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Prognostic role and clinicopathological features of pretreatment mean platelet volume in cancer: A Meta-Analysis

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Abstract

Objective: Our study aimed to evaluate the prognostic value and of mean platelet volume (MPV) prior to initial treatment on cancer survival by using meta-analysis of published studies.

Design: Meta-analysis.

Data sources: Relevant studies available before 22 December 2019 were identified by searching PubMed, EMBASE.

Eligibility criteria: All published studies, which assessed the prognostic value and of mean platelet volume (MPV) prior to initial treatment on cancer survival, were included.

Data extraction and synthesis: Studies were identified and extracted by two reviewers independently. The hazard ratio (HR) /Odds Ratio (OR) and its 95% confidence (CI) of survival outcomes and clinicopathological parameters were calculated.

Results: A total of 38 eligible studies (41 subsets) with 9,894 cancer patients were included in the final meta-analysis. Pooled hazard ratios (HRs) were estimated for overall survival (OS) and combined disease-free survival, progression-free survival, and recurrence-free survival (DFS/PFS/RFS). MPV level was not significantly associated with both OS (HR: 0.98, 95% CI: 0.84−1.14) and DFS/PFS/RFS (HR: 1.22, 95% CI: 0.86−1.73) of cancer patients. High MPV had the strongest relationship with poor OS (HR:2.01; 95%CI: 1.08−3.41) in gastric cancer, followed by pancreatic cancer (HR: 1.54; 95%CI: 1.31−1.82). Urothelial carcinoma and hematologic malignancies with low MPV had significant association with poor OS (HR: 0.41; 95% CI: 0.29−0.58. HR: 0.51, 95% CI: 0.32−0.81). Furthermore, neither advanced nor mixed

stage tumor patients showed significant relationship between high MPV and poor OS (HR:1.36, 95% CI: 0.96−1.94. HR: 0.90, 95% CI: 0.74−1.09). Region under the curve (ROC) analysis was used widely to define cut-off values and had relatively closer relationship with poorer HRs. In addition, MPV had no significant association with age (OR: 0.96, 95% CI: 0.90–1.02), sex (OR: 1.04, 95% CI: 1.00–1.09) , depth of cancer invasion (OR: 0.90, 95% CI: 0.77–1.04) and tumor stage (OR: 0.91, 95% CI: 0.78–1.07).

Conclusions: Pretreatment MPV level cannot serve as a prognostic predictor for all cancers and has no significant association with clinicopathological parameters of patients with cancers, but it can predict poor OS for certain specific cancers.

Keywords

Mean platelet volume, Malignant tumor, Meta-Analysis, Prognosis

Strengths and limitations of this study

- This is the first meta-analysis of the association between pretreatment mean platelet volume and cancer prognosis.
- The current study provided a comprehensive assessment of relationship between mean platelet volume and cancer survival, and showed significant findings.
- Strong and reliable methodological and statistical procedures were applied.
- Almost all of the included studies were retrospective, and the patients included were all but composed of Asian, which may have led to greater susceptibility to bias.

Introduction

Cancer is one of the main causes of morbidity and mortality worldwide(1). Despite the development of new drugs and advances in surgical techniques, the survival of most tumors is still not optimistic(2). Therefore, finding potent indicators to predict the prognosis of cancer is very important. Because it can provide an important evidence for selecting the tailor treatment to improve the prognosis of tumors.

Mean platelet volume(MPV), the most commonly used measure of platelet size, is considered to be an effective hallmark of platelet activation(3). The Complicated interactions between activated platelets and cancer cells lead to tumor growth, aberrant angiogenesis, invasion, and metastasis(4-6). A mounting body of evidence suggests that MPV plays an important prognostic role in various types of tumors, which included upper gastrointestinal tumors(7-14), colorectal cancer(15, 16), lung cancer(17-19), breast cancer(20-22), and urothelial carcinoma(23, 24). However, the relationship between MPV level and cancer prognosis has not been comprehensively investigated due to the inevitable heterogeneity of the samples studied.

Therefore, we performed this meta-analysis to investigate the possible association between MPV level and clinical outcomes of cancer patients and evaluate whether MPV could be an effective biomarker of cancer prognosis.

Methods

Search strategy and election criteria

Relevant studies were obtained from the PubMed and EMBASE databases up to December 22, 2019. Language restrictions were not applied during the database search.

We performed a search of titles and abstracts using the following terms: ("mean platelet volume OR platelet volume, mean OR MPV") and ("neoplasm OR cancer OR tumor OR carcinoma"). The references of the included articles were also scanned to find additional relevant studies. The search results were then reviewed according to the following inclusion and exclusion criteria: (1) studies should assess the value of MPV prior to any treatment in patients with proven pathological diagnosis of cancer, (2) studies should evaluate the relationship between MPV and prognostic value or clinicopathological features of cancer patients, (3)studies should provide hazard ratio (HR) with a 95% confidence interval (CI) for clinical outcomes, or abundant data to estimate these quantities, (4)articles published in English were excluded, (5) non-human studies or basic research papers, reviews, meta-analyses, case reports, letters and irrelevant topics were not eligible for our meta-analysis. Two reviewers independently performed the study selection and resolved any disagreements via discussion.

Data extraction and quality evaluation

In current meta-analysis, two researchers (Xunlei Zhang and Yushan Liu) independently checked each included article and collect relative data, such as name of first author, publication year, country, study type, study period, follow-up time, sample size, cancer type, cancer stage, cut-off value of MPV, definition of cut-offs, HR data (univariate or multivariate), and the number of patients with various clinicopathological features, such as tumor location, differentiation, size, depths of tumor invasion and

TNM stage. HRs and 95% CIs were extracted for overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), and recurrence-free survival (RFS). The Newcastle-Ottawa quality assessment scale (NOS) was utilized to evaluate the quality of each study with 8 items on methodology from 3 dimensions: selection, comparability, and exposure(25). Two investigators each assessed all studies and scored them, among which scores of 6 or higher were qualified. All disagreements were settled by consensus.

Outcomes

We defined OS as the time from the study enrollment to the date of death from any cause or last follow-up. Since DFS, PFS, and RFS share similar endpoints, they were analyzed together as one outcome, DFS/PFS/RFS(26-28).

Statistical analyses

All analyses were performed by using STATA version 14.0 (STATA, College Station, TX). Hazard ratio (HR) with 95% confidence interval (CI) was obtained directly from each included study if available or were calculated from the necessary data according to the methods published for the analysis of pooled outcomes(29). The heterogeneity in the analysis was assessed using Cochran's Q test and Higgins I-squared statistic. A random effects model (DerSimonian-Laird method) was applied when a p-value < 0.1 for the Q-test or I^2 > 50%(30), which suggested the presence of significantly heterogeneity among the included studies. Otherwise, a fixed effects

model (Mantel-Haenszel method) was conducted for pooled data(31). Odds ratios (OR) and 95% CI were used to analyze the relationship between MPV and clinicopathological factors. Subgroup analysis based on tumor type, tumor stage, age, country of origin, cut-off value, and method of defining the cut-off value were conducted to determine whether there was potential heterogeneity among the eligible studies. Moreover, sensitivity analysis was performed by removing every single study sequentially at a time to evaluate whether individual study influenced the combined effect and validate the robustness and credibility of the pooled outcomes. Publication bias of literature was estimated by Begg's funnel plot(32) and Egger's linear regression tests(33), and $p > 0.05$ indicated that there was no significant publication bias.

Results

Selection and characteristics of studies

In the current study, identified 449 records were potentially relevant through our literature search. After screening titles and abstracts, four-hundred and four studies with irrelevant content were excluded. A full-text review of the selected 45 articles was conducted. Among them, seven reports were excluded for insufficient or no data to evaluate the association between MPV and prognostic value or clinicopathologic characteristics of cancer patients. Finally, after applying the inclusion and exclusion criteria, 38 eligible studies (41 subsets) with 9,894 patients were included in our meta-analysis(7-24, 34-53). In one of these studies, tumor patients were divided into two groups according to pathological classification (Shi 2018 ADC and Shi 2018

SqCC)(38), and according to whether tumor patients had type 2 diabetes, the subjects in two other studies were also respectively divided into two groups (Li 2019 T2DM and Li 2019 non-T2DM) (Yin 2019 T2DM and Yin 2019 non-T2DM)(20, 44). Therefore, a total of six subsets were extracted. The selection process of the included studies according to the PRISMA guidelines was shown in Figure 1. The characteristics of the included studies are shown in Table 1. OS and DFS/PFS/RFS were reported in 34 studies (37 subsets) and 13 articles, respectively. Eleven different solid cancer types and two different hematological malignancies were investigated in the eligible studies. Among solid tumors, the most frequently evaluated cancer was upper gastrointestinal cancer (UGI) (including patients with esophageal, gastric, and pancreatic cancer) (n = 11), followed by lung cancer (n = 8) , breast cancer (n = 4), colorectal cancer (CRC) (n = 3), head and neck cancer (HNC) (n = 3), hepatic cancer (HCC) (n = 2), urothelial carcinoma (n = 2), melanoma (n = 1) and osteosarcoma (n = 1). Multiple myeloma (MM) (n = 1) and diffuse large B-cell lymphoma (DLBCL) (n = 1) were the only two evaluated diseases in hematological malignancies. A majority of studies (75.7%) enrolled patients with mixed-stage cancer, whereas only a few studies (24.3%) specifically investigated patients with advanced-stage cancer. Four different types of methods for defining cut-off values were observed in the included studies. The Region under the curve (ROC) analysis had the highest frequency of use (n = 22), followed by the empirical value based on previous studies (n = 9) and the calculated value obtained via certain computing software (n = 2). The cut-off values ranged from 7.4 to 12.2 in the included studies. In addition, ten studies (33.3%) included older population, the

median or mean age of whom was ≥60 years. Almost all of the studies (94.7%) were originally from Asia, while the only two remaining studies were from Europe and North America. In our study quality assessment, the quality score of four studies is 6, and the remaining 32 studies had scores ≥7.

MPV level and prognosis of cancer

Thirty-four studies including 37 subsets with 9,238 patients were analyzed for OS. The pooled HRs of high MPV level was 0.98 (95% CI: 0.84−1.14; Fig. 2). Table 2 shows the results for subgroup analysis, which was performed stratified by six factors, including tumor type, tumor stage, age, country of origin, cut-off value, and method of defining the cut-off value. In solid tumors, gastric cancer with high MPV had the strongest relationship with poor OS (HR: 2.01, 95% CI: 1.08−3.41), followed by pancreatic cancer (HR: 1.54, 95% CI: 1.31−1.82). Whereas other cancers with higher MPV were not associated with worse OS (NSCLC: HR = 0.85, 95% CI: 0.64−1.15; Esophageal cancer: HR = 1.05, 95% CI: 0.63−1.77; Breast cancer: HR = 1.19, 95% CI: 0.54−2.16; CRC: HR = 0.86, 95% CI: 0.52−1.42; HCC: HR = 0.80, 95% CI: 0.51−1.27; HNC: HR = 0.77, 95% CI: 0.33−1.77). Interestingly, only the urothelial carcinoma in solid cancer and hematologic malignancies with low MPV had significant association with poor OS (HR: 0.41, 95% CI: 0.29−0.58; HR: 0.51, 95% CI: 0.32−0.81). In addition, neither advanced nor mixed stage tumor patients showed significant relationship between high MPV and poor OS (HR: 1.36, 95% CI: 0.96−1.94; HR: 0.90, 95% CI: 0.74−1.09). There were considerable variations in the methodologies used to define

cutoff values. ROC analysis was the most widely used method and was closely related to poor HRs. However, other subgroups did not show significant correlations between MPV and poor OS. Sensitivity analysis for OS was performed. The results showed no significant change in the corresponding combined HR, which indicated that our meta-analysis results are stable and robust (Fig. 3).

Thirteen studies with 3,014 patients provided HRs and 95% CIs for DFS/PFS/RFS. Overall, the pooled data indicated that MPV was not associated with DFS/PFS/RFS (HR: 1.22, 95% CI: 0.86−1.73; Fig. 4).

Relationship between MPV level and clinicopathological parameters

To further explore the association between MPV and the clinicopathological parameters in cancer, we extracted parts of included studies according to age, sex, depth of cancer invasion and tumor stage. As shown in Table 3, MPV was not shown to be associated with age (n =13, OR: 0.96, 95% CI: 0.90–1.02), sex (n =17, OR: 1.04, 95% CI: 1.00–1.09) , depth of cancer invasion (n =10, OR: 0.90, 95% CI: 0.77–1.04) and tumor stage (n =11, OR: 0.91, 95% CI: 0.78–1.07).

Publication bias

We did not detect any evidence of obvious asymmetry by the inspection of the Begg's funnel plot (Fig. 5), which was further confirmed by Egger's tests ($P < 0.001$). Egger's tests (p= 0.468) showed that no noteworthy publication bias was observed in this meta-analysis either.

Discussion

The mean platelet volume (MPV) is a useful parameter for predicting activation of platelets by estimating the average size of platelets(54). It is an attractive index to study in clinical scenarios. Many arguments have been made in regard to whether MPV can be a valuable biomarker capable of predicting cancer prognosis. A few researches indicated that MPV as an effective indicator can provide important prognostic information for certain cancers(7, 15, 18), but others failed to show its prognostic value on patients with cancers(45, 47, 53). The present study is the first meta-analysis to comprehensively evaluate the prognostic role of MPV for OS and DFS/PFS/RFS in cancers. Pooled results demonstrated that high MPV was not associated with poor survival outcome. Moreover, MPV level was not correlated with age, sex, tumor size, depth of cancer invasion and tumor stage.

Subgroup analysis was conducted by age, country of origin, cut-off value, method of defining the cut-off value, tumor stage, and tumor type. High MPV was not related to poor OS in older and younger patients with cancers. Similarly, there was no correlation between high MPV and unfavorable OS in subgroups with cutoff values $\geqslant$ 10.5 and <10.5. Neither Asian nor non-Asian patients with high MPV exhibited poor OS. Although it was demonstrated that MPV in patients in an early stage of cancer were similar to those found in healthy subjects and increased with the cancer progression(55), we observed no significant correlation between high MPV and poor OS in patients with advanced cancers, nor in patients from the mixed-stage subgroup in our analysis.

Whereas only in the ROC curves method subgroup, high MPV was significantly associated with unfavorable OS, suggesting that cut-off values defined by ROC curves were more likely to predict poor OS. But there are currently no commonly used and uniform cut-off values for cancer survival prediction, so more studies need to be implemented to explore unified cut-off values for specific cancer types. What's more, there was an important and thought-provoking finding in present study. High MPV level was obviously related to unfavorable OS for gastric cancer and pancreatic cancer, while low MPV level was significantly associated with poor OS for urothelial carcinoma and hematologic malignancy. According to the finding above, we drew two following conclusions. First, MPV was correlated with unfavorable prognosis in certain specific tumor types. Second, the association between MPV level and the cancer prognosis varies in different cancer types.

However, the mechanism underlying the association between MPV and cancer prognosis is not entirely clear. It is well-known that malignant tumors are accompanied by systemic inflammatory response(56), which has an important role in carcinogenesis, tumor progression and angiogenesis(57). Numerous inflammatory cytokines (e.g., IL-1, IL-6 and TNF-alpha) can promote the proliferation of macrophages and further lead to platelet activation and enhanced release of larger platelets(58). Activated platelets were suggested to promote tumor growth, angiogenesis, and metastasis mainly by secreting a cocktail of predominantly proangiogenic cytokines within a potentially prothrombotic tumor microcirculation and coating circulating tumor cells to protect tumor cells from physical factors such as shear stress and the host's immune

response(5). Therefore, we conclude the mechanisms underlying the prognostic impact of MPV on cancers were due to inflammation and platelet activation.

