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

Zhenhua Zhang
The Affiliated Hospital of Southwest Medical University
Saber Imani
First Affiliated Hospital of Southwest Medical University
Marzieh Dehghan Shasaltaneh
"University of Zanjan"
Hossein Hosseinifard
Tabriz University of Medical Sciences
Zou Linglin
First Affiliated Hospital of Southwest Medical University
Yu Fan
The Affiliated Hospital of Southern Medical University
QingLian Wen (wql73115@hotmail.com)
oncology

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Abstract

Background Vasculogenic mimicry (VM), a brand-new tumor microvascular model of non-endothelial cells, is proposed as an important therapeutic target in malignant melanoma (MM). We performed a systematic review to evaluate the diagnostic and prognostics accuracy of VM for overall survival of MM patients. Methods The quality of the included studies was assessed by QUADAS-2 tool. Diagnostic capacity of VM variables were pooled by the Meta-Disc software in term of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the 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 are 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 the highly conserving of VM as a biomarker. Importantly, subgroup results suggested that VM+ tumor was significantly accurate prognostics biomarkers when diagnosed by CD31-/PAS+ staining methods in Asian MM samples (P-value > 0.001). Conclusions Our finding supports the VM+ tumor as a promising prognostic biomarker and effective adjuvant therapeutic strategy in prognostics of Asian MM patients.

Background

Malignant melanoma (MM) is the most aggressive skin cancer and the most common skin disorders 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 increasing over the last 10 years in Asian and Mediterranean population, and it is diagnosed as a seventh and the eight most common cancer among men and women in Singapore, respectively [3-6]. Although Asian population have a notably lower risk of MM than Caucasians; ethnic differences, anatomic distribution, with regard to histologic subtypes and stage at diagnosis have been well recognized [6, 7]. Interestingly, the Caucasians melanoma patients have aggregative and progressive disease state, leading 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 increase of melanoma related-mortality [8-12]. Early-stage detection and prevention of melanoma can reduce the mortality of MM and present the best survival [12, 13]. Dermoscopy and intrinsic molecular subtyping of melanoma have been widely accepted as an accuracy diagnostic method by more than 50% compared to the clinical diagnosis in patients from Asian-Pacific and Central European countries [14, 15].

Recent investigations introduced a novel non-angiogenesis dependent pathway entitled vasculogenic mimicry (VM); which refers to the highly aggressive cancer cells that imitate endothelial cells form a vessel-like structure [16, 17]. Eventually, VM is considered as cancer hallmark that can independently facilitate tumor neovascularization by formation of fluid-conducting and vascular endothelial cells [18-

20]. VM was dedifferentiated into multiple cellular phenotypes and obtained endothelial-like characteristics, resulting formation of de novo matrix-rich vascular- like network, such as plasma and red blood cells [21, 22]. The co-expressing of endothelial cells, channels formation, lamini structures, and heparin sulfate proteoglycans are the main pathophysiological characterizations of VM in human melanoma patients [23-25]. Aggressive VM+ tumor cells have a higher expression of the basement membrane extracellular matrix (ECM) component laminin5γ2, metalloproteinase (MMP)-1, -2, -9, and -14 [21, 22, 26]. In highly aggressive melanoma cells, perfusion pathway of VM downregulated expression of vascular endothelial cadherin and upregulated expression of specific localization of ECM components; which are able to modify ECM to initiate or promote VM [19, 21]. Ultimately, the VM+ melanoma cells are associated with more aggressive and metastatic tumor biology.

Accumulated evidence suggests that VM is related with a poor prognosis in various malignant human tumor , including breast cancer [27], colorectal cancer [28], prostate cancer [29], hepatocellular carcinoma [30], lung cancer [29], ovarian cancers [31], gastric cancer [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 could help developing 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 prognostics accuracy of VM+ cancer patients to predict other clinical pathological feature outcomes of MM.

Methods

This systematic review and meta-analysis were carried out based on 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 using Boolean “OR” and main terms were linked using Boolean “AND” to identify all the relevant studies. The search string was conducted by 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 included 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 examination. (*ii*). VM+ tumor tissues samples were assessed by a classical staining in the tissue specimens, positive Periodic acid schiff's (PAS) and/or negative endothelial cell markers, CD31 or CD34; (*iii*) No any previously received systemic treatment for metastatic disease. Likewise, we excluded all non-comparative, review, case-control, conference abstracts, meeting, comments, family-based studies, and unrelated articles, *in vitro* and animal studies. In addition, 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 inconsistencies or disagreements in a search process were resolved through consultations and debate. If they could not reach an acceptable consensus, a third partner (QW) would resolve these disagreements according to the original data. The key demographics and clinicopathological information of all qualified data-collection were summarized in Table 1 and Table 2; including the first author's name, publication year, total cases, gender, country of origin population, age, flow up time, VM+ or VM- rate, analyzing methods of VM, Clark level and location of sampling. We also e-mailed corresponding authors to obtain any missing and additional information, as well as original data required for the meta-analysis. If the above data were not cited in the original study or no replay was received by email, the item was reported as "not reported (NR)". All eligible studies were assessed according to the Newcastle-Ottawa scale (NOS) [37] and Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) [38] protocols. Also, the risk of bias was calculated according to 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 performed using Comprehensive Meta-Analysis (CMA) software (USA, version 2.2.064). The diagnostic accuracy and ROC curves were conducted on MetaDiSc (version 1.4). Also, the quality of study was calculated by RevMan version 5.2 [39, 40]. Pooled sensitivity,

pooled specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR), by corresponding 95% CIs were calculated to evaluate the diagnostic value of VM. Furthermore, the summary receiver operating characteristic (SROC) curve for the included studies with an overall area under the curve (AUC) were calculated. The results of the meta-analysis were reported as proportion (P) with 95% confidence intervals (CIs). All data were reported as means ± Std. Deviation (SD) or median (range), as well as description of qualitative variables as number and percentage. The chi-square based Q-test was applied to testify between-study heterogeneity. Subgroup analysis was conducted to determine the source of existing heterogeneity between the VM+ and available sub analysis such as sample size, race, and VM detestation methods. Publication bias was evaluated by 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 left 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 evaluated by abstract reviewing, and 67 studies were discarded either due to cell or animal studies data. After carefully reviewing titles and abstracts, 60 studies were considered in full-text articles assessed for suitability. 20 studies were precluded 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].

Fig. 1

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], 4 studies (33.4%) in European countries [44, 46, 49, 55], one study in USA (8.2%) [43], and without any studies from African populations. Gender subgroups among 978 patients, 377 and 307 patients were male and female, respectively. The main clinicopathological characteristics of

the included studies are shown in Table 2. More than 80% of the MM patients were diagnosed by histopathological examination. 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]. Also, significant predictors of VM+ in both adjusted and unadjusted analyses were Clark level IV/V (84.4%). Finally, eleven studies reported the relationship between VM and clinicopathological parameters regarding OS [43-54], with the follow-up period ranged from 39 to 480 months.

