarker for surgical and effective adjuvant therapy of MM patients.

Abbreviations
MM: Malignant melanoma; UV: Ultraviolet; VM: Vasculogenic mimicry; ECM: Extracellular matrix; PRISMA: Preferred reporting items for systematic reviews and meta-analysis; PAS: Periodic acid schiff's; NOS: Newcastle-Ottawa scale; QUADAS-2: Quality assessment of diagnostic accuracy studies 2; CAM: Comprehensive meta-analysis; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; DOR: Diagnostic odds ratio; SROC: Summary receiver operating characteristic; AUC: Under the curve; P: Proportion; CI: Confidence interval; Twist1: Twist-related protein 1; Notch4: Neurogenic locus notch homolog protein 4; HIF-1a: hypoxia inducible factor 1a; EphA2: EPH receptor A2; MMP: Matrix metalloproteinase; VE: Vascular endothelial; EKR: Extracellular signal-regulated kinas.

Declarations
Ethics approval and consent to participate
This study was approved by an independent ethics committee/institutional review board at Department of Oncology, Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they no competing interests.

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Authors' contributions

ZZ, SI, MDS participated in the design of the study. HH performed the statistical analysis. ZL, SI, and YF carried out the data extraction. SI and QW conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All Authors read and approved the final manuscript.

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Additional Files

**Additional file 1: Table S1.** The detailed search strategy. **Table S2.** The excluded full-text articles. **Table S3.** Quality assessment of the included studies according to the Newcastle-Ottawa Scale (NOS)

**Additional file 2: Figure S1.** Risk of bias graph. The overall risk of bias was regarded as low in all qualified studies, in term of the QUADAS-2 assessment

Figures
Figure 1

Flow diagram of included studies (following PRISMA guidelines, n = number of studies).
**Figure 2**

Forest plot of proportion ratios (P) in the random effect model. These plots show the prognostics accuracy for all objective response analyses.
Summary receiver operating characteristic (SROC) curve for VM in the diagnosis of MM cancer.

orest plot of pooled sensitivity (a) and specificity (b) for VM in the diagnosis of MM cancer.
Funnel plot of the sub-analysis parameters. Forest plots showed that MM cancer was associated with detection methods of VM (a), sample size (b), and race (c). CIs, confidence intervals. Weights are from random effects analysis.
Funnel plots for the detection of a publication bias. All enrolled 12 studies represent by each point for the specified association, individually. The vertical and horizontal axes represent the standard error of a logarithmic proportion and the proportion limits, respectively.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

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