Literatures indicated that MPV level can be influenced by a number of lifestyles and various diseases like smoking(59, 60), hypertension(61, 62), diabetes(63, 64), dyslipidemia and Obesity(65, 66), cardio-cerebrovascular disease(67, 68) and inflammatory disorders(69, 70). In essence, the two root causes those are inflammation and thrombosis may play a key role in alteration of MPV level. On the one hand, the elevated MPV is mainly caused by chronic inflammation accompanied by elevated level of IL-6. Because This cytokine via receptor binding on the surface of megakaryocyte progenitor cells causes their maturation and proliferation and in consequence enhances platelet release and elevates MPV level(55). The development of gastric cancer and pancreatic cancer has been known to be closely associated with chronic inflammation accompanied by elevated level of IL-6(71, 72), Therefore, the strong association between high MPV level and negative prognosis in these two types of cancers may be attributed to this. On the other hand, the key to explaining a decrease in MPV may be inflammation aggravation(55, 58) and thrombosis(54, 58). Firstly, when inflammation aggravating, increased release rate of small size platelets due to excessive pro-inflammatory cytokines' interference with megakaryopoiesis and selective consumption of large amount of highly reactive large-sized platelets result in a decline in MPV(73, 74). This suggests that the level of MPV depends heavily on the intensity of the systemic inflammation. A recent study indicated that low levels of MPV were associated with severe inflammatory diseases and that they were reversed during

anti-inflammatory treatment(58), further confirming the above statement. Secondly, tumor cells release tumor necrosis factor-α, interleukin-1 β, vascular endothelial growth factor and basic fibroblast growth factor(75), which may promote the formation of vascular endothelial thrombi and enhance the consumption of larger-sized platelets, leading to a decreased MPV in the circulating platelets(76). Considering that thrombosis is associated with poor survival in patients with hematologic malignancies who have an increased risk of thromboembolic events(77-79). Therefore, decreased MPV might indicate thrombosis, predicting poor survival outcome in patients with hematologic malignancies.

In sum, pretreatment MPV plays a valuable prognostic role in certain specific cancer types. However, there are several limitations in our meta-analysis. Firstly, the inclusion criteria for this meta-analysis were limited to studies published in English and thus publication bias cannot be ruled out. Secondly, almost all of the included studies were retrospective, and the patients included were all but composed of Asian cohort, which may have led to greater susceptibility to bias. Fortunately, there was no significant publication bias due to the asymmetry of the funnel plot, thus maintaining the substantial consistency of the results. Thirdly, there was considerable heterogeneity when pooling HRs for OS results. Subgroup analysis showed the cut-off values in the included studies were various, which could lead to heterogeneity between studies. Finally, we do not have complete and detailed information about the factors affecting MPV, so we cannot adjust the relationship between MPV and the risk of death from these factors. Therefore, more informative studies should be implemented to assess the

relationship between MPV and tumor prognosis more accurately.

Conclusions

In conclusion, MPV level prior to initial treatment do not play an effective prognostic role for all cancers and are independent of age sex, tumor size, depth of invasion and tumor stage. But it is a predictor for poor OS and may provide a strong evidence for precision and personalized therapy in certain specific cancer types. Moreover, optimal MPV cut-off values defined by ROC analysis are more likely to predict poor OS. In order to better predict prognosis, more cumulative studies for specific tumors are needed for the exploration and evaluation of uniform cut-off values in clinical practice and further robust clinical studies are warranted focusing on MPV as prognostic factor of cancer patients.

Abbreviations

HR: hazard ratio; OR: odds ratio; 95% CI: 95% confidence interval; P_h: p values of Q test for heterogeneity test; OS: overall survival; DFS: disease-free survival; PFS: progression-free survival; RFS: recurrence-free survival; MPV: mean platelet volume; UGI: upper gastrointestinal cancer; ESCC: esophageal squamous cell carcinoma; NSCLC: non-small cell lung cancer; ADC: adenocarcinoma; SqCC: squamous cell carcinoma; CRC: colorectal cancer; HCC: hepatocellular carcinoma; PNET: pancreatic neuroendocrine tumor; RCC: renal cell carcinoma; HNC: head and neck cancer; LSCC: Laryngeal Squamous Cell Carcinoma; MM: multiple myeloma; DLBCL: diffuse large B-cell lymphoma; T2DM: type 2 diabetes mellitus; NOS: Newcastle-Ottawa Scale;

Declarations

Ethics approval and consent to participate

All the data supporting our findings in this paper were freely downloaded from the PubMed and EMBASE. No ethical approval or written informed consent for participation was required.

Patient and Public Involvement

Patients and public were not involved.

Consent for publication

Not applicable.

Availability of data and materials

All data for this study are publicly available and are ready for the public to download at no cost from the official websites of the PubMed and EMBASE. There is no need to have the formal permission to use data for this study. The sources and data robustness have been described in the section of "Methods".

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XC and JL were involved in drafting the manuscript. XLZ and YSL made contributions to the concepts, acquisition and analysis of the data. JDW and YCL was involved in acquisition of data and preparing the Figs. XHJ and XPC designed and revised the manuscript. All authors have read and approved the final manuscript.

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Table 1. Main characteristics of 38 included studies (41 subsets) in meta-analysis.

First author	Year	Country	Study design	Sample size	Age* (year)	Cancer type	Cancer stage	Cut-off value	Definition of cut-offs	Outcome of HR	NOS score
JingJing Wang	2019	China	Retrospective	101	60(27-80)	Lung cancer	Mixed	10.282	Median	OS	7
Abdullah Sakin	2019	Turkey	Retrospective	115	61.3(22-82)	NSCLC	Advanced	9	ROC	OS	8
Abdullah Sakin	2019	Istanbul	Retrospective	90	59(42-83)	NSCLC	Mixed	NA	NA	OS	7
JiFeng Feng	2019	China	Retrospective	277	59.2(36-80)	ESCC	Mixed	8.5	ROC	OS	8
Jinjia Chang	2019	China	Retrospective	264	55.5	CRC	Advanced	9.75	ROC	OS;PFS	7
Weihua Qian	2019	China	Retrospective	153	56(27-85)	CRC	Mixed	10.4	Median	OS	7
Na Li T2DM	2019	China	Retrospective	264	57.5 ± 9.6	Breast cancer	Mixed	8	ROC	OS	8
Na Li Non-T2DM	2019	China	Retrospective	266	50.5 ± 9.6	Breast cancer	Mixed	8	ROC	OS	8
Ke Zhang	2019	China	Retrospective	320	60(30-81)	Pancreatic cancer	Advanced	12.2	X-tile	OS	7
ShuaiShuai Xu	2019	China	Retrospective	112	54(25-82)	PNET	Mixed	11.1	Median	OS;RFS	6
Jibin Yin T2DM	2019	China	Retrospective	165	57.0 ± 7.9	HCC	NA	9.4	ROC	OS	8
Jibin Yin Non-T2DM	2019	China	Retrospective	166	52.9 ± 9.6	HCC	NA	9.4	ROC	OS	8
Xiaomin Zuo	2019	China	Retrospective	269	50.1±11.3	HCC	Mixed	11	ROC	OS	7
Tristan Tham	2019	USA	Retrospective	113	NA	HNC	Mixed	10.3	ROC	OS	7
Youfang Xun	2019	China	Retrospective	151	65(44-84)	LSCC	Mixed	10.8	ROC	OS;PFS	7
Bo gou	2019	China	Retrospective	188	NA	Osteosarcoma	Mixed	10.25	Cutoff Finder	PFS	6
Muhyettin Omar	2018	Turkey	Retrospective	496	NA	NSCLC	Advanced	9.1	ROC	OS;PFS	8
Liang Shi ADC	2018	China	Retrospective	90	53.3(27–73)	NSCLC	Advanced	10.85	ROC	OS	7
Liang Shi SqCC	2018	China	Retrospective	79	57(44–72)	NSCLC	Advanced	9.3	ROC	OS	7
Wenjie Shen	2018	China	Retrospective	236	NA	Esopheal cancer	Mixed	7.4	ROC	OS	8
Yiru Huang	2018	China	Retrospective	271	50.7(21-80)	Breast cancer	Mixed	8.1	NA	OS	8
Jibin Yin	2018	China	Retrospective	411	59.6(29-89)	Pancreatic cancer	Advanced	8.7	ROC	OS	8
Anna L Lembeck	2018	Austria	Retrospective	527	NA	Pancreatic cancer	Advanced	11.3	75th percentile	OS	8
Liuwei Gao	2017	China	Retrospective	546	60(24-82)	NSCLC	Mixed	11	ROC	OS;DFS	8
Na Li	2017	China	Retrospective	509	58.1(30-87)	CRC	Mixed	8.6	ROC	OS	8
Hideya Takeuchi	2017	Japan	Retrospective	327	64.5(31-92)	Breast cancer	Mixed	9	ROC	PFS	7
Zhiyuan Yun	2017	China	Retrospective	306	57.8(37-80)	RCC	Mixed	7.5	ROC	OS	8
Xin Wang	2017	China	Retrospective	218	63.2(31-82)	Bladder cancer	Mixed	9.1	ROC	OS	8
Huan Zhang	2017	China	Retrospective	241	57.8(37-80)	Laryngeal cancer	Mixed	9.3	ROC	OS	8
Na Li	2017	China	Retrospective	220	56.3(21-86)	Melanoma	Mixed	NA	NA	OS	8
Shujuan Zhou	2017	China	Retrospective	161	59(18-80)	DLBCL	Mixed	9.1	ROC	OS;PFS	8
Mingming Cui	2016	China	Retrospective	270	57.3(32-80)	NSCLC	Mixed	NA	NA	OS	8
Fan Zhang	2016	China	Retrospective	468	59.9±9	ESCC	Mixed	10.6	ROC	OS;DFS	7
XiaoMing Shen	2016	China	Retrospective	168	56.5(31-82)	Gastric Cancer	Mixed	10.51	Median	OS;DFS	8
Xin Zhou	2016	China	Retrospective	451	NA	Gastric cancer	Mixed	9.83	NA	OS	8
Qiang Zhuang	2016	China	Retrospective	62	60.5(37-78)	MM	Mixed	8.5	ROC	OS	8
Keriyuki Hirahara	2015	Japan	Retrospective	144	NA	ESCC	Mixed	11.5	Upper limit	NA	6
Lian Lian	2015	China	Retrospective	148	68(32-82)	Gastric cancer	Advanced	11.65	Median	OS;PFS	8
Meiling Gu	2015	China	Retrospective	170	51.6	Breast cancer	Mixed	8.45	Median	OS	7
Shogo Kumagai	2014	Japan	Retrospective	308	69(19-87)	NSCLC	Mixed	8.5	ROC	OS;DFS	8
Tolga Tuncel	2014	Turkey	Retrospective	53	NA	CRC	Advanced	7.89	Mean	PFS	6

Note: * Age reported as either mean ± standard deviation or median (range), if not otherwise specified.
Abbreviations: ESCC, esophageal squamous cell carcinoma; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; PNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma; HNC, head and neck cancer; LSCC, Laryngeal Squamous Cell Carcinoma; MM, multiple myeloma; DLBCL, diffuse large B-cell lymphoma; NA, not available; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; RFS, recurrence-free survival; NOS, Newcastle-Ottawa Scale.

Table 2. Subgroup analyses of the associations between MPV and OS in cancer.

Stratified analyses	No. of studies	No. of patients	Model	Pooled HR (95%CI)	P value	Heterogeneity	
						I^2	P_H value
Cancer Type							
NSCLC	7	1994	Random	0.85(0.64,1.15)	0.295	83.90%	0.000
ESCC	3	981	Random	1.05(0.63,1.77)	0.844	88.40%	0.000
Gastric Cancer	3	767	Random	2.01(1.08,3.41)	0.010	82.60%	0.003
CRC	3	926	Random	0.86(0.52,1.42)	0.549	81.50%	0.004
Breast cancer	3	971	Random	1.19(0.54,2.61)	0.672	85.90%	0.000
Pancreatic cancer	3	1095	Fixed	1.54(1.31,1.82)	0.000	0.00%	0.645
HCC	2	600	Random	0.80(0.51,1.27)	0.350	66.60%	0.050
HNC	3	392	Random	0.77(0.33,1.77)	0.543	77.20%	0.012
Urothelial carcinoma	2	524	Fixed	0.41(0.29,0.58)	0.000	0.00%	0.792
Hematologic malignancy	2	223	Fixed	0.51(0.32,0.81)	0.005	0.00%	0.504
Cancer stage							
Mixed	25	6401	Random	0.9(0.74,1.09)	0.278	83.40%	0.000
Advanced	8	2287	Random	1.36(0.96,1.94)	0.082	87.90%	0.000
Age							
＜60	18	4691	Random	1.05(0.88,1.26)	0.557	82.50%	0.000
≥60	9	1969	Random	0.83(0.54,1.28)	0.409	91.40%	0.000
Ethnicity							
Asian	32	8542	Random	0.97(0.83,1.14)	0.753	84.90%	0.000
Non-Asian	2	477	Random	0.97(0.24,3.89)	0.962	86.00%	0.007
Cut-off Value							
＜10	19	5436	Random	0.84(0.68,1.04)	0.103	84.10%	0.000
≥10	13	3166	Random	1.23(0.88,1.72)	0.235	87.90%	0.000
Definition of cut-offs							
ROC	21	6181	Random	0.78(0.64,0.95)	0.014	83.30%	0.000
Median	6	852	Random	1.51(0.92,2.47)	0.103	82.20%	0.000

Abbreviations: NSCLC, non-small cell lung cancer; ESCC, esophageal squamous cell carcinoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; HNC, head and neck cancer; HR, hazard ratio; 95% CI, 95% confidence interval; $P_{h,}$ p values of Q test for heterogeneity test.

Table 3. Association between MPV level and clinicopathological parameters

Clinical features	No. of studies	No. of patients	Model	OR (95%CI)	P value	Heterogeneity	
						I^2	P_H value
Age (older vs. younger)	13	2968	Fixed	0.96(0.90,1.02)	0.155	25.40%	0.188
Sex (Male vs. Female)	17	4077	Fixed	1.04(1.00,1.09)	0.077	0.00%	0.533
Depth of invasion (T1+T2 vs T3+T4)	10	2420	Random	0.90(0.77,1.04)	0.149	78.10%	0.000
Tumor stage (I/II vs III/IV)	11	2425	Random	0.91(0.78,1.07)	0.257	78.90%	0.000

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; $P_{h,}$ *p* values of Q test for heterogeneity test.