Table 1 Demographics information of included studies

Table 2 Main clinicopathological and vasculogenic mimicry characteristics of all relevant studies

Quality assessment

All 12 papers were methodologically essayed by NOS and QUADAS-2 quality evaluation standards of the Cochrane Reviewer handbook. Both systems' tools focus on the study as dependent on methodology. Overall, the average NOS score was approximately 7.4 out of 12, which were classified in the high quality relatively. For each study, NOS score is sorted in the Table 1. Furthermore, QUADAS-2 results confirmed that significant bias was not presented in current 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 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 selected studies.

Outcome of the meta-analysis

The association between VM+ and overall survival of MM patients was identified using 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).

Fig. 2

Diagnostic accuracy

To assess the heterogeneity from threshold effect, we conducted analysis of diagnostic threshold with the spearman correlation coefficient. The forest plots of pooled sensitivity, specificity, with their 95% CIs for individual studies are shown in the Fig. 3. The overall pooled sensitivity of VM+ tumor was 0.82 (95% CI: 0.79-0.84, Fig. 4a), while the specificity of VM+ tumor 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.

Fig. 3

Fig. 4

Subgroup analysis

Associations between VM+ and the possible demographics and clinicopathological features of MM patients are sorted in the Table 3. Table 3 reveals none of the above covariates contributed to the heterogeneity (all *P-value > 0.05*). Therefore, on the basis of those covariates, the pooled sensitivity, specificity, PLR, NLR, DOR, and AUC for significant sub-analysis parameters were measured. We found statistically significant associations between VM and sample size, VM and race, as well as between expression of VM and staining method of VM (Fig. 5). As shown in Fig. 5a and Table 3, VM+ is a potentially accurate prognostic biomarker in CD31-/PAS+ staining subgroup (P = 0.24, 95% CI: 0.15-0.35) than CD34-/PAS+ staining subgroup (P = 0.39, 95% CI: 0.27–0.42) and PAS+ staining subgroup (P = 0.40, 95% CI: 0.30–0.52). So, 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 conducted 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, highest specificity, NLR, and AUC in sample size less than 100 suggested that VM is more accurate in less sample size diagnosis. 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 the 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).

Table 3 Subgroup analyses of the included studies

Fig. 5

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 carried out by precluding a single study at a time. A symmetric inverted funnel shape in this study shows from a 'well-behaved' data set, in which publication bias is unlikely. After the ten studies were excluded, 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 stable and credible, due no noticeable publications bias influencing overall results.

Fig. 6

Discussion

To the best of our knowledge, this is the first meta-analysis study to identify prognostic value of VM+ in advanced melanoma patients. Overall, we weighted a comprehensive analysis of the data from 12 clinical studies representing 978 MM 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 influences cancer survival. In our study, we compiled a research that provides a framework to pooled sensitivity, specificity, PLR, NLR, and DOR; which were 0.82, 0.69, 2.56, 0.17, and 17.75, respectively. The AUC of SROC was 0.63, indicating the highly accuracy of VM as a biomarker for MM. In addition, our pooled results provide compelling evidence of a significant positive association between VM and a less sample size.

Accumulating evidences indicated that VM is a new model of tumor microcirculation in highly aggressive malignant tumor cells [16]. Independently, VM provided blood supply to mosaic vessels by the sprouting of pre-existing host blood vessels to new vascular networks, resulting thrombomodulin and cytokeratin in the during pluripotency [16, 17]. Recently, *in vivo* and *in vitro* studies shows 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]. Plasticity and heterogeneity differential of the MM samples made the multiple problems in early and high-sensitivity prognosis [57]. These remarkable different prognoses are triggered by the different functional pathways

of rapidly growing tumor cells and perfusion [57-59]. According to the heterotopic xenograft MM model study, the extracellular signal-regulated kinas (ERK)-1/PI3K/MMP-2 signaling pathway is the main molecular cascade that involved in the differentiation of the hybrid mesothelial cells to the endothelial cells [60]. Moreover, these studies suggest that VM+ tumor samples are the midst of emerging resistance to comment antiangiogenic drugs, such as apatinib, bevacizumab, and sunitinib [23, 34, 61]. High ration of neovascularization in VM+ tumor promote angiogenesis, metastasis, and tumor growth by extensive hypoxia and necrosis as well as induced recruitment of various pro-angiogenic factors, such as bone marrow-derived $CD45^+$ myeloid cells, mature $F4/80^+$ tumor -associated macrophages, and pericyte progenitor cells [62, 63]. Location variety and heterogenic morphology of MM tumors have a close relationship with the VM formation, represented noteworthy challenge for dermatologist [16, 64].

Our results clearly showed that VM is considered has 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 sub-analysis findings 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 finding suggested that VM+ was a significantly accurate prognostic biomarker when diagnosed by CD31-/PAS+ staining methods, with relatively accurate diagnostic value for VM detection, with a 75% sensitivity and 70% specificity. Also results of subgroup analyses implied a better diagnosis of VM in less sample size than that in high of 100 cases (P: 0.31, 95% CI: 0.23-0.41; *P-value < 0.001*), with a pooled sensitivity of 85% and specificity of 78%. We also have interesting results that proposed VM as a promising accuracy 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 have synergistic effects on prevalence of MM [65, 66]. Compared to Caucasians, there was a trend to Asian MM patients being older, having a higher proportion of MM and a late diagnosis [4, 12]. But considering that our study was limited to a small sample size of cases in the Caucasian group (475 cases), further large-size studies among Caucasian MM population should be designed to provide a comprehensive outcome [65]. It is already well-established that VM+ tumor samples profiling could be more precise in the Asian population than the Caucasian population [66]. The meta-analysis showed that the CD31-/PAS+ staining are more accurate detection methods 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 only OS in the meta-analysis, taking into account that the great majority of the studies do not report the information [66].

Several published meta-analyses have concerned to evaluate the dissimilarity of tumor VM relevant to the prognosis of cancers [27, 28, 30, 53, 67]. For example, *Cao Z.* et al., suggested that VM+ cancer patients have a poor 5-year overall survival rate compared with VM- cancer patients, particularly in metastatic disease of lung, colon, liver, sarcomas, and melanoma cancer [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, *P-value = 0.003*) [68]. In line with our results, Yang JP. et al. finding shows that tumor VM is significantly associated with cancer differentiation, lymph node metastasis and distant metastasis, (P = 2.16; 95% CI: 1.98-2.38; *P-value < 0.001*) [69]. 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 by 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: Firstly, 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 don't consider the sensitivity analysis when reflecting on the significant difference of any individual article. Importantly, in most selected studies, the comments detection methods were IHC technique. The different primary antibodies with wide range of the antibody dilution might also affect the IHC sensibility as well as contradiction of tumor VM-detection with contribution to the bias. Furthermore, the small sample size, short follow-up times and no homogeneous distribution of the population (no studies upon the African publication) might also affects the precision of the estimate with high study base risk. Finally, the publication bias results show that these limitations were not sufficiently long for an analysis of late-stage and fatal complications; undoubtedly, future well-accepted clinical studies with larger samples size, standardized protocols and more homogenizes populations would be needed to fully research the prognostics potential of tumor VM in melanoma patients.

