BMJ Open

Prognostic and clinicopathological significance of pretreatment mean platelet volume in cancer: a meta-analysis

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To cite: Chen X, Li J, Zhang X, *et al*. Prognostic and clinicopathological significance of pretreatment mean platelet volume in cancer: a meta-analysis. *BMJ Open* 2020;**10**:e037614. doi:10.1136/bmjopen-2020-037614

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-037614).

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Received 21 February 2020
Revised 03 August 2020
Accepted 23 August 2020

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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 MPV on cancer were included.

Data extraction and synthesis Studies were identified and extracted by two reviewers independently. The HR/OR and its 95% CIs of survival outcomes and clinicopathological parameters were calculated.

Results A total of 38 eligible studies (41 subsets) with 9894 patients with cancer were included in the final meta-analysis. MPV level was not significantly associated with both overall survival (HR 0.98, 95% CI 0.84 to 1.14) and disease-free survival (HR 1.22, 95% CI 0.86 to 1.73) of patients with cancer. Neither advanced nor mixed-stage tumour patients showed significant association between MPV and overall survival (HR 1.36, 95% CI 0.96 to 1.94, HR 0.90, 95% CI 0.74 to 1.09). However, high MPV had the strongest relationship with poor overall survival (HR 2.01; 95% CI 1.08 to 3.41) in gastric cancer, followed by pancreatic cancer (HR 1.54; 95% CI 1.31 to 1.82). Whereas in the subgroup using receiver operating characteristic curve method to define cut-off values, low MPV was significantly related to poor overall survival (HR 0.78, 95% CI 0.64 to 0.95). In addition, MPV had no significant association with age (OR 0.96, 95% CI 0.90 to 1.02), sex (OR 1.04, 95% CI 1.00 to 1.09), depth of cancer invasion (OR 0.90, 95% CI 0.77 to 1.04) and tumour stage (OR 0.91, 95% CI 0.78 to 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.

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 anticancer drug application and surgical techniques, the survival of most tumours 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 tumour 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 tumours, including upper gastrointestinal tumours,[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 22 December 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 online supplemental 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 HR with a 95% 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 (XZ and YL) 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 tumour location, differentiation, size, depth of tumour invasion and TNM (Tumor, Lymph Node, Metastasis) 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 Scale was used to evaluate the quality of each study with eight items on methodology from three 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 OS as the time from the study enrolment to the date of death from any cause or last follow-up. Since DFS, PFS and RFS share similar endpoints, they were analysed together as one outcome, DFS.[26–28]

Statistical analyses

All analyses were performed by using STATA V.14.0 (STATA). HR with 95% 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 $p<0.1$ 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] ORs and 95% CIs were used to analyse the relationship between MPV and clinicopathological factors by using χ^2 test. Subgroup analysis based on tumour type, tumour 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. two hundred and seventy-six duplicates were excluded. After screening titles and abstracts, 579 studies with

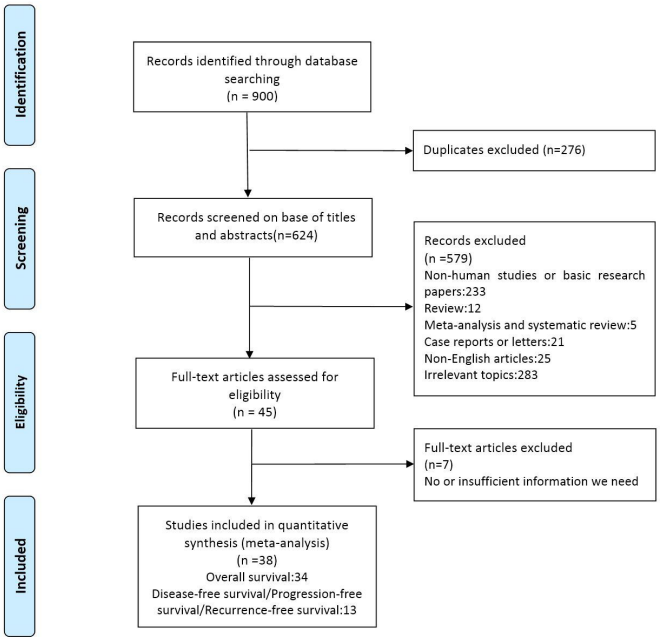

Figure 1 The flow diagram of publications selection.