Figure legends

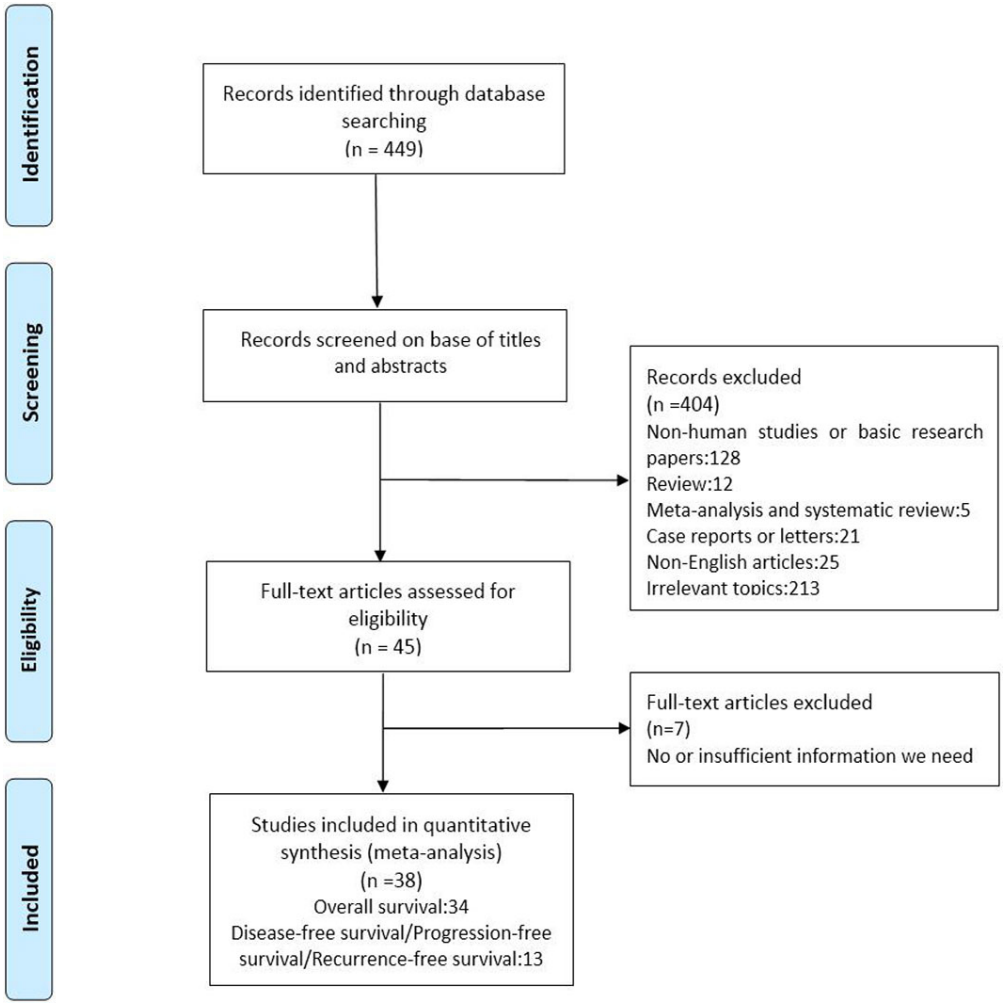
Figure 1: PRISMA 2009 flow diagram.

Figure 2: The forest plot between MPV level and OS in cancer patients.

Figure 3: Sensitivity analysis of MPV for OS in cancer patients.

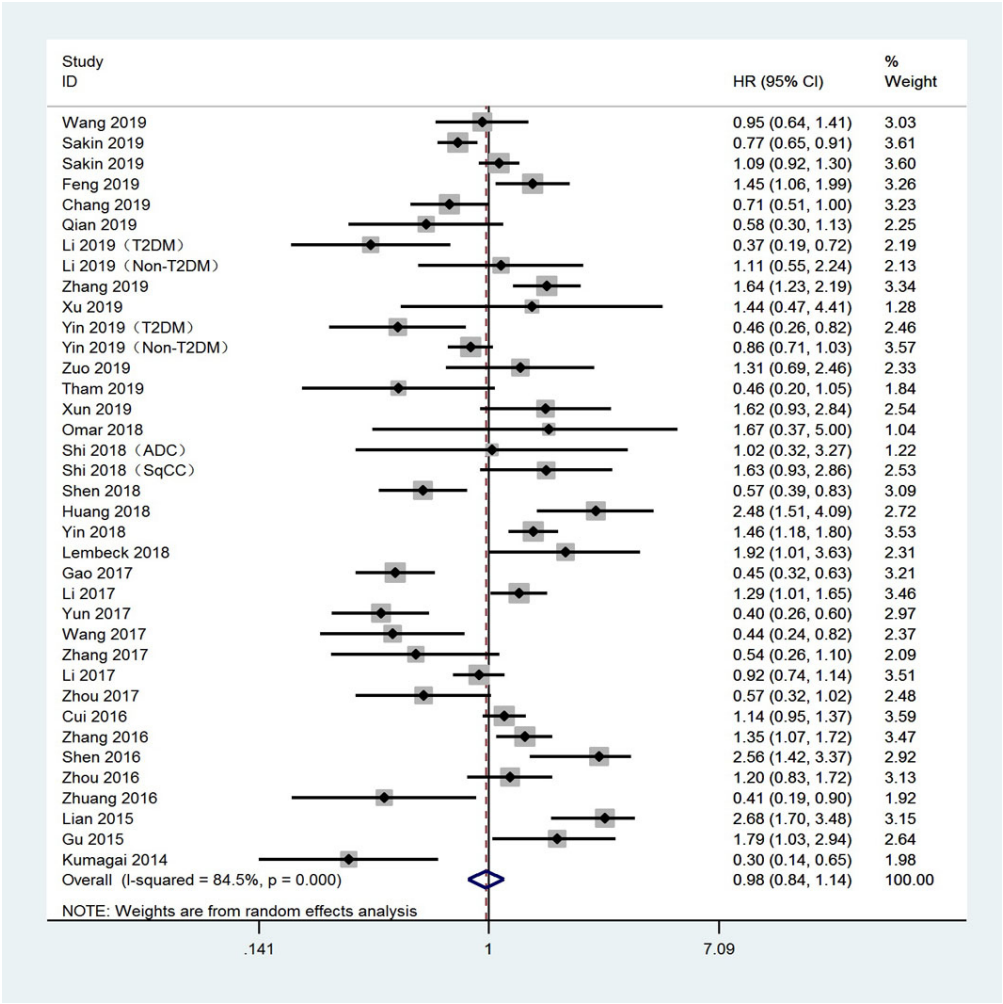
Figure 4: The forest plot between MPV level and DFS/PFS/RFS in cancer patients.

Figure 5: Begg's funnel plot of publication bias test for OS in cancer patients.



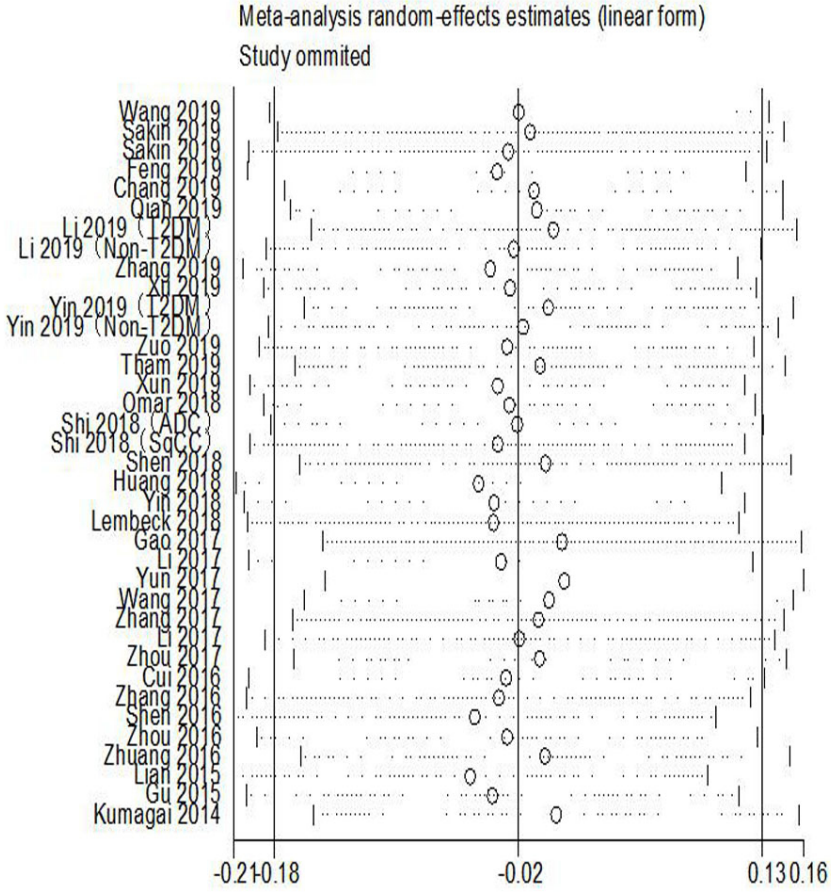
The flow diagram of publications selection.

90x90mm (300 x 300 DPI)



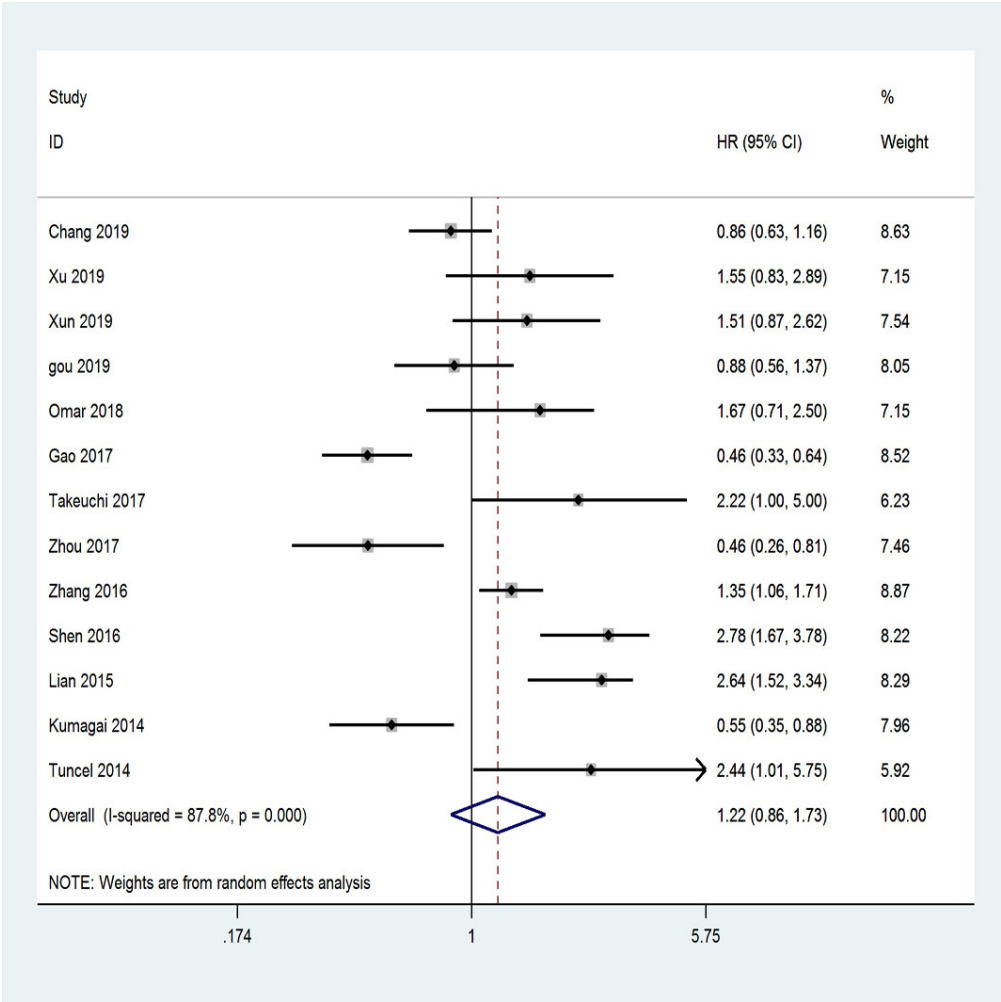
The forest plot between MPV level and OS in cancer patients.

90x90mm (300 x 300 DPI)



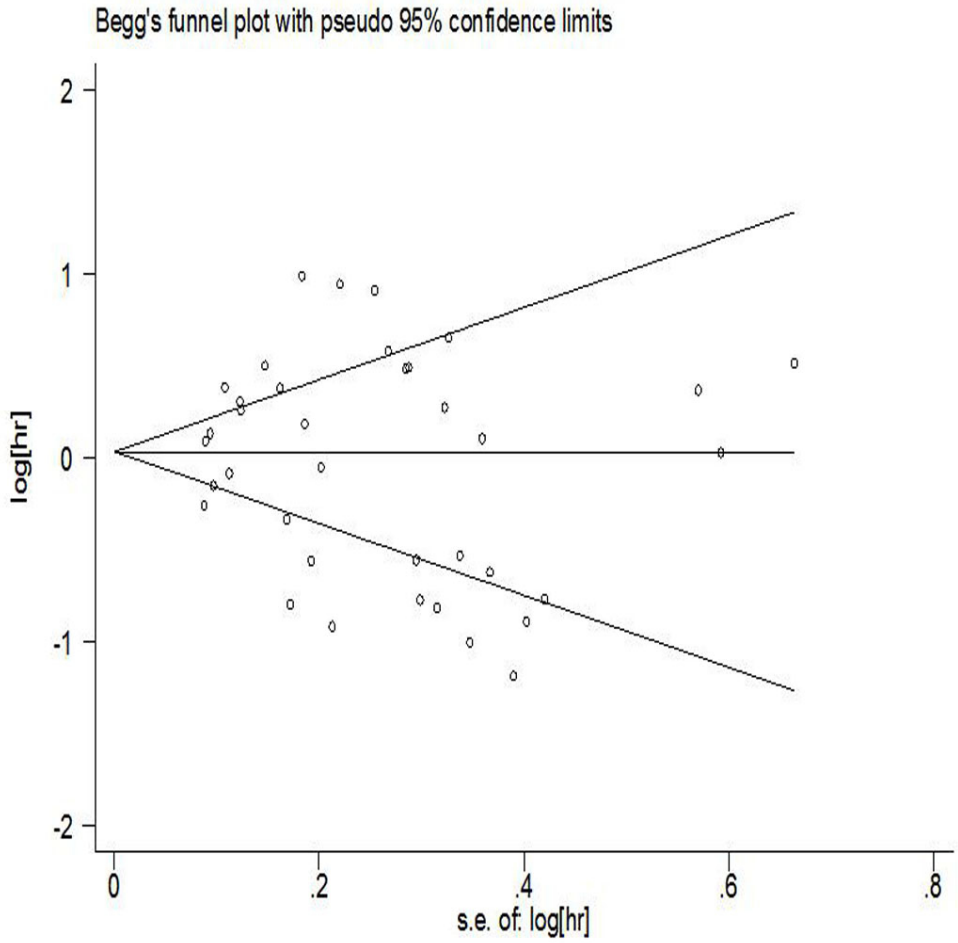
Sensitivity analysis of MPV for OS in cancer patients. No significant change in the corresponding combined HR was observed, which indicated that our meta-analysis results were stable and robust.