Conclusions

The results of the present meta-analysis for the first time suggest 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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References

1. Tas F: **Metastatic behavior in melanoma: timing, pattern, survival, and influencing factors**. *Journal of oncology* 2012, **2012**:647684.
2. Jemal A, Saraiya M, Patel P, Cherala SS, Barnholtz-Sloan J, Kim J, Wiggins CL, Wingo PA: **Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992-2006**. *Journal of the American Academy of Dermatology* 2011, **65**(5 Suppl 1):S17-25 e11-13.
3. Teh YL, Goh WL, Tan SH, Yong G, Sairi ANH, Soo KC, Ong J, Chia C, Tan G, Soeharno H *et al*: **Treatment and outcomes of melanoma in Asia: Results from the National Cancer Centre Singapore**. *Asia-Pacific journal of clinical oncology* 2017.
4. Chang JW, Yeh KY, Wang CH, Yang TS, Chiang HF, Wei FC, Kuo TT, Yang CH: **Malignant melanoma in Taiwan: a prognostic study of 181 cases**. *Melanoma Res* 2004, **14**(6):537-541.
5. Sng J, Koh D, Siong WC, Choo TB: **Skin cancer trends among Asians living in Singapore from 1968 to 2006**. *Journal of the American Academy of Dermatology* 2009, **61**(3):426-432.
6. Koh D, Wang H, Lee J, Chia KS, Lee HP, Goh CL: **Basal cell carcinoma, squamous cell carcinoma and melanoma of the skin: analysis of the Singapore Cancer Registry data 1968-97**. *Br J Dermatol* 2003, **148**(6):1161-1166.
7. Shoo BA, Kashani-Sabet M: **Melanoma arising in African-, Asian-, Latino- and Native-American populations**. *Semin Cutan Med Surg* 2009, **28**(2):96-102.
8. Shoo BA, Sagebiel RW, Kashani-Sabet M: **Discordance in the histopathologic diagnosis of melanoma at a melanoma referral center**. *Journal of the American Academy of Dermatology* 2010, **62**(5):751-756.
9. Kim HK, Lee S, Kim K, Heo MH, Lee H, Cho J, Kim NKD, Park W, Lee SJ, Kim JH *et al*: **Efficacy of BRAF Inhibitors in Asian Metastatic Melanoma Patients: Potential Implications of Genomic Sequencing in BRAF-Mutated Melanoma**. *Translational oncology* 2016, **9**(6):557-564.
10. Lv J, Dai B, Kong Y, Shen X, Kong J: **Acral Melanoma in Chinese: A Clinicopathological and Prognostic Study of 142 cases**. *Scientific reports* 2016, **6**:31432.
11. Tsoutsos D, Papadopoulos S, Kehagias G, Mara A, Kyriopoulou E, Karonidis A, Spiliopoulos K, Mpalitsaris E, Karapiperis G, Panayotou P *et al*: **Epidemiological trends in the diagnosis of melanoma in a Southern European population: analysis of a large database from a tertiary referral center**. *Melanoma Res* 2018, **28**(4):348-358.
12. Brunssen A, Jansen L, Eisemann N, Waldmann A, Weberpals J, Kraywinkel K, Eberle A, Holleczek B, Zeissig SR, Brenner H *et al*: **Long-term relative survival from melanoma in Germany 1997-2013**. *Melanoma Res* 2018.
13. Yamazaki N, Kiyohara Y, Uhara H, Uehara J, Fujimoto M, Takenouchi T, Otsuka M, Uchi H, Ihn H, Minami H: **Efficacy and safety of nivolumab in Japanese patients with previously untreated advanced melanoma: A phase II study**. *Cancer science* 2017, **108**(6):1223-1230.
14. Mun JH, Ohn J, Kim WI, Park SM, Kim MB: **Dermoscopy of Melanomas on the Trunk and Extremities in Asians**. *PloS one* 2016, **11**(7):e0158374.

15. Tringali C, Silvestri I, Testa F, Baldassari P, Anastasia L, Mortarini R, Anichini A, Lopez-Requena A, Tettamanti G, Venerando B: **Molecular subtyping of metastatic melanoma based on cell ganglioside metabolism profiles**. *BMC Cancer* 2014, **14**:560.
16. Zhang J, Qiao L, Liang N, Xie J, Luo H, Deng G, Zhang J: **Vasculogenic mimicry and tumor metastasis**. *Journal of BUON : official journal of the Balkan Union of Oncology* 2016, **21**(3):533-541.
17. Delgado-Bellido D, Serrano-Saenz S, Fernandez-Cortes M, Oliver FJ: **Vasculogenic mimicry signaling revisited: focus on non-vascular VE-cadherin**. *Molecular cancer* 2017, **16**(1):65.
18. Hendrix MJ, Seftor EA, Seftor RE, Chao JT, Chien DS, Chu YW: **Tumor cell vascular mimicry: Novel targeting opportunity in melanoma**. *Pharmacology & therapeutics* 2016, **159**:83-92.
19. Cao Z, Bao M, Miele L, Sarkar FH, Wang Z, Zhou Q: **Tumour vasculogenic mimicry is associated with poor prognosis of human cancer patients: a systemic review and meta-analysis**. *European journal of cancer* 2013, **49**(18):3914-3923.
20. Wu S, Yu L, Wang D, Zhou L, Cheng Z, Chai D, Ma L, Tao Y: **Aberrant expression of CD133 in non-small cell lung cancer and its relationship to vasculogenic mimicry**. *BMC Cancer* 2012, **12**:535.
21. Abazis-Stamboulieh D, Oikonomou P, Papadoulis N, Panayiotidis P, Vrakidou E, Tsezou A: **Association of interleukin-1A, interleukin-1B and interleukin-1 receptor antagonist gene polymorphisms with multiple myeloma**. *Leuk Lymphoma* 2007, **48**(11):2196-2203.
22. Caramel J, Papadogeorgakis E, Hill L, Browne GJ, Richard G, Wierinckx A, Saldanha G, Osborne J, Hutchinson P, Tse G *et al*: **A switch in the expression of embryonic EMT-inducers drives the development of malignant melanoma**. *Cancer Cell* 2013, **24**(4):466-480.
23. Vartanian A, Baryshnikov AY: **Crosstalk between apoptosis and antioxidants in melanoma vasculogenic mimicry**. *Advances in experimental medicine and biology* 2007, **601**:145-153.
24. Paulis YW, Soetekouw PM, Verheul HM, Tjan-Heijnen VC, Griffioen AW: **Signalling pathways in vasculogenic mimicry**. *Biochimica et biophysica acta* 2010, **1806**(1):18-28.
25. Cao Z, Yu D, Fu S, Zhang G, Pan Y, Bao M, Tu J, Shang B, Guo P, Yang P *et al*: **Lycorine hydrochloride selectively inhibits human ovarian cancer cell proliferation and tumor neovascularization with very low toxicity**. *Toxicology letters* 2013, **218**(2):174-185.
26. Xu XD, Yang L, Zheng LY, Pan YY, Cao ZF, Zhang ZQ, Zhou QS, Yang B, Cao C: **Erratum to: Suberoylanilide hydroxamic acid, an inhibitor of histone deacetylase, suppresses vasculogenic mimicry and proliferation of highly aggressive pancreatic cancer PaTu8988 cells**. *BMC Cancer* 2016, **16**(1):374.
27. Shirakawa K, Kobayashi H, Heike Y, Kawamoto S, Brechbiel MW, Kasumi F, Iwanaga T, Konishi F, Terada M, Wakasugi H: **Hemodynamics in vasculogenic mimicry and angiogenesis of inflammatory breast cancer xenograft**. *Cancer research* 2002, **62**(2):560-566.
28. Baeten CI, Hillen F, Pauwels P, de Bruine AP, Baeten CG: **Prognostic role of vasculogenic mimicry in colorectal cancer**. *Diseases of the colon and rectum* 2009, **52**(12):2028-2035.
29. Ding J, Jia X, Zuo B, He J, Yang J, He Y: **A novel monoclonal antibody targeting a novel epitope of VEcadherin inhibits vasculogenic mimicry of lung cancer cells**. *Oncol Rep* 2018, **39**(6):2837-2844.