90x90mm (300 x 300 DPI)



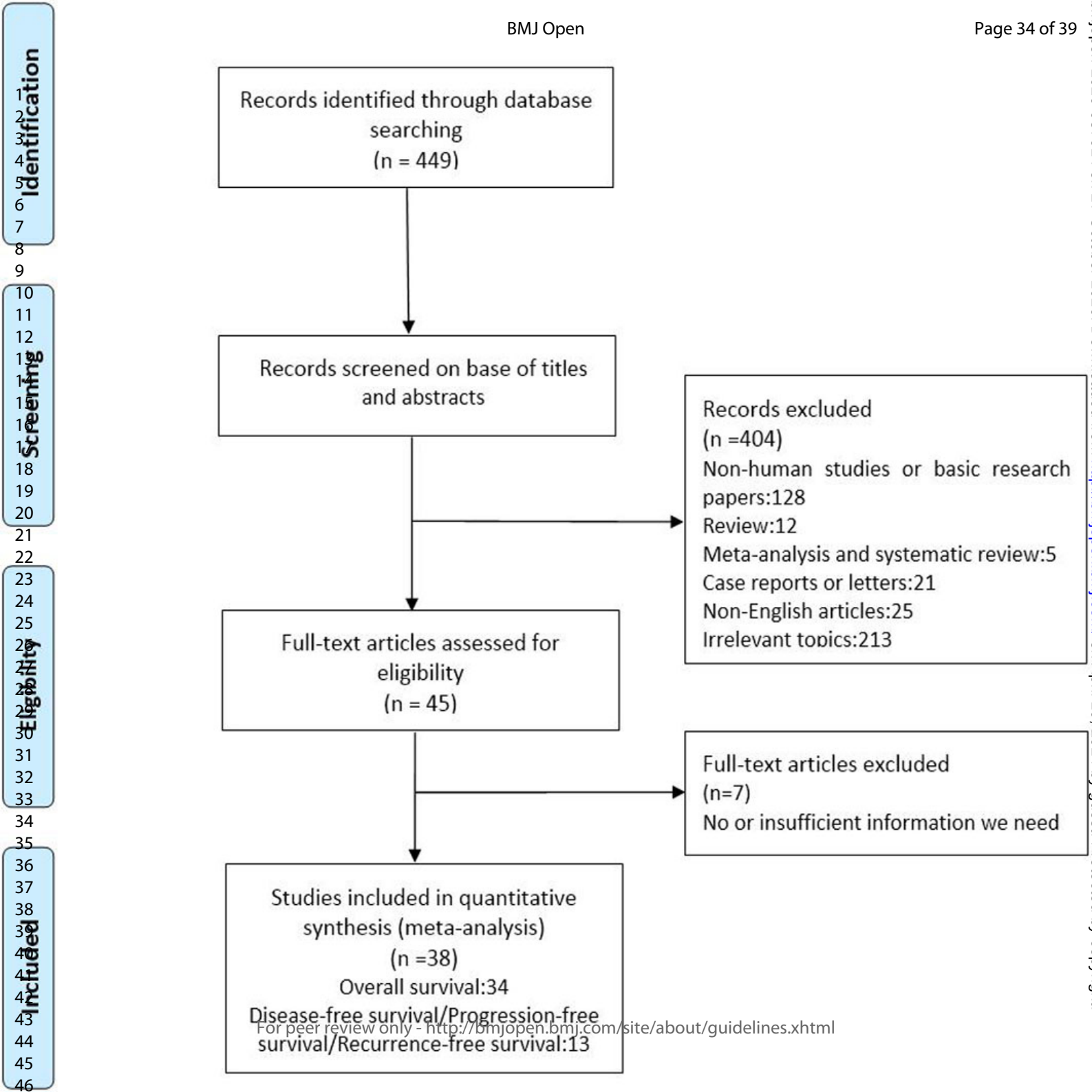
The forest plot between MPV level and DFS/PFS/RFS in cancer patients.

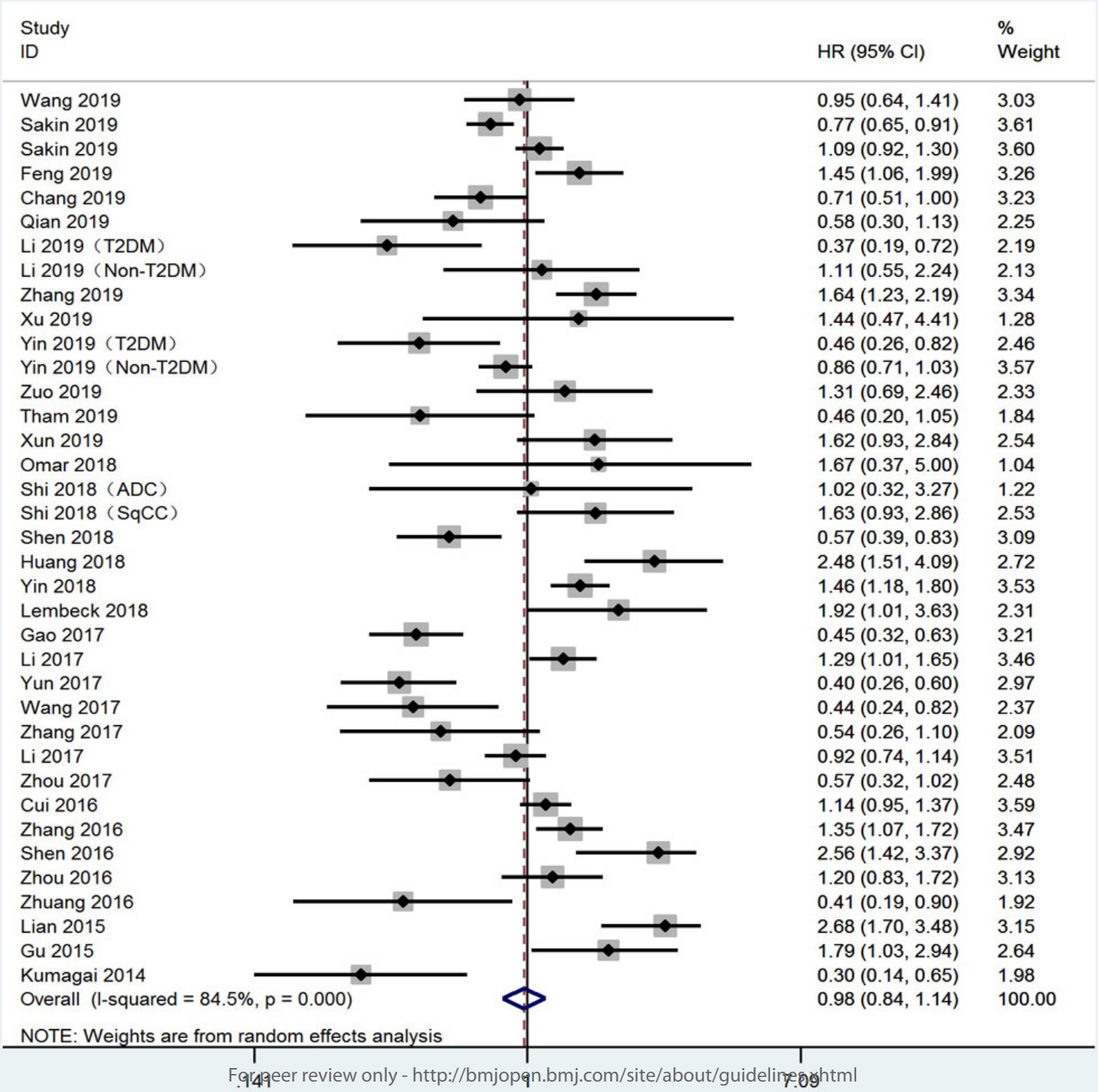
90x90mm (300 x 300 DPI)

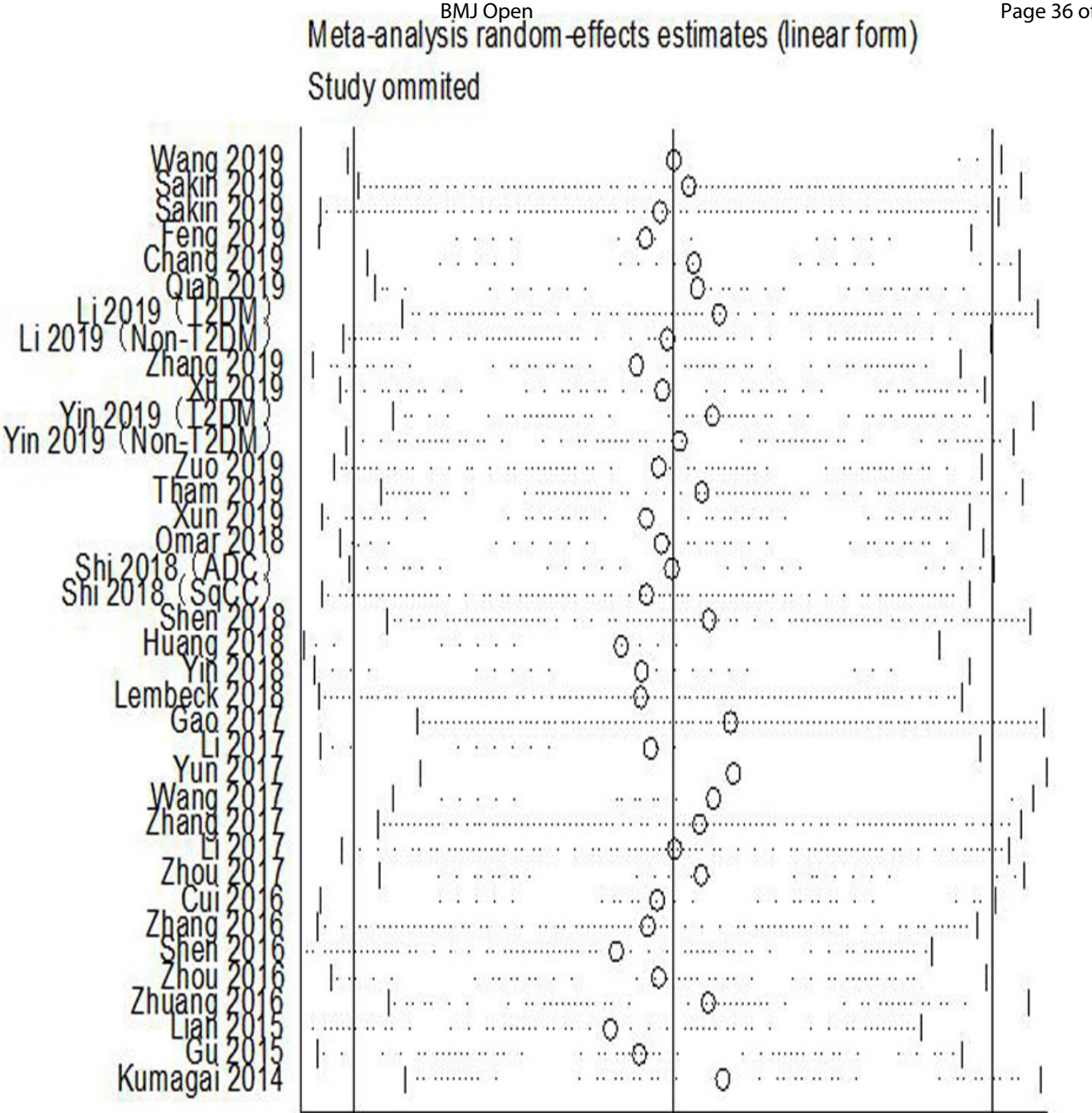


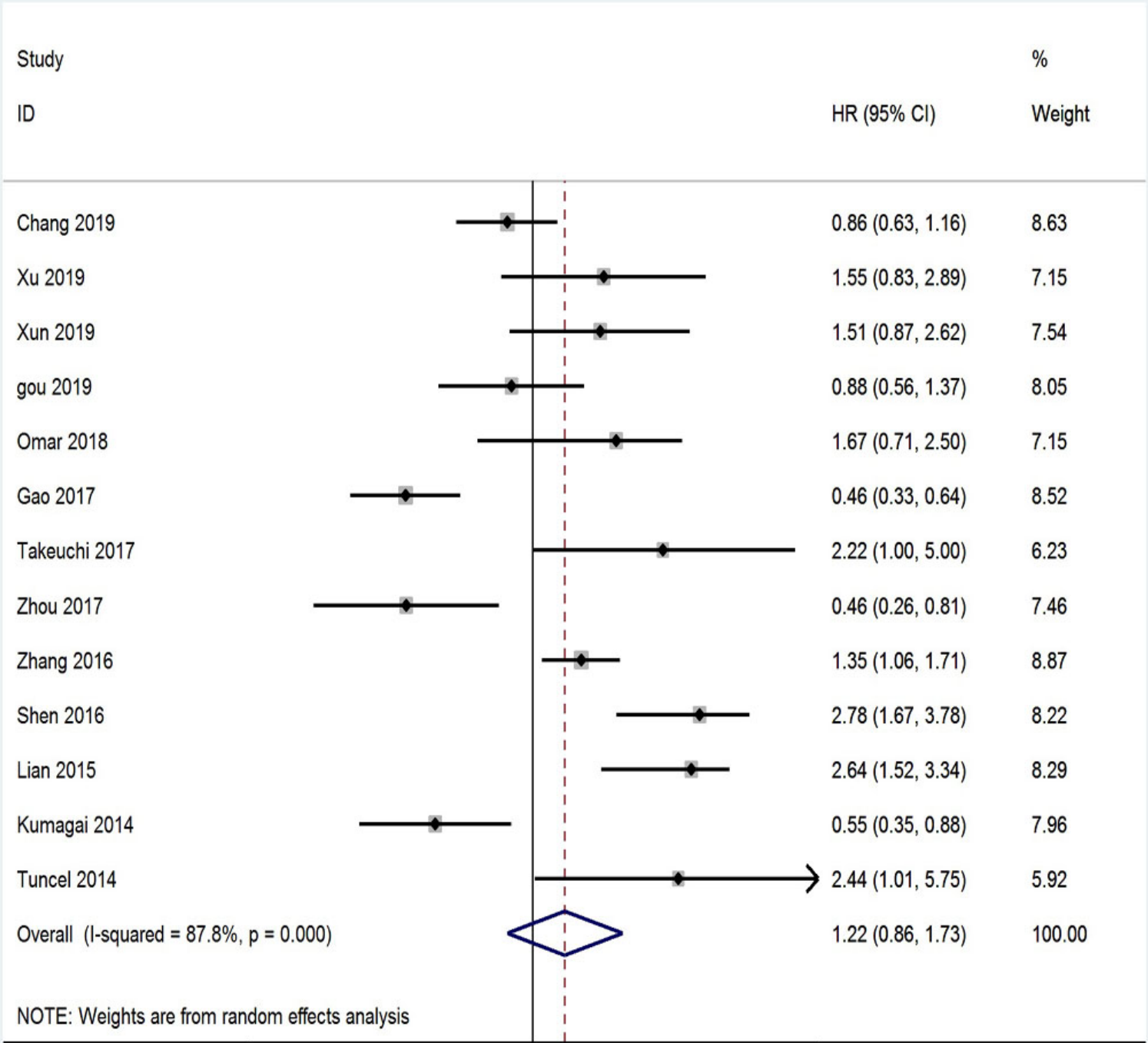
Begg's funnel plot of publication bias test for OS in cancer patients. No significant publication bias for studies evaluating the association between MPV level and OS was obeserved.

90x90mm (300 x 300 DPI)






Meta-analysis random-effects estimates (linear form)
Study ommited
Wang 2019
Sakin 2019
Sakin 2019
Feng 2019
Chang 2019
Qian 2019
Li 2019 (T2DM)
Li 2019 (Non-T2DM)
Zhang 2019
Xu 2019
Yin 2019 (T2DM)
Yin 2019 (Non-T2DM)
Zuo 2019
Tham 2019
Xun 2019
Omar 2018
Shi 2018 (ADC)
Shi 2018 (SqCC)
Shen 2018
Huang 2018
Yin 2018
Lembeck 2018
Gao 2017
Li 2017
Yun 2017
Wang 2017
Zhang 2017
Li 2017
Zhou 2017
Cui 2016
Zhang 2016
Shen 2016
Zhou 2016
Zhuang 2016
Lian 2015
Gu 2015
Kumagai 2014
-0.21
-0.18
-0.02
0.13
0.16


Study
ID
HR (95% CI)
%
Weight
Chang 2019
0.86 (0.63, 1.16)
8.63
Xu 2019
1.55 (0.83, 2.89)
7.15
Xun 2019
1.51 (0.87, 2.62)
7.54
gou 2019
0.88 (0.56, 1.37)
8.05
Omar 2018
1.67 (0.71, 2.50)
7.15
Gao 2017
0.46 (0.33, 0.64)
8.52
Takeuchi 2017
2.22 (1.00, 5.00)
6.23
Zhou 2017
0.46 (0.26, 0.81)
7.46
Zhang 2016
1.35 (1.06, 1.71)
8.87
Shen 2016
2.78 (1.67, 3.78)
8.22
Lian 2015
2.64 (1.52, 3.34)
8.29
Kumagai 2014
0.55 (0.35, 0.88)
7.96
Tuncel 2014
2.44 (1.01, 5.75)
5.92
Overall (I-squared = 87.8%, p = 0.000)
1.22 (0.86, 1.73)
100.00
NOTE: Weights are from random effects analysis
.174
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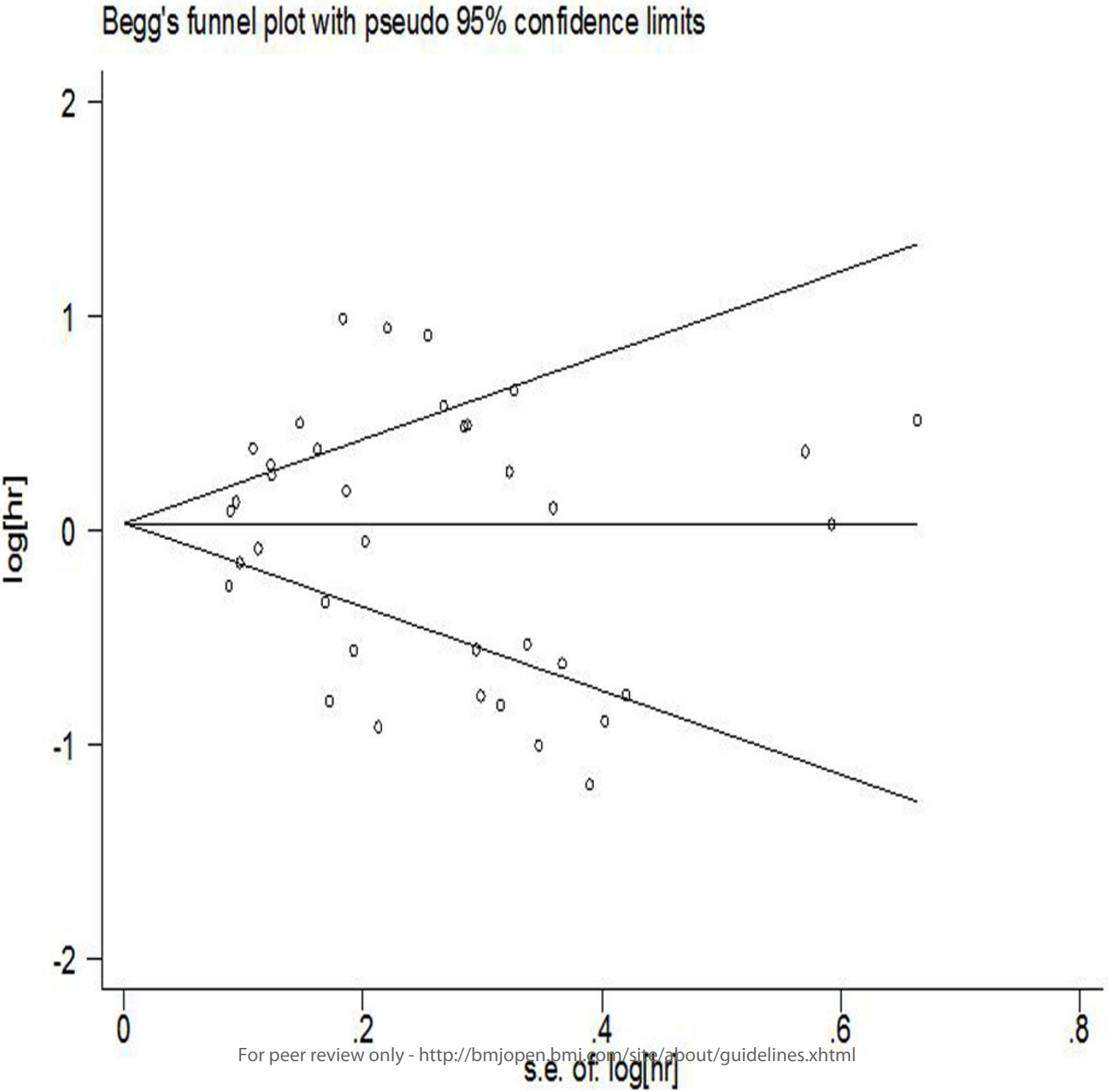

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

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Prognostic and clinicopathological significance of pretreatment mean platelet volume in cancer: A Meta-Analysis

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Prognostic and clinicopathological significance of pretreatment mean platelet volume in cancer: A Meta-Analysis

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Prognostic and clinicopathological significance of pretreatment mean platelet volume in cancer: A Meta-Analysis

Abstract

Objective: Our study aimed to evaluate the prognostic and clinicopathological significance of pretreatment mean platelet volume (MPV) on cancer by using meta-analysis of published studies.

Design: Meta-analysis.

Data sources: Relevant studies available before 22 December 2019 were identified by searching MEDLINE, EMBASE.

Eligibility criteria: All published studies that assessed the prognostic and clinicopathological significance of pretreatment mean platelet volume (MPV) on cancer were included.

Data extraction and synthesis: Studies were identified and extracted by two reviewers independently. The hazard ratio (HR) /Odds Ratio (OR) and its 95% confidence (CI) of survival outcomes and clinicopathological parameters were calculated.

Results: A total of 38 eligible studies (41 subsets) with 9,894 cancer patients were included in the final meta-analysis. MPV level was not significantly associated with both overall survival (HR: 0.98, 95% CI: 0.84−1.14) and disease-free survival (HR: 1.22, 95% CI: 0.86−1.73) of cancer patients. Neither advanced nor mixed stage tumor patients showed significant association between MPV and overall survival (HR:1.36, 95% CI: 0.96−1.94. HR: 0.90, 95% CI: 0.74−1.09). However, High MPV had the strongest relationship with poor overall survival (HR:2.01; 95%CI: 1.08−3.41) in gastric cancer, followed by pancreatic cancer (HR: 1.54; 95%CI: 1.31−1.82). Whereas in the subgroup using receiver operating characteristic curve

(ROC) method to define cutoff values, low MPV was significantly related to poor overall survival (HR: 0.78, 95%CI: 0.64-0.95). In addition, MPV had no significant association with age (OR: 0.96, 95% CI: 0.90–1.02), sex (OR: 1.04, 95% CI: 1.00–1.09) , depth of cancer invasion (OR: 0.90, 95% CI: 0.77–1.04) and tumor stage (OR: 0.91, 95% CI: 0.78–1.07).

Conclusions: Pretreatment MPV level is of no clearly prognostic significance in cancers and no significant association with clinicopathological parameters of patients with cancers.

Keywords

Mean platelet volume, Malignant tumor, Meta-Analysis, Prognosis

Strengths and limitations of this study

- This is the first meta-analysis of exploring the association between pretreatment mean platelet volume and cancer prognosis.
- The current study provided a comprehensive assessment of association between mean platelet volume and cancer survival, and showed significant findings.
- Strong and reliable methodological and statistical procedures were applied.
- Almost all of the included studies were retrospective, and the patients included were all but composed of Asian, which may have led to greater susceptibility to bias.

Introduction

Cancer is one of the main causes of morbidity and mortality worldwide(1). Despite the advance of new anti-cancer drug application and surgical techniques, the survival of most tumors is still not optimistic(2). Therefore, finding potent indicators to predict

the prognosis of cancer patient is justified with the purpose to design an appropriate therapeutic scheme to improve the patient survival.

Mean platelet volume(MPV), the most commonly used measure of platelet size, is considered to be an effective hallmark of platelet activation(3). The Complicated interactions between activated platelets and cancer cells lead to tumor growth, aberrant angiogenesis, invasion, and metastasis(4-6). A mounting body of evidence suggests that MPV plays an important prognostic role in various types of tumors, including upper gastrointestinal tumors(7-14), colorectal cancer(15, 16), lung cancer(17-19), breast cancer(20-22), and urothelial carcinoma(23, 24). However, the association between MPV level and cancer prognosis has not been comprehensively investigated due to the inevitable heterogeneity of the samples in different studies.

Therefore, we performed this meta-analysis to investigate the possible association between MPV level and clinical outcomes of cancer patients and evaluate the significance of MPV as an effective biomarker of cancer prognosis.

Methods

Search strategy and election criteria

Relevant studies were obtained from MEDLINE and EMBASE up to December 22, 2019. Language restrictions were not applied during the database search. Medical subject headings were searched and we performed a search of titles and abstracts combined with the following key-words: (“mean platelet volume OR platelet volume, mean OR MPV”) and (“neoplasms OR cancer OR tumor OR carcinoma”). The

references of the included articles were also scanned to find additional relevant studies. A detailed search strategy was showed in supplementary Table 1 (using MEDLINE as an example). The search results were then reviewed according to the following inclusion and exclusion criteria: (1) studies should assess the value of MPV prior to any treatment in patients with proven pathological diagnosis of cancer, (2) studies should evaluate the relationship between MPV and prognostic value or clinicopathological features of cancer patients, (3)studies should provide hazard ratio (HR) with a 95% confidence interval (CI) for clinical outcomes, or abundant data to estimate these quantities, (4) non-English articles were excluded, (5) non-human studies or basic research papers, reviews, meta-analyses, case reports, letters and irrelevant topics were not eligible for our meta-analysis. Two reviewers independently performed the study selection and resolved any disagreements via discussion.

Data extraction and quality evaluation

In current meta-analysis, two researchers (Xunlei Zhang and Yushan Liu) independently checked each included article and collected relative data, such as name of first author, publication year, country, study type, study period, follow-up time, sample size, cancer type, cancer stage, cut-off value of MPV, definition method of cut-offs, HR data (univariate or multivariate), and the number of patients with various clinicopathological features, such as tumor location, differentiation, size, depth of tumor invasion and TNM stage. HRs and 95% CIs were extracted for overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), and recurrence-free

survival (RFS). The Newcastle-Ottawa quality assessment scale (NOS) was utilized to evaluate the quality of each study with 8 items on methodology from 3 dimensions: selection, comparability, and exposure(25). Two investigators indepentently assessed all studies and scored them, among which scores of 6 or higher were qualified. All disagreements were settled by consensus.

Outcomes

We defined overall survival (OS) as the time from the study enrollment to the date of death from any cause or last follow-up. Since disease-free survival (DFS), progression-free survival (PFS), and recurrence-free survival (RFS) share similar endpoints, they were analyzed together as one outcome, disease free survival (DFS)(26-28).

Statistical analyses

All analyses were performed by using STATA version 14.0 (STATA, College Station, TX). Hazard ratio (HR) with 95% confidence interval (CI) was obtained directly from each included study if available or were calculated from the necessary data according to the methods published for the analysis of pooled outcomes(29). The heterogeneity in the analysis was assessed using Cochran's Q test and Higgins I-squared statistic. A random effects model (DerSimonian-Laird method) was applied when a p-value < 0.1 for the Q-test or $I^2 > 50\%$(30), suggesting the presence of significantly heterogeneity among the included studies. Otherwise, a fixed effects

model (Mantel-Haenszel method) was conducted for pooled data(31). Odds ratios (OR) and 95% CI were used to analyze the relationship between MPV and clinicopathological factors by using chi-square test. Subgroup analysis based on tumor type, tumor stage, age, country of origin, cut-off value, and method of defining the cut-off value were conducted to determine whether there was potential heterogeneity among the eligible studies. Moreover, sensitivity analysis was performed by removing every single study sequentially at a time to evaluate whether individual study influenced the combined effect and validate the robustness and credibility of the pooled outcomes. Publication bias of literature was estimated by Begg's funnel plot(32) and Egger's linear regression tests(33), and $p > 0.05$ indicated no significant publication bias.

Results

Selection and characteristics of studies

In the current study, identified 900 records were identified as potentially relevants through our literature search. 276 duplicates were excluded. After screening titles and abstracts, 579 studies with irrelevant content were excluded. A full-text review of the remaining 45 articles was conducted. Among them, seven reports were excluded for insufficient or no data to evaluate the association between MPV and prognostic outcomes or clinicopathologic characteristics of cancer patients. Finally, after applying the inclusion and exclusion criteria, 38 eligible studies (41 subsets) including 9,894 patients were included in our meta-analysis(7-24, 34-53). In one of these studies, tumor patients were divided into two groups according to pathological classification (Shi1

2018 and Shi2 2018)(38), and according to whether tumor patients had type 2 diabetes, the subjects in two other studies were also respectively divided into two groups (Li1 2019 and Li2 2019) (Yin1 2019 and Yin2 2019)(20, 44). Therefore, a total of six subsets were extracted. The selection process of the included studies according to the PRISMA guidelines was shown in Figure 1. The characteristics of the included studies were shown in Table 1. OS and DFS/PFS/RFS were reported in 34 studies (37 subsets) and 13 articles, respectively. Eleven different solid cancer types and two different hematological malignancies were investigated in the eligible studies. Among solid tumors, the most frequently evaluated cancer was upper gastrointestinal cancer (UGI) (including patients with esophageal, gastric, and pancreatic cancer) (n = 11), followed by lung cancer (n = 8) , breast cancer (n = 4), colorectal cancer (CRC) (n = 3), head and neck cancer (HNC) (n = 3), hepatic cancer (HCC) (n = 2), urothelial carcinoma (n = 2), melanoma (n = 1) and osteosarcoma (n = 1). Multiple myeloma (MM) (n = 1) and diffuse large B-cell lymphoma (DLBCL) (n = 1) were the two hematological malignancies evaluated. A majority of studies (75.7%) enrolled patients with mixed-stage cancer, whereas only a few studies (24.3%) specifically investigated patients with advanced-stage cancer. Three different types of methods for defining cut-off values were observed in the included studies. The receiver operating characteristic (ROC) curve analysis had the highest frequency of use (n = 22), followed by the empirical value based on previous studies (n = 9) and the calculated value obtained via certain computing software (n = 2). The cut-off values ranged from 7.4 to 12.2 in the included studies. In addition, ten studies (33.3%) included older population, the median or mean

age of whom was ≥60 years. Almost all of the studies (94.7%) were originally from Asia, while the only two remaining studies were from Europe and North America. Among the quality assessment of 38 studies, the quality score of four studies is 6, and the remaining 32 studies is ≥7.