30. Liu WB, Xu GL, Jia WD, Li JS, Ma JL, Chen K, Wang ZH, Ge YS, Ren WH, Yu JH *et al*: **Prognostic significance and mechanisms of patterned matrix vasculogenic mimicry in hepatocellular carcinoma**. *Medical oncology* 2011, **28 Suppl 1**:S228-238.
31. Tang HS, Feng YJ, Yao LQ: **Angiogenesis, vasculogenesis, and vasculogenic mimicry in ovarian cancer**. *Int J Gynecol Cancer* 2009, **19**(4):605-610.
32. Guo Q, Yuan Y, Jin Z, Xu T, Gao Y, Wei H, Li C, Hou W, Hua B: **Association between Tumor Vasculogenic Mimicry and the Poor Prognosis of Gastric Cancer in China: An Updated Systematic Review and Meta-Analysis**. *Biomed Res Int* 2016, **2016**:2408645.
33. Fujimoto A, Onodera H, Mori A, Nagayama S, Yonenaga Y, Tachibana T: **Tumour plasticity and extravascular circulation in ECV304 human bladder carcinoma cells**. *Anticancer research* 2006, **26**(1A):59-69.
34. Qiao L, Liang N, Zhang J, Xie J, Liu F, Xu D, Yu X, Tian Y: **Advanced research on vasculogenic mimicry in cancer**. *Journal of cellular and molecular medicine* 2015, **19**(2):315-326.
35. Panic N, Leoncini E, de Belvis G, Ricciardi W, Boccia S: **Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses**. *PloS one* 2013, **8**(12):e83138.
36. Richardson WS, Wilson MC, Nishikawa J, Hayward RS: **The well-built clinical question: a key to evidence-based decisions**. *ACP journal club* 1995, **123**(3):A12-13.
37. Stang A: **Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses**. *European journal of epidemiology* 2010, **25**(9):603-605.
38. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM, Group Q-: **QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies**. *Annals of internal medicine* 2011, **155**(8):529-536.
39. Imani S, Zhang X, Hosseinifard H, Fu S, Fu J: **The diagnostic role of microRNA-34a in breast cancer: a systematic review and meta-analysis**. *Oncotarget* 2017, **8**(14):23177-23187.
40. Imani S, Hosseinifard H, Cheng J, Wei C, Fu J: **Prognostic Value of EMT-inducing Transcription Factors (EMT-TFs) in Metastatic Breast Cancer: A Systematic Review and Meta-analysis**. *Scientific reports* 2016, **6**:28587.
41. Munafo MR, Clark TG, Flint J: **Assessing publication bias in genetic association studies: evidence from a recent meta-analysis**. *Psychiatry research* 2004, **129**(1):39-44.
42. Egger M, Davey Smith G, Schneider M, Minder C: **Bias in meta-analysis detected by a simple, graphical test**. *Bmj* 1997, **315**(7109):629-634.
43. Maniotis AJ, Folberg R, Hess A, Seftor EA, Gardner LM, Pe'er J, Trent JM, Meltzer PS, Hendrix MJ: **Vascular channel formation by human melanoma cells in vivo and in vitro: vasculogenic mimicry**. *The American journal of pathology* 1999, **155**(3):739-752.
44. Massi D, Franchi A, Paglierani M, Ketabchi S, Borgognoni L, Reali UM, Santucci M: **Vasculogenic mimicry has no prognostic significance in pT3 and pT4 cutaneous melanoma**. *Human pathology* 2004, **35**(4):496-502.

45. Sun B, Zhang S, Zhao X, Zhang W, Hao X: **Vasculogenic mimicry is associated with poor survival in patients with mesothelial sarcomas and alveolar rhabdomyosarcomas**. *International journal of oncology* 2004, **25**(6):1609-1614.
46. Hillen F, Baeten CI, van de Winkel A, Creytens D, van der Schaft DW, Winnepenninckx V, Griffioen AW: **Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma**. *Cancer immunology, immunotherapy : CII* 2008, **57**(1):97-106.
47. Zhang S, Li M, Zhang D, Xu S, Wang X, Liu Z, Zhao X, Sun B: **Hypoxia influences linearly patterned programmed cell necrosis and tumor blood supply patterns formation in melanoma**. *Laboratory investigation; a journal of technical methods and pathology* 2009, **89**(5):575-586.
48. Shi L, Lei D, Ma C, Xu F, Li Y, Wang Y, Cong N, Liu D, Pan XL: **Clinicopathological implications of tumour-associated macrophages and vascularization in sinonasal melanoma**. *The Journal of international medical research* 2010, **38**(4):1276-1286.
49. van Beurden A, Schmitz RF, van Dijk CM, Baeten CI: **Periodic acid Schiff loops and blood lakes associated with metastasis in cutaneous melanoma**. *Melanoma Res* 2012, **22**(6):424-429.
50. Baocun S, Shiwu Z, Xiulan Z, Danfang Z, Xishan H: **Pilot Study of Molecular Mechanism on Vasculogenic Mimicry in Bi-directional Differentiated Malignant Tumors**. *The Chinese-German Journal of Clinical Oncology* 2015, **4**(1):50-52.
51. Zhao X, Sun B, Li Y, Liu Y, Zhang D, Wang X, Gu Q, Zhao J, Dong X, Liu Z *et al*: **Dual effects of collagenase-3 on melanoma: metastasis promotion and disruption of vasculogenic mimicry**. *Oncotarget* 2015, **6**(11):8890-8899.
52. Liang X, Sun R, Zhao X, Zhang Y, Gu Q, Dong X, Zhang D, Sun J, Sun B: **Rictor regulates the vasculogenic mimicry of melanoma via the AKT-MMP-2/9 pathway**. *Journal of cellular and molecular medicine* 2017, **21**(12):3579-3591.
53. Zhang W, Zhou P, Meng A, Zhang R, Zhou Y: **Down-regulating Myoferlin inhibits the vasculogenic mimicry of melanoma via decreasing MMP-2 and inducing mesenchymal-to-epithelial transition**. *Journal of cellular and molecular medicine* 2017.
54. Song H, Jing G, Wang L, Guo W, Ren G: **Periodic acid-Schiff-positive loops and networks as a prognostic factor in oral mucosal melanoma**. *Melanoma Res* 2016, **26**(2):145-152.
55. Itzhaki O, Greenberg E, Shalmon B, Kubi A, Treves AJ, Shapira-Frommer R, Avivi C, Ortenberg R, Ben-Ami E, Schachter J *et al*: **Nicotinamide inhibits vasculogenic mimicry, an alternative vascularization pathway observed in highly aggressive melanoma**. *PloS one* 2013, **8**(2):e57160.
56. Liu Q, Qiao L, Liang N, Xie J, Zhang J, Deng G, Luo H, Zhang J: **The relationship between vasculogenic mimicry and epithelial-mesenchymal transitions**. *Journal of cellular and molecular medicine* 2016, **20**(9):1761-1769.
57. Mihic-Probst D, Ikenberg K, Tinguely M, Schraml P, Behnke S, Seifert B, Civenni G, Sommer L, Moch H, Dummer R: **Tumor cell plasticity and angiogenesis in human melanomas**. *PloS one* 2012, **7**(3):e33571.

58. Folberg R, Arbieva Z, Moses J, Hayee A, Sandal T, Kadkol S, Lin AY, Valyi-Nagy K, Setty S, Leach L *et al*: **Tumor cell plasticity in uveal melanoma: microenvironment directed dampening of the invasive and metastatic genotype and phenotype accompanies the generation of vasculogenic mimicry patterns**. *The American journal of pathology* 2006, **169**(4):1376-1389.
59. Zhang JG, Zhang DD, Wu X, Wang YZ, Gu SY, Zhu GH, Li XY, Li Q, Liu GL: **Incarvine C suppresses proliferation and vasculogenic mimicry of hepatocellular carcinoma cells via targeting ROCK inhibition**. *BMC Cancer* 2015, **15**:814.
60. Pachmann K, Willecke-Hochmuth R, Schneider K, Kaatz M: **Circulating epithelial tumor cells as a prognostic tool for malignant melanoma**. *Melanoma Res* 2018, **28**(1):37-43.
61. Francis JH, Kim J, Lin A, Folberg R, Iyer S, Abramson DH: **Growth of Uveal Melanoma following Intravitreal Bevacizumab**. *Ocular oncology and pathology* 2017, **3**(2):117-121.
62. Schnegg CI, Yang MH, Ghosh SK, Hsu MY: **Induction of Vasculogenic Mimicry Overrides VEGF-A Silencing and Enriches Stem-like Cancer Cells in Melanoma**. *Cancer research* 2015, **75**(8):1682-1690.
63. Liu J, Qu X, Shao L, Hu Y, Yu X, Lan P, Guo Q, Han Q, Zhang J, Zhang C: **Pim-3 enhances melanoma cell migration and invasion by promoting STAT3 phosphorylation**. *Cancer biology & therapy* 2018, **19**(3):160-168.
64. Pulford E, Hocking A, Griggs K, McEvoy J, Bonder C, Henderson DW, Klebe S: **Vasculogenic mimicry in malignant mesothelioma: an experimental and immunohistochemical analysis**. *Pathology* 2016, **48**(7):650-659.
65. Chen L, Jin S: **Trends in mortality rates of cutaneous melanoma in East Asian populations**. *PeerJ* 2016, **4**:e2809.
66. Matthews NH, Li WQ, Qureshi AA, Weinstock MA, Cho E: **Epidemiology of Melanoma**. In: *Cutaneous Melanoma: Etiology and Therapy.* edn. Edited by Ward WH, Farma JM. Brisbane (AU); 2017.
67. Qin L, Ren Y, Chen AM, Guo FJ, Xu F, Gong C, Cheng P, Du Y, Liao H: **Peroxisome proliferator-activated receptor gamma ligands inhibit VEGF-mediated vasculogenic mimicry of prostate cancer through the AKT signaling pathway**. *Molecular medicine reports* 2014, **10**(1):276-282.
68. Shen Y, Quan J, Wang M, Li S, Yang J, Lv M, Chen Z, Zhang L, Zhao X, Yang J: **Tumor vasculogenic mimicry formation as an unfavorable prognostic indicator in patients with breast cancer**. *Oncotarget* 2017, **8**(34):56408-56416.
69. Yang JP, Liao YD, Mai DM, Xie P, Qiang YY, Zheng LS, Wang MY, Mei Y, Meng DF, Xu L *et al*: **Tumor vasculogenic mimicry predicts poor prognosis in cancer patients: a meta-analysis**. *Angiogenesis* 2016, **19**(2):191-200.