MPV level and prognosis of cancer

Thirty-four studies including 37 subsets with 9,238 patients were analyzed for OS. The pooled HRs of high MPV level was 0.98 (95% CI: 0.84−1.14; Fig. 2), indicating no association between MPV level and overall survival in cancer patients. Table 2 shows the results for subgroup analysis, which was performed and stratified by six factors including tumor type, tumor stage, age, country of origin, cut-off value, and method of defining the cut-off value. In solid tumors, gastric cancer with high MPV had the strongest relationship with poor OS (HR: 2.01, 95% CI: 1.18−3.41; Supplementary Fig. 1), followed by pancreatic cancer (HR: 1.54, 95% CI: 1.31−1.82; Supplementary Fig. 2). Whereas other cancers with higher MPV were not associated with worse OS (NSCLC: HR = 0.85, 95% CI: 0.64−1.15; Esophageal cancer: HR = 1.05, 95% CI: 0.63−1.77; Breast cancer: HR = 1.19, 95% CI: 0.54−2.16; CRC: HR = 0.86, 95% CI: 0.52−1.42; HCC: HR = 0.80, 95% CI: 0.51−1.27; HNC: HR = 0.77, 95% CI: 0.33−1.77). In addition, neither advanced nor mixed stage tumor patients showed significant relationship between high MPV and poor OS (HR: 1.36, 95% CI: 0.96−1.94; HR: 0.90, 95% CI: 0.74−1.09). There were considerable variations in the methodologies used to define cutoff values. Receiver operating characteristic curve

(ROC) analysis was used widely to define cut-off values and low MPV was significantly related to poor overall survival in the subgroup of ROC-based cutoffs (HR: 0.78, 95%CI: 0.64-0.95). However, the other subgroup did not show a significant correlation between MPV and poor OS (HR: 1.51, 95%CI: 0.92-2.47). Sensitivity analysis for OS was performed. The results showed no significant change in the corresponding combined HR, indicating results in this meta-analysis are stable and robust (Fig. 3).

Thirteen studies with 3,014 patients provided HRs and 95% Cis for DFS. Overall, the pooled data indicated that MPV was not associated with DFS (HR: 1.22, 95% CI: 0.86−1.73; Fig. 4).

Relationship between MPV level and clinicopathological parameters

To further explore the association between MPV and the clinicopathological parameters in cancer, we extracted parts of included studies based on age, sex, depth of cancer invasion and tumor stage. As shown in Table 3, MPV was not shown to be associated with age (n =13, OR: 0.96, 95% CI: 0.90–1.02), sex (n =17, OR: 1.04, 95% CI: 1.00–1.09) , depth of cancer invasion (n =10, OR: 0.90, 95% CI: 0.77–1.04) and tumor stage (n =11, OR: 0.91, 95% CI: 0.78–1.07).

Publication bias

We detected no evidence of obvious asymmetry by the inspection of the Begg's funnel plot (Fig. 5), and was further confirmed by Egger's tests (p= 0.468), showing no

noteworthy publication bias in this meta-analysis. Moreover, no publication bias was observed in gastric cancer subgroup (p= 0.783) (Supplementary Fig. 3) and pancreatic cancer subgroup (p= 0.255) (Supplementary Fig. 4).

Discussion

The mean platelet volume (MPV) is a useful parameter for predicting activation of platelets by estimating the average size of platelets(54). It is an attractive index to study in clinical scenarios. The argument of MPV being a valuable biomarker predicting cancer prognosis was triggered due to controversial studies in variety of related cancer studies. A few researches indicated that MPV as an effective indicator can provide important prognostic information for certain cancers(7, 15, 18), but others failed to show its prognostic value on patients with cancers(45, 47, 53). This inspires us to perform this first meta-analysis to comprehensively evaluate the prognostic significance of MPV for OS and DFS/PFS/RFS in cancers. Pooled results demonstrated that high MPV was not associated with poor survival outcome. It was also not correlated with age, sex, tumor size, depth of cancer invasion and tumor stage. Although the final results of this meta-analysis were negative, they are still very helpful because they can clarify and show the real possible relationship between MPV and cancer prognosis when faced with contradictory study results, thereby further providing reference for clinical work and even guiding it to a certain extent. In addition, the results may provide new ideas and evidence for clinical applications aimed at assessing the prognosis of cancer. And it may inspire to further clinical research of prognostic prediction in cancer

patients. A more accurate biological prediction method may therefore be developed in the near future.

Subgroup analysis was conducted by age, country of origin, cut-off value, method of defining the cut-off value, tumor stage, and tumor type. High MPV was not related to poor overall survival in older and younger patients with cancers. Similarly, there was no correlation between high MPV and unfavorable overall survival in subgroups with cutoff values $\geqslant$10.5 and <10.5. Neither Asian nor non-Asian patients with high MPV exhibited poor overall survival. Although it was demonstrated that MPV in patients in an early stage of cancer was similar to those found in healthy subjects and increased with the cancer progression(55), we observed no significant correlation between high MPV and poor overall survival in patients with advanced cancers, nor in patients from the mixed-stage subgroup in our analysis. Whereas in the subgroup based on ROC curves method, low MPV was significantly associated with unfavorable overall survival. But we believe this result requires to verify prognostic significance of a ROC-based cut-off value in validation cohort, since the ROC-based cut-off value is actually a high risk of bias leading to overestimation of sensitivity and specificity in predicting cancer prognosis. Moreover, although high MPV level was obviously related to unfavorable overall survival for gastric cancer and pancreatic cancer, we still could not rashly conclude that high MPV can predict the poor prognosis of these two types of cancers. Because none of the three pancreatic cancer studies we included had a validation cohort and uniform MPV cutoff values, and these values varied widely. The same goes for three studies on gastric cancer. So more high quality studies need to be

implemented to explore unified cut-off values or priori defined cut off values (e.g.median) for specific cancers. In summary, although the data on gastric and pancreatic cancer were in question, the current results were valuable and could provide a good reference and inspiration for higher quality studies on these specific cancers in the future.

Although the final results of this study showed that pretreatment MPV did not play a significantly effective role in predicting prognosis in cancer, there might be a close association between alteration of MPV level and poor prognosis in certain tumors. We believe there may be some biological reasons behind this. Literatures indicated that MPV level could be influenced by a number of lifestyles and various diseases like smoking(56, 57), hypertension(58, 59), diabetes(60, 61), dyslipidemia and Obesity(62, 63), cardio-cerebrovascular disease(64, 65) and inflammatory disorders(66, 67). In essence, inflammation and thrombosis may play a key role in the increase and decrease of MPV level that is closely related to cancer prognosis. It is well-known that malignant tumors are accompanied by systemic inflammatory response(68, 69). Numerous inflammatory cytokines (e.g., IL-1, IL-6 and TNF-alpha) can promote the maturation and proliferation of macrophages (70, 71) and further lead to platelet activation and enhanced release of larger platelets, therefore elevating MPV level(55, 72). Activated platelets can secret a cocktail of predominantly proangiogenic cytokines within a potentially prothrombotic tumor microcirculation and coat circulating tumor cells to protect tumor cells from shear stress and the host's immune response(5), which promote tumor growth, angiogenesis, and metastasis. Therefore, the close association between

high MPV level and poor prognosis of cancers may be reasonable hypotheses. On the other hand, inflammation aggravation(55, 72) and thrombosis(54, 72) can lead to a decrease in MPV. When inflammation aggravating, increased release rate of small size platelets due to excessive pro-inflammatory cytokines' interference with megakaryopoiesis and selective consumption of large amount of highly reactive large-sized platelets result in a decline in MPV(73, 74). This suggests that the level of MPV depends heavily on the intensity of the systemic inflammation with the evidence in a recent study that low levels of MPV were associated with severe inflammatory diseases and were reversed during anti-inflammatory treatment(72). Moreover, tumor cells release tumor necrosis factor-α, interleukin-1 β, vascular endothelial growth factor and basic fibroblast growth factor(75) promoting the formation of vascular endothelial thrombi, in which process the consumption of larger-sized platelets is increased, leading to a decreased MPV in the circulating platelets(76). Although decreased MPV might indicate thrombosis that is closely associated with poor survival in patients with cancers (77-79), it is still not enough to support the notion for low MPV being an indicator of predicting the poor prognosis of cancer. Instead, it indicates the complicated role of MPV in the cancer development, which is justified to further study.

We admit that there are several limitations in our study. First, the inclusion criteria for this meta-analysis were limited to the studies published in English. And some studies without sufficient data were excluded. Thus publication or data availability bias may exist. Second, almost all of the included studies were retrospective, and the patients included were all but composed of Asian cohort, which may have led to greater

susceptibility to bias. However, there was no significant publication bias occurred based on the result in the asymmetry of the funnel plot, thus maintaining the substantial consistency among the results. Third, there was considerable heterogeneity when pooling HRs for OS results. Subgroup analysis showed the cut-off values in the included studies were various, which could lead to heterogeneity between studies. Finally, the majority of the included studies have no validation cohort. Therefore, higher quality studies are expected to more accurately assess the relationship between MPV and tumor prognosis to obtain more reliable results. This is one of the reasons why we conducted this meta-analysis.

Conclusions

In conclusion, the findings of this meta-analysis suggested that MPV level prior to initial treatment is of no prognostic significance in cancer patients and no relation with age, sex, tumor size, depth of invasion and tumor stage, providing new ideas and evidence for the clinical application of MPV. Although the results obtained by subgroup analysis were positive, further research is needed. Therefore, cumulative high quality studies for specific tumors are needed for the exploration and evaluation of reliable and uniform MPV cut-off values in clinical practice and further robust clinical studies are warranted focusing on MPV as prognostic factor of cancer patients.

Abbreviations

HR: hazard ratio; OR: odds ratio; 95% CI: 95% confidence interval; P_h: p values of Q test for heterogeneity test; OS: overall survival; DFS: disease-free survival; PFS:

progression-free survival; RFS: recurrence-free survival; MPV: mean platelet volume; UGI: upper gastrointestinal cancer; ESCC: esophageal squamous cell carcinoma; NSCLC: non-small cell lung cancer; ADC: adenocarcinoma; SqCC: squamous cell carcinoma; CRC: colorectal cancer; HCC: hepatocellular carcinoma; PNET: pancreatic neuroendocrine tumor; RCC: renal cell carcinoma; HNC: head and neck cancer; LSCC: Laryngeal Squamous Cell Carcinoma; MM: multiple myeloma; DLBCL: diffuse large B-cell lymphoma; T2DM: type 2 diabetes mellitus; NOS: Newcastle-Ottawa Scale;

Declarations

Ethics approval and consent to participate

All the data supporting our findings in this paper were freely downloaded from the PubMed and EMBASE. No ethical approval or written informed consent for participation was required.

Patient and Public Involvement

Patients and public were not involved.

Consent for publication

Not applicable.

Availability of data and materials

All data for this study are publicly available and are ready for the public to download

at no cost from the official websites of the PubMed and EMBASE. There is no need to have the formal permission to use data for this study. The sources and data robustness have been described in the section of "Methods".

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XC and JL were involved in drafting the manuscript. XLZ and YSL made contributions to the concepts, acquisition and analysis of the data. JDW and YCL was involved in acquisition of data and preparing the Figs. XHJ and XPC designed and revised the manuscript. All authors have read and approved the final manuscript.

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Table 1. Main characteristics of 38 included studies (41 subsets) in meta-analysis.

First author	Year	Country	Study design	Sample size	Age*（year）	Cancer type	Cancer stage	Cut-off value	Definition of cut-offs	Follow-up(month)	Outcome of HR	HR(OS)	HR(DFS/PFS/RFS)
Zhiyuan Yun	2017	China	Retrospective	306	57.8(37-80)	RCC	Mixed	7.5	ROC	60	OS	0.398(0.262,0.603)	
ShuaiShuai Xu(43)	2019	China	Retrospective	112	54(25-82)	PNET	Mixed	11.1	Median	NA	OS;RFS	1.442(0.472,4.411)	1.547(0.827,2.893)
Ke Zhang	2019	China	Retrospective	320	60(30-81)	Pancreatic cancer	Advanced	12.2	X-tile	NA	OS	1.64(1.23,2.19)	
Jibin Yin	2018	China	Retrospective	411	59.6(29-89)	Pancreatic cancer	Advanced	8.7	ROC	36	OS	1.461(1.183,1.804)	
Anna L Lembeck(13)	2018	Austria	Retrospective	527	NA	Pancreatic cancer	Advanced	11.3	75th percentile	54	OS	1.92(1.01,3.63)	
Bo gou	2019	China	Retrospective	188	NA	Osteosarcoma	Mixed	10.25	Cutoff Finder	33	PFS		0.879(0.563,1.372)
Abdullah Sakin	2019	Turkey	Retrospective	115	61.3(22-82)	NSCLC	Advanced	9	ROC	16.2	OS	0.767(0.646, 0.91)	
Abdullah Sakin	2019	Istanbul	Retrospective	90	59(42-83)	NSCLC	Mixed	NA	NA	NA	OS	1.092(0.917,1.3)	
Muhyettin Omar	2018	Turkey	Retrospective	496	NA	NSCLC	Advanced	9.1	ROC	33	OS;PFS	1.667(0.37,5)	1.667(0.714,2.5)
Liang Shi1	2018	China	Retrospective	90	53.3(27–73)	NSCLC	Advanced	10.85	ROC	NA	OS	1.025(0.321,3.271)	
Liang Shi2	2018	China	Retrospective	79	57(44–72)	NSCLC	Advanced	9.3	ROC	NA	OS	1.629(0.927,2.863)	
Liuwei Gao	2017	China	Retrospective	546	60(24-82)	NSCLC	Mixed	11	ROC	44.6	OS;DFS	0.45(0.322,0.631)	0.46(0.328,0.643)
Mingming Cui	2016	China	Retrospective	270	57.3(32-80)	NSCLC	Mixed	NA	NA	60	OS	1.14(0.949,1.37)	
Shogo Kumagai	2014	Japan	Retrospective	308	69(19-87)	NSCLC	Mixed	8.5	ROC	36	OS;DFS	0.303(0.141,0.65)	0.551(0.346,0.879)
Qiang Zhuang	2016	China	Retrospective	62	60.5(37-78)	MM	Mixed	8.5	ROC	42	OS	0.41(0.186,0.901)	
Na Li	2017	China	Retrospective	220	56.3(21-86)	Melanoma	Mixed	NA	NA	60	OS	0.918(0.737,1.143)	
JingJing Wang(34)	2019	China	Retrospective	101	60(27-80)	Lung cancer	Mixed	10.282	Median	NA	OS	0.947（0.637, 1.406）	
Youfang Xun	2019	China	Retrospective	151	65(44-84)	LSCC	Mixed	10.8	ROC	NA	OS;PFS	1.62(0.93,2.84)	1.51(0.87,2.62)
Huan Zhang	2017	China	Retrospective	241	57.8(37-80)	Laryngeal cancer	Mixed	9.3	ROC	60	OS	0.535(0.261,1.098)	
Tristan Tham	2019	USA	Retrospective	113	NA	HNC	Mixed	10.3	ROC	NA	OS	0.463(0.203,1.053)	
Jibin Yin1	2019	China	Retrospective	165	57.0 ± 7.9	HCC	NA	9.4	ROC	36	OS	0.46(0.256,0.824)	
Jibin Yin2	2019	China	Retrospective	166	52.9 ± 9.6	HCC	NA	9.4	ROC	36	OS	0.855(0.707,1.034)	
Xiaomin Zuo	2019	China	Retrospective	269	50.1±11.3	HCC	Mixed	11	ROC	NA	OS	1.308(0.695,2.461)	
XiaoMing Shen(11)	2016	China	Retrospective	168	56.5(31-82)	Gastric Cancer	Mixed	10.51	Median	60	OS;DFS	2.56(1.42,3.37)	2.78(1.67,3.78)
Xin Zhou	2016	China	Retrospective	451	NA	Gastric cancer	Mixed	9.83	NA	37.7	OS	1.195(0.83,1.718)	
Lian Lian(10)	2015	China	Retrospective	148	68(32-82)	Gastric cancer	Advanced	11.65	Median	36	OS;PFS	2.68(1.7,3.48)	2.64(1.52,3.34)
Wenjie Shen	2018	China	Retrospective	236	NA	Esopheal cancer	Mixed	7.4	ROC	48	OS	0.57(0.391,0.83)	
JiFeng Feng	2019	China	Retrospective	277	59.2(36-80)	ESCC	Mixed	8.5	ROC	45	OS	1.451(1.057,1.992)	
Fan Zhang	2016	China	Retrospective	468	59.9±9	ESCC	Mixed	10.6	ROC	48	OS;DFS	1.354(1.066,1.72)	1.347(1.06,1.71)
Noriyuki Hirahara(39)	2015	Japan	Retrospective	144	NA	ESCC	Mixed	11.5	Upper limit	NA	NA		
Shujuan Zhou	2017	China	Retrospective	161	59(18-80)	DLBCL	Mixed	9.1	ROC	24	OS;PFS	0.572(0.321,1.019)	0.461(0.262,0.814)
Jinjia Chang	2019	China	Retrospective	264	55.5	CRC	Advanced	9.75	ROC	NA	OS;PFS	0.715(0.514,0.995)	0.855(0.628,1.163)
Weihua Qian(40)	2019	China	Retrospective	153	56(27-85)	CRC	Mixed	10.4	Median	NA	OS	0.585(0.302,1.132)	
Na Li	2017	China	Retrospective	509	58.1(30-87)	CRC	Mixed	8.6	ROC	60	OS	1.293(1.015,1.648)	
Tolga Tuncel(41)	2014	Turkey	Retrospective	53	NA	CRC	Advanced	7.89	Mean	NA	PFS		2.44(1.014,5.747)
Na Li1	2019	China	Retrospective	264	57.5 ± 9.6	Breast cancer	Mixed	8	ROC	60	OS	0.365(0.185,0.721)	
Na Li2	2019	China	Retrospective	266	50.5 ± 9.6	Breast cancer	Mixed	8	ROC	60	OS	1.107(0.548,2.237)	
Yiru Huang	2018	China	Retrospective	271	50.7(21-80)	Breast cancer	Mixed	8.1	NA	60	OS	2.483(1.509,4.087)	
Hideya Takeuchi	2017	Japan	Retrospective	327	64.5(31-92)	Breast cancer	Mixed	9	ROC	45	PFS		2.222(1,5)
Meiling Gu(21)	2015	China	Retrospective	170	51.6	Breast cancer	Mixed	8.45	Median	NA	OS	1.786(1.031,2.941)	
Xin Wang	2017	China	Retrospective	218	63.2(31-82)	Bladder cancer	Mixed	9.1	ROC	60	OS	0.44(0.237,0.816)	

Note: * Age reported as either mean ± standard deviation or median (range), if not otherwise specified.

Abbreviations: ESCC, esophageal squamous cell carcinoma; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; PNET, pancreatic

neuroendocrine tumor; RCC, renal cell carcinoma; HNC, head and neck cancer; LSCC, Laryngeal Squamous Cell Carcinoma; MM, multiple myeloma; DLBCL, diffuse large B-cell lymphoma; NA, not available; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; RFS, recurrence-free survival; NOS, Newcastle-Ottawa Scale.

Table 2. Subgroup analyses of the associations between MPV and OS in cancer.

Stratified analyses	No. of studies	No. of patients	Model	Pooled HR (95%CI)	P value	Heterogeneity	
						I^2	P_H value
Cancer Type							
NSCLC	7	1994	Random	0.85(0.64,1.15)	0.295	83.90%	0.000
ESCC	3	981	Random	1.05(0.63,1.77)	0.844	88.40%	0.000
Gastric Cancer	3	767	Random	2.01(1.18,3.41)	0.010	82.60%	0.003
CRC	3	926	Random	0.86(0.52,1.42)	0.549	81.50%	0.004
Breast cancer	3	971	Random	1.19(0.54,2.61)	0.672	85.90%	0.000
Pancreatic cancer	3	1095	Fixed	1.54(1.31,1.82)	0.000	0.00%	0.645
HCC	2	600	Random	0.80(0.51,1.27)	0.350	66.60%	0.050
HNC	3	392	Random	0.77(0.33,1.77)	0.543	77.20%	0.012
Cancer stage							
Mixed	25	6401	Random	0.9(0.74,1.09)	0.278	83.40%	0.000
Advanced	8	2287	Random	1.36(0.96,1.94)	0.082	87.90%	0.000
Age							
＜60	18	4691	Random	1.05(0.88,1.26)	0.557	82.50%	0.000
≥60	9	1969	Random	0.83(0.54,1.28)	0.409	91.40%	0.000
Ethnicity							
Asian	32	8542	Random	0.97(0.83,1.14)	0.753	84.90%	0.000
Non-Asian	2	477	Random	0.97(0.24,3.89)	0.962	86.00%	0.007
Cut-off Value							
＜10	19	5436	Random	0.84(0.68,1.04)	0.103	84.10%	0.000
≥10	13	3166	Random	1.23(0.88,1.72)	0.235	87.90%	0.000
Definition of cut-offs							
ROC	21	6181	Random	0.78(0.64,0.95)	0.014	83.30%	0.000
Median	6	852	Random	1.51(0.92,2.47)	0.103	82.20%	0.000

Abbreviations: NSCLC, non-small cell lung cancer; ESCC, esophageal squamous cell carcinoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; HNC, head and neck cancer; HR, hazard ratio; 95% CI, 95% confidence interval; $P_{h,}$ p values of Q test for heterogeneity test.

Table 3. Association between MPV level and clinicopathological parameters

Clinical features	No. of studies	No. of patients	Model	OR (95%CI)	P value	Heterogeneity	
						I^2	P_H value
Age (older vs. younger)	13	2968	Fixed	0.96(0.90,1.02)	0.155	25.40%	0.188
Sex (Male vs. Female)	17	4077	Fixed	1.04(1.00,1.09)	0.077	0.00%	0.533
Depth of invasion (T1+T2 vs T3+T4)	10	2420	Random	0.90(0.77,1.04)	0.149	78.10%	0.000
Tumor stage (I/II vs III/IV)	11	2425	Random	0.91(0.78,1.07)	0.257	78.90%	0.000

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; $P_{h,}$ *p* values of Q test for heterogeneity test.

Figure legends

Figure 1: The flow diagram of publications selection.

Figure 2: The forest plot between MPV level and OS in cancer patients. Results are presented as individual and pooled hazard ratios (HRs) with 95% confidence intervals (CIs). HR >1 indicates worse overall survival for the group.

Figure 3: Sensitivity analysis of MPV for OS in cancer patients. No significant change in the corresponding combined HR was observed, which indicated that our meta-analysis results were stable and robust.

Figure 4: The forest plot between MPV level and DFS in cancer patients. Results are presented as individual and pooled hazard ratios (HRs) with 95% confidence intervals (CIs). HR >1 indicates worse overall survival for the group.

Figure 5: Begg's funnel plot of publication bias test for OS in cancer patients. No significant publication bias for studies evaluating the association between MPV level and OS was observed.

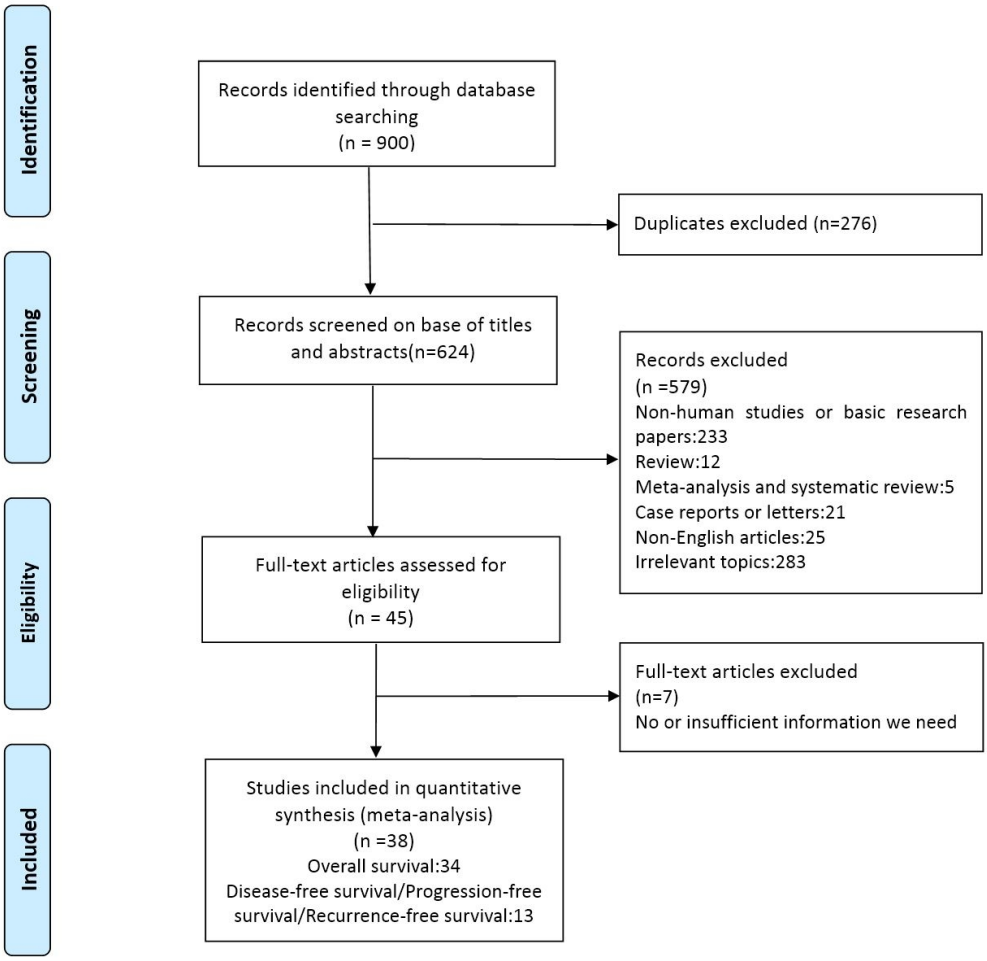
Supplementary Figure 1: The forest plot between MPV level and OS in gastric cancer patients. HR >1 indicates worse overall survival for the group.

Supplementary Figure 2: The forest plot between MPV level and OS in pancreatic cancer patients. HR >1 indicates worse overall survival for the group.

Supplementary Figure 3: Begg's funnel plot of publication bias test for OS in gastric cancer patients. No significant publication bias was observed in the gastric cancer subgroup.

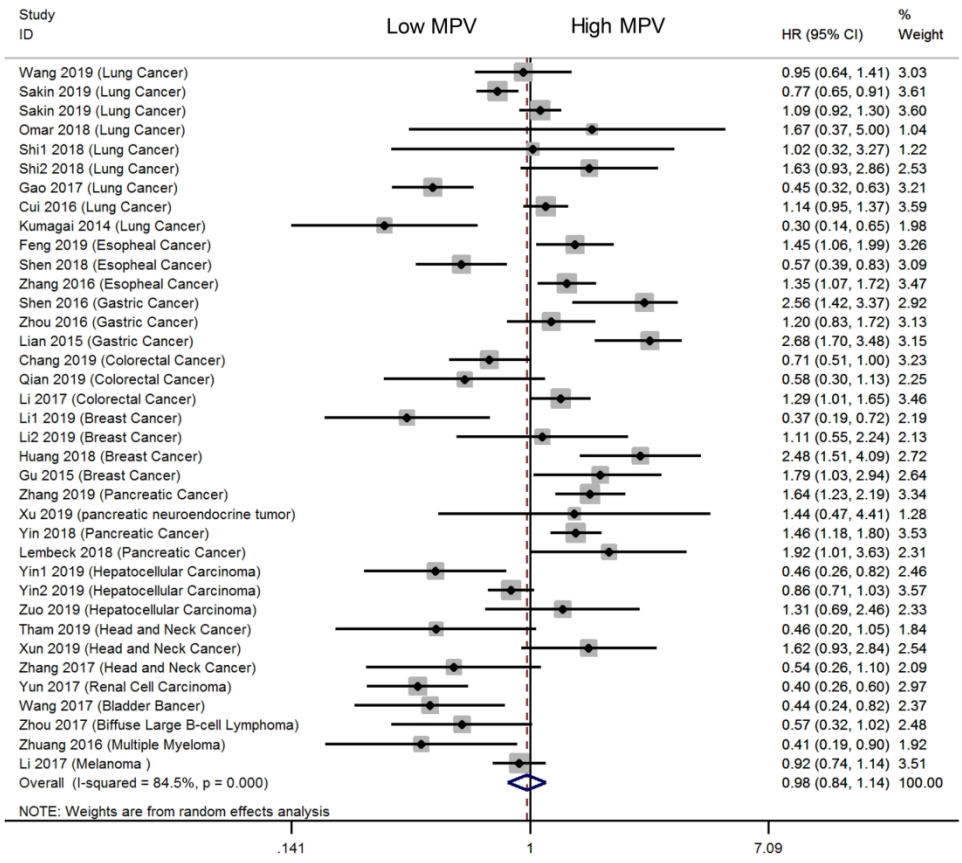
Supplementary Figure 4: Begg's funnel plot of publication bias test for OS in

pancreatic cancer patients. No significant publication bias was observed in the pancreatic cancer subgroup.