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

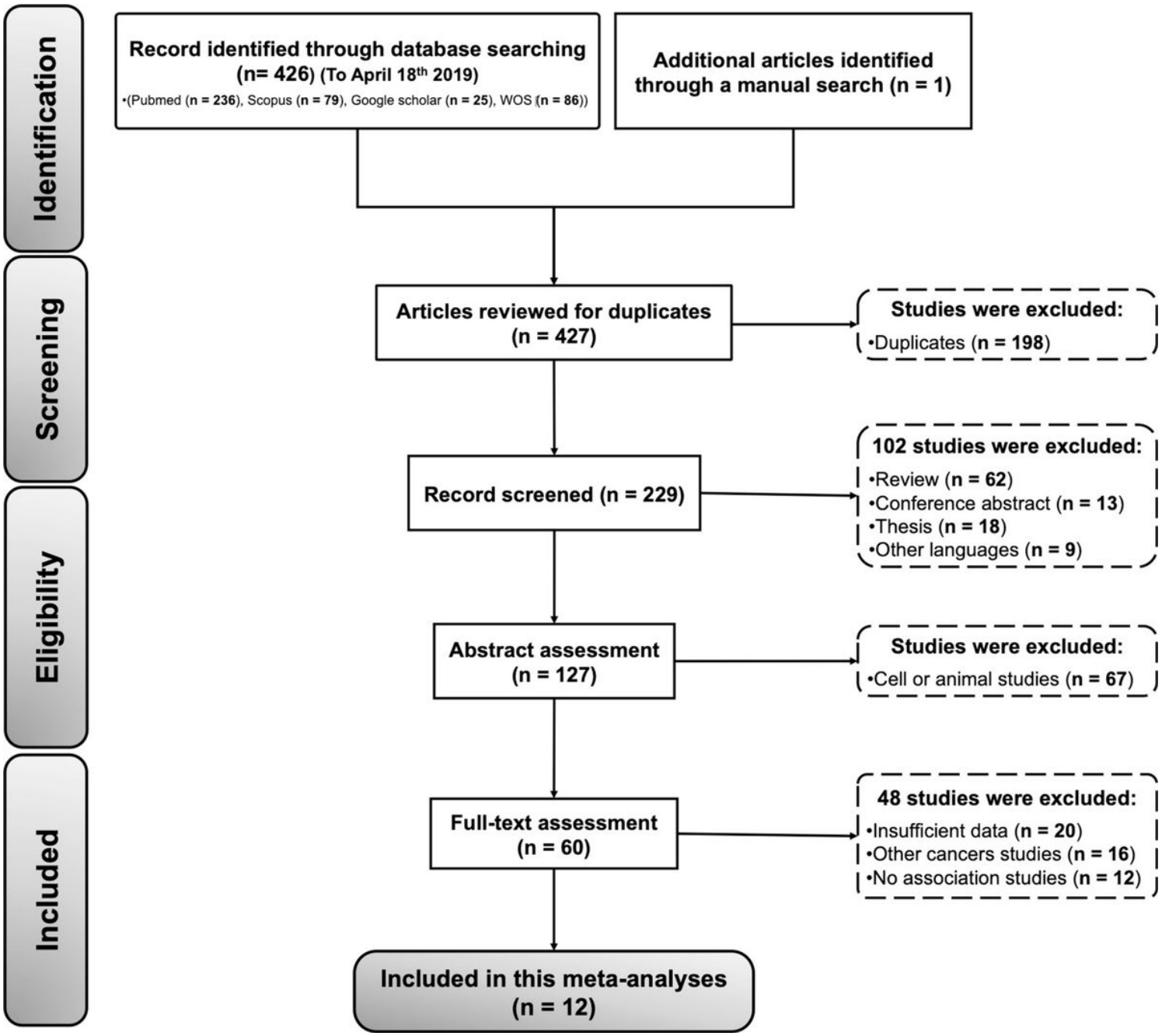

Figure 1

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

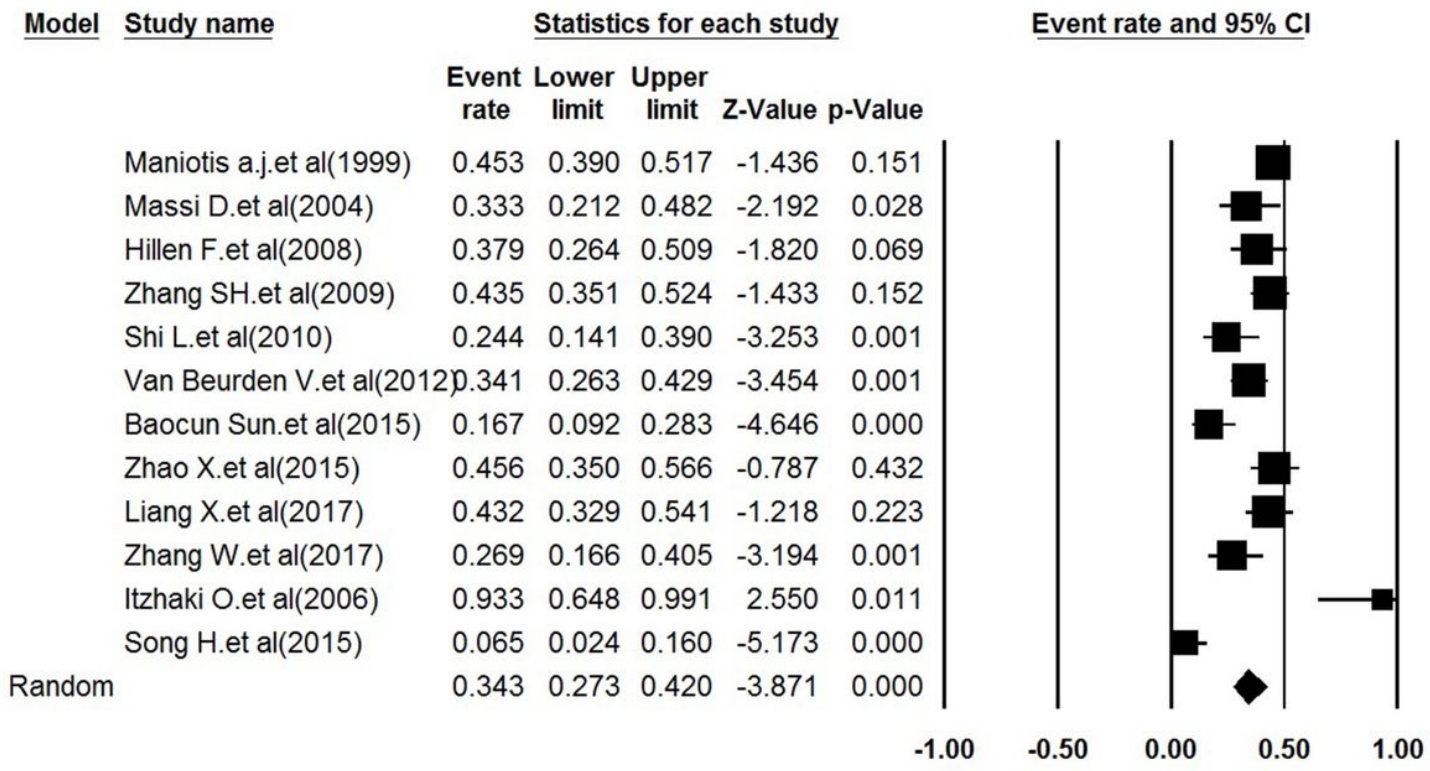

Figure 2

Forest plot of proportion ratios (P) in the random effect model. These plots show the prognostics accuracy for all objective response analysis.