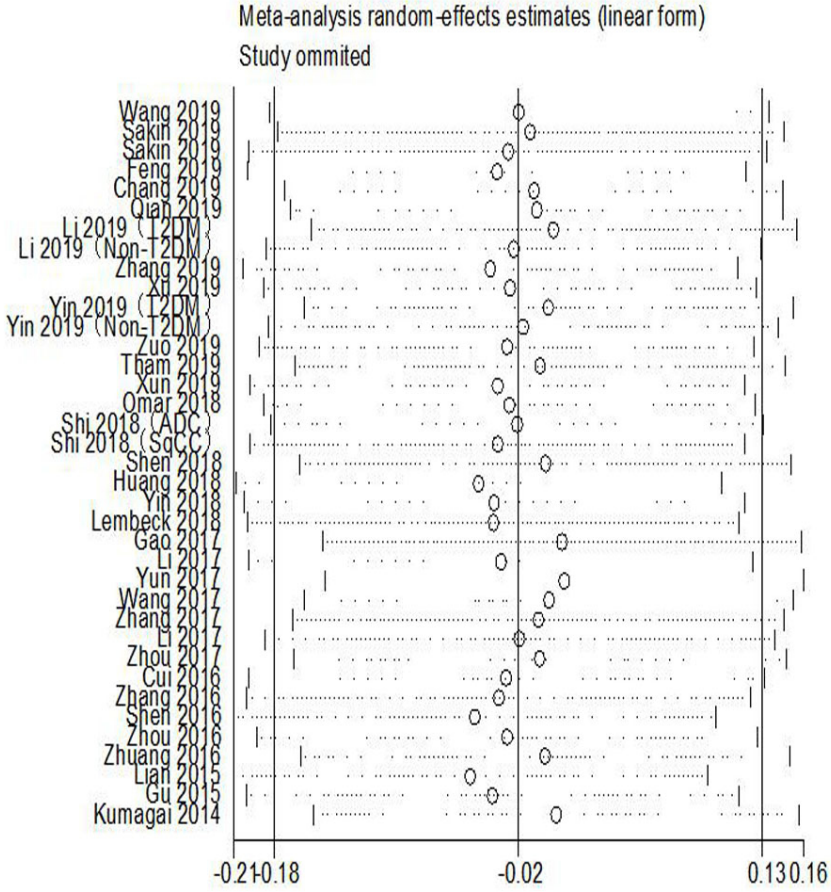
The flow diagram of publications selection.

217x210mm (144 x 144 DPI)



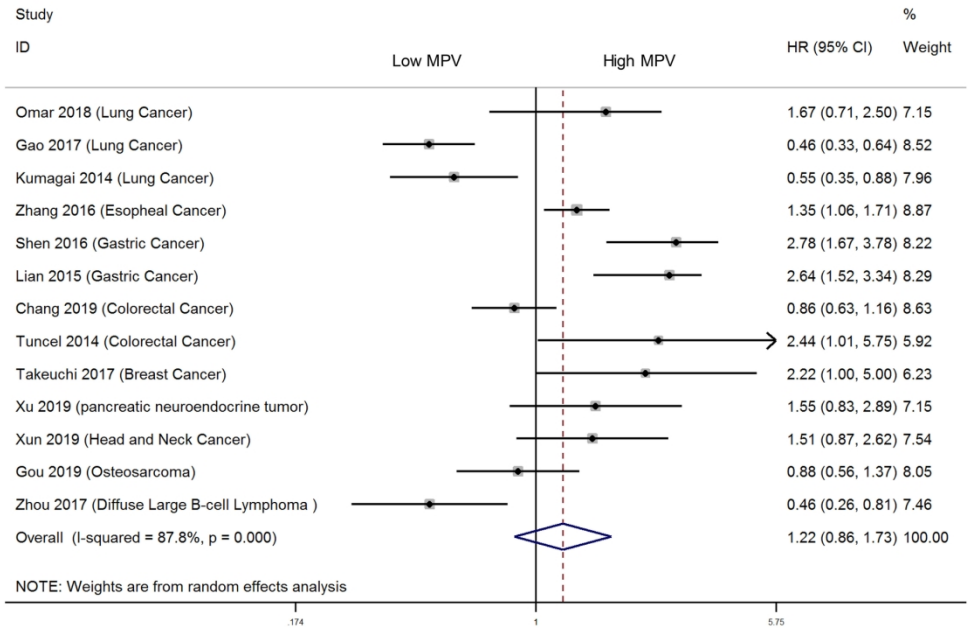
The forest plot between MPV level and OS in cancer patients. Results are presented as individual and pooled hazard ratios (HRs) with 95% confidence intervals (CIs). HR >1 indicates worse overall survival for the group.

169x152mm (300 x 300 DPI)



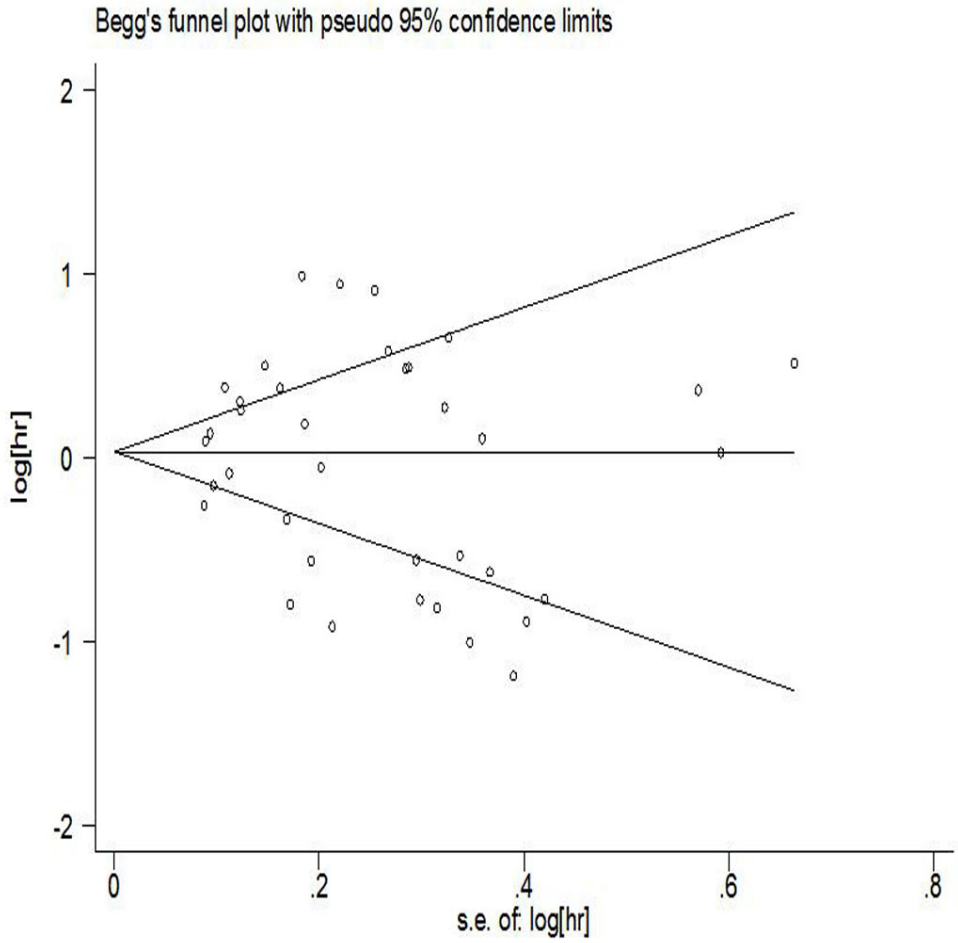
Sensitivity analysis of MPV for OS in cancer patients. No significant change in the corresponding combined HR was observed, which indicated that our meta-analysis results were stable and robust.

90x90mm (300 x 300 DPI)



The forest plot between MPV level and DFS in cancer patients. Results are presented as individual and pooled hazard ratios (HRs) with 95% confidence intervals (CIs). HR >1 indicates worse overall survival for the group.

170x117mm (300 x 300 DPI)

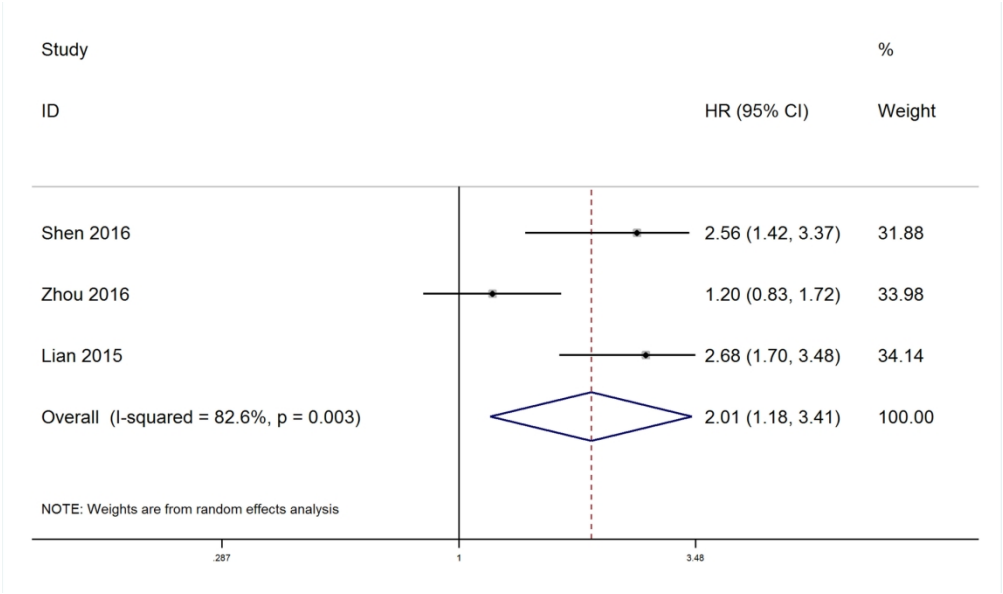


Begg's funnel plot of publication bias test for OS in cancer patients. No significant publication bias for studies evaluating the association between MPV level and OS was obeserved.

90x90mm (300 x 300 DPI)

Supplementary Table 1. The full search strategy for MEDLINE. Relevant studies were obtained from MEDLINE up to December 22, 2019.

1. "neoplasms"[Mesh]
2. “cancer” [Title/Abstract]
3. “tumor” [Title/Abstract]
4. “carcinoma” [Title/Abstract]
5. 1 OR 2 OR 3 OR 4
6. "mean platelet volume"[MeSH Terms]
7. "platelet volume mean"[Title/Abstract]
8. "MPV" [Title/Abstract]
9. 6 OR 7 OR 8
10. 5 AND 9



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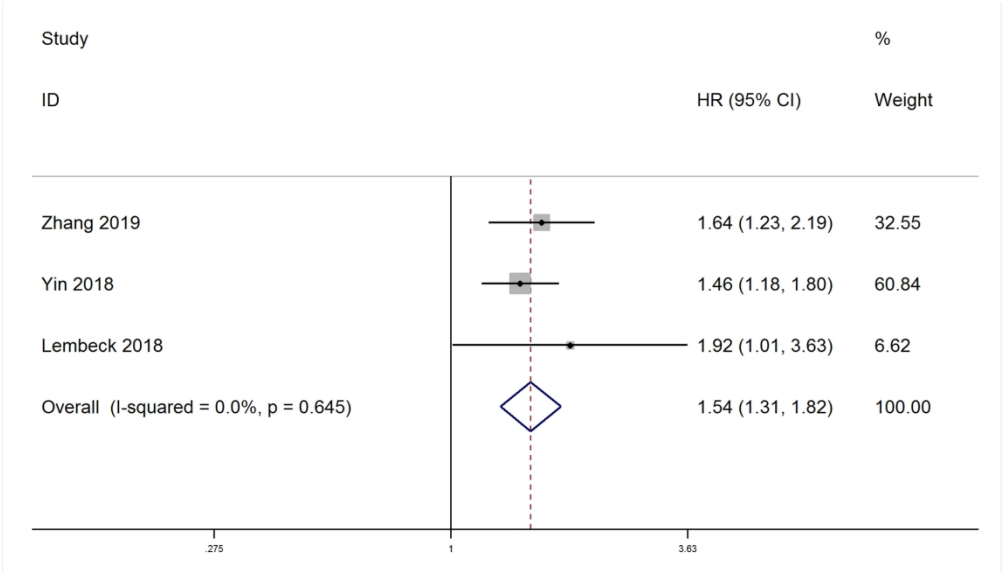

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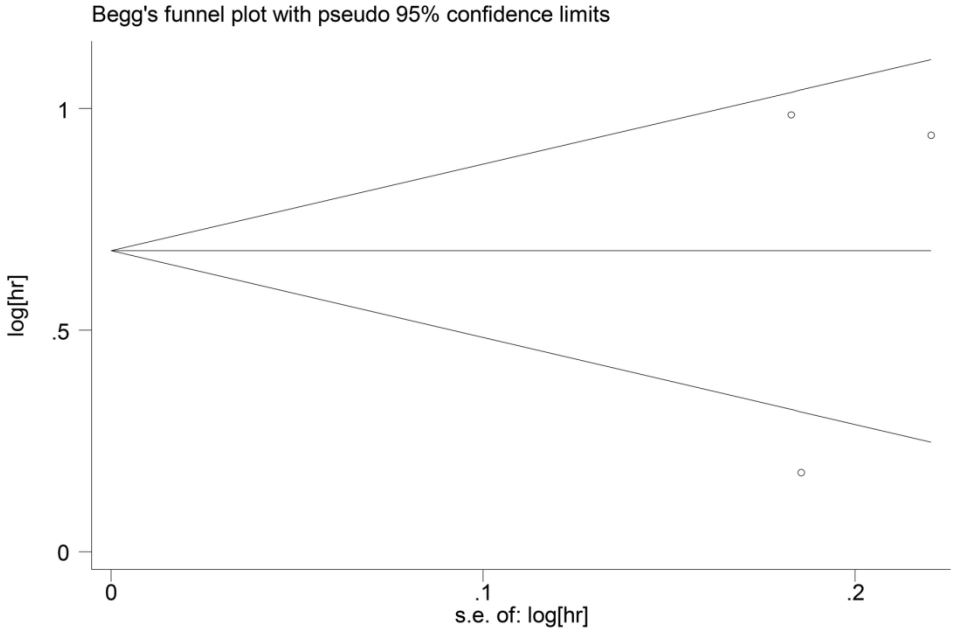
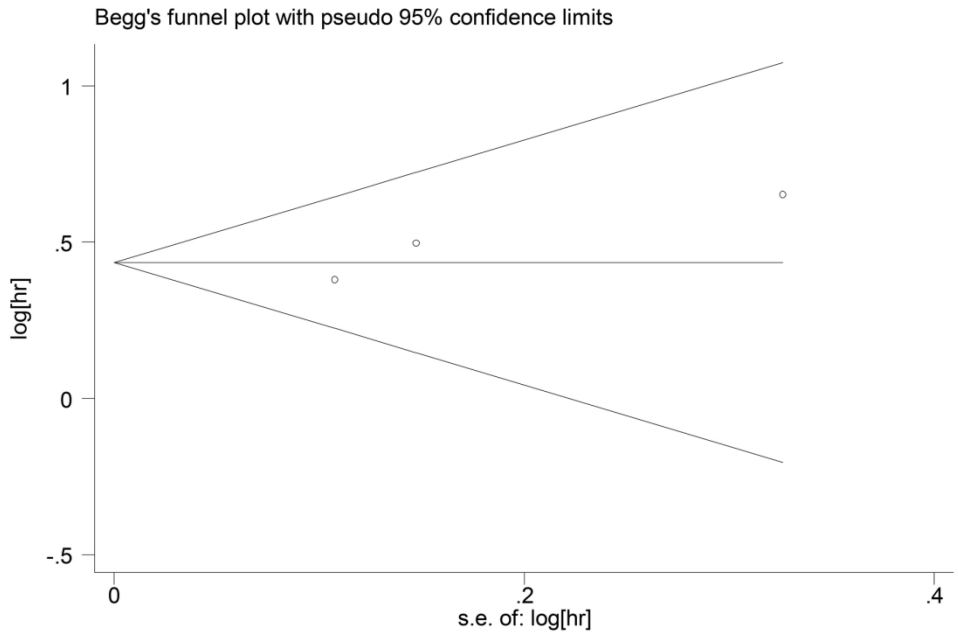


170x120mm (300 x 300 DPI)



170x120mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	27
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11-12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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