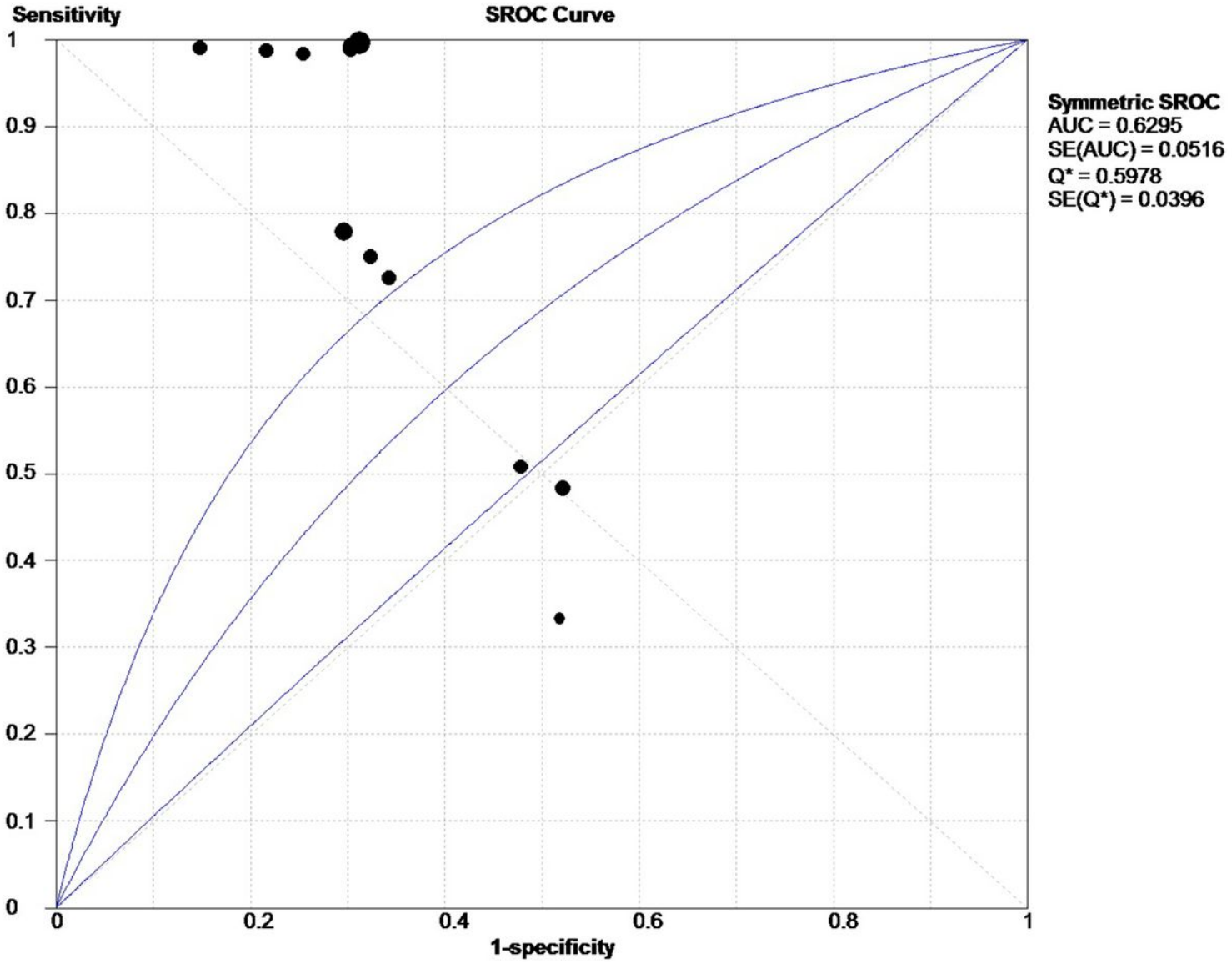

Figure 3

Summary receiver operating characteristic (SROC) curve for VM in the diagnosis of MM cancer.

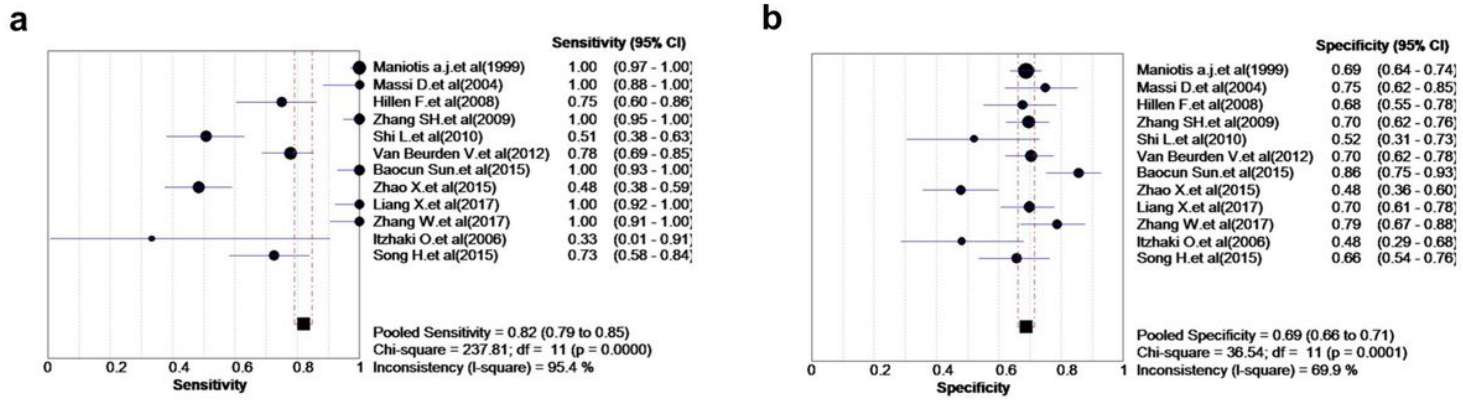

Figure 4

Forest plot of pooled sensitivity (a) and specificity (b) for VM in the diagnosis of MM cancer.

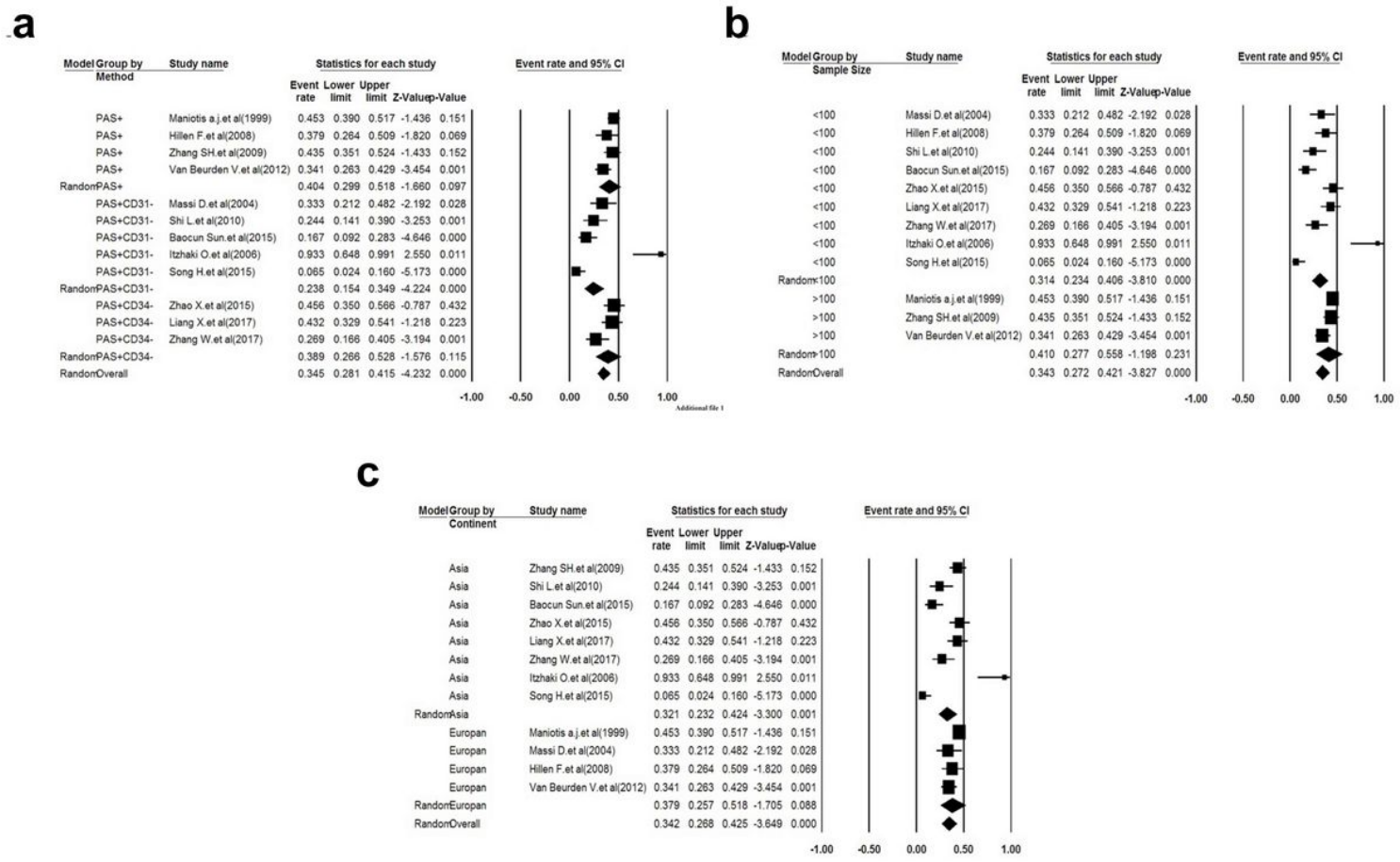

Figure 5

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.

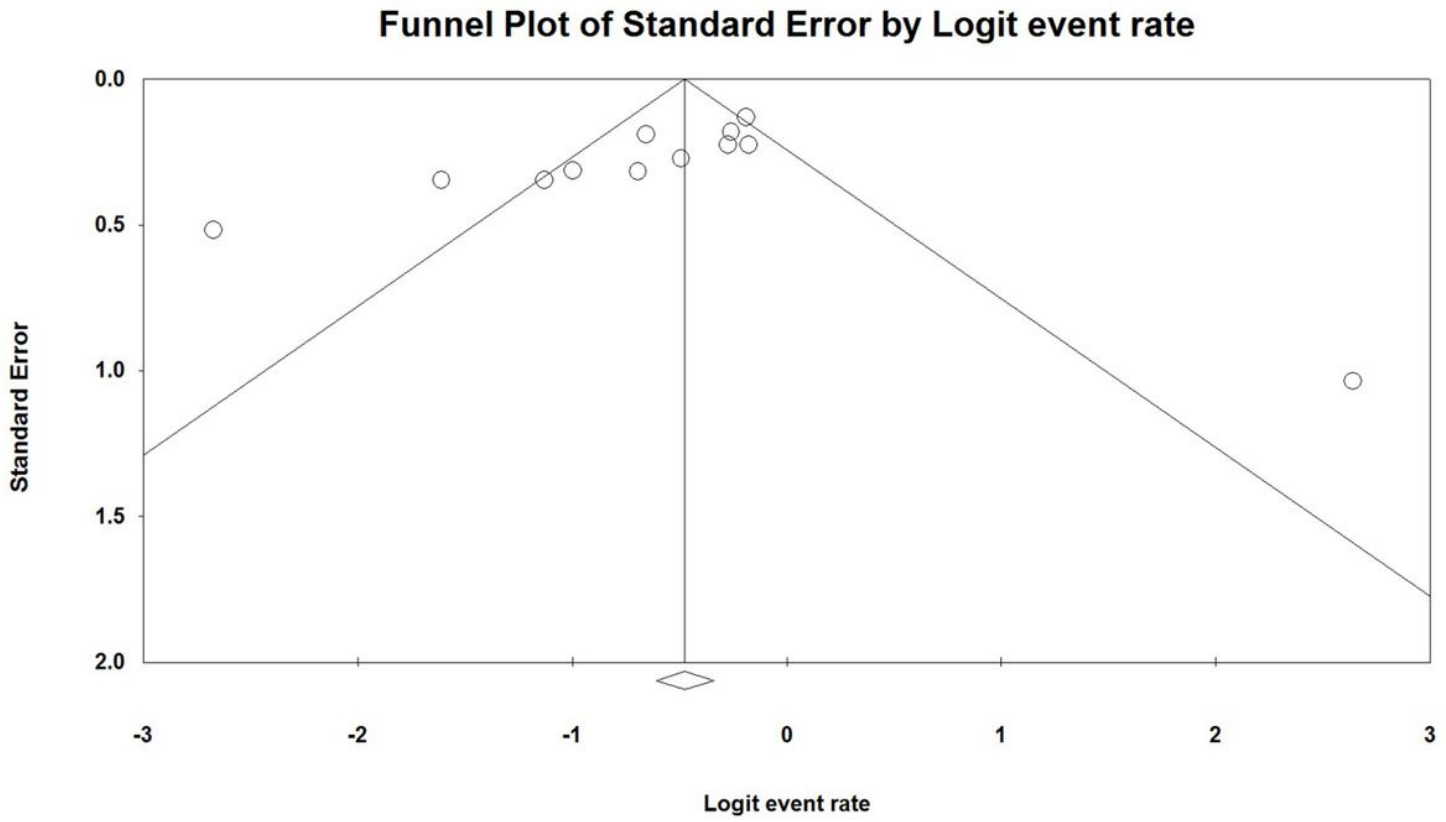

Figure 6

Funnel plots for the detection a publication bias. All enrolled 12 studies represent by each point for specified association, individually. The vertical axis represents standard error of logarithmic proportion and horizontal axis represents the proportion limits.

Supplementary Files

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

- supplement1.doc
- supplement2.pdf