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)
Yun[23]	2017	China	Retrospective	306	57.8 (37–80)	RCC	Mixed	7.5	ROC	60	OS	0.398 (0.262, 0.603)	
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)
Zhang[14]	2019	China	Retrospective	320	60 (30–81)	Pancreatic cancer	Advanced	12.2	X-tile	NA	OS	1.64 (1.23, 2.19)	
Yin[12]	2018	China	Retrospective	411	59.6 (29–89)	Pancreatic cancer	Advanced	8.7	ROC	36	OS	1.461 (1.183, 1.804)	
Lembeck[13]	2018	Austria	Retrospective	527	NA	Pancreatic cancer	Advanced	11.3	75th percentile	54	OS	1.92 (1.01, 3.63)	
Gou[50]	2019	China	Retrospective	188	NA	Osteosarcoma	Mixed	10.25	Cut-off Finder	33	PFS		0.879 (0.563, 1.372)
Sakin[17]	2019	Turkey	Retrospective	115	61.3 (22–82)	NSCLC	Advanced	9	ROC	16.2	OS	0.767 (0.646, 0.91)	
Sakin[17]	2019	Istanbul	Retrospective	90	59 (42–83)	NSCLC	Mixed	NA	NA	NA	OS	1.092 (0.917, 1.3)	
Omar[37]	2018	Turkey	Retrospective	496	NA	NSCLC	Advanced	9.1	ROC	33	OS;PFS	1.667 (0.37, 5)	1.667 (0.714, 2.5)
Shi[38]	2018	China	Retrospective	90	53.3 (27–73)	NSCLC	Advanced	10.85	ROC	NA	OS	1.025 (0.321, 3.271)	
Shi[38]	2018	China	Retrospective	79	57(44–72)	NSCLC	Advanced	9.3	ROC	NA	OS	1.629 (0.927, 2.863)	
Gao[19]	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)
Cui[35]	2016	China	Retrospective	270	57.3 (32–80)	NSCLC	Mixed	NA	NA	60	OS	1.14 (0.949, 1.37)	
Kumagai[18]	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)
Zhuang[51]	2016	China	Retrospective	62	60.5 (37–78)	MM	Mixed	8.5	ROC	42	OS	0.41 (0.186, 0.901)	
Li	2017	China	Retrospective	220	56.3 (21–86)	Melanoma	Mixed	NA	NA	60	OS	0.918 (0.737, 1.143)	
Wang[34]	2019	China	Retrospective	101	60 (27–80)	Lung cancer	Mixed	10.282	Median	NA	OS	0.947 (0.637, 1.406)	
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)
Zhang	2017	China	Retrospective	241	57.8 (37–80)	Laryngeal cancer	Mixed	9.3	ROC	60	OS	0.535 (0.261, 1.098)	
Tham	2019	USA	Retrospective	113	NA	HNC	Mixed	10.3	ROC	NA	OS	0.463 (0.203, 1.053)	
Yin	2019	China	Retrospective	165	57.0±7.9	HCC	NA	9.4	ROC	36	OS	0.46 (0.256, 0.824)	
Yin	2019	China	Retrospective	166	52.9±9.6	HCC	NA	9.4	ROC	36	OS	0.855 (0.707, 1.034)	
Zuo	2019	China	Retrospective	269	50.1±11.3	HCC	Mixed	11	ROC	NA	OS	1.308 (0.695, 2.461)	
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)
Zhou	2016	China	Retrospective	451	NA	Gastric cancer	Mixed	9.83	NA	37.7	OS	1.195 (0.83, 1.718)	
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)
Shen	2018	China	Retrospective	236	NA	Esopheal cancer	Mixed	7.4	ROC	48	OS	0.57 (0.391, 0.83)	
Feng	2019	China	Retrospective	277	59.2 (36–80)	ESCC	Mixed	8.5	ROC	45	OS	1.451 (1.057, 1.992)	
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)

Continued

Table 1 Continued

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)
Hirahara[39]	2015	Japan	Retrospective	144	NA	ESCC	Mixed	11.5	Upper limit	NA	NA		
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)
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)
Qian[40]	2019	China	Retrospective	153	56 (27–85)	CRC	Mixed	10.4	Median	NA	OS	0.585 (0.302, 1.132)	
Li	2017	China	Retrospective	509	58.1 (30–87)	CRC	Mixed	8.6	ROC	60	OS	1.293 (1.015, 1.648)	
Tuncel[41]	2014	Turkey	Retrospective	53	NA	CRC	Advanced	7.89	Mean	NA	PFS		2.44 (1.014, 5.747)
Li	2019	China	Retrospective	264	57.5±9.6	Breast cancer	Mixed	8	ROC	60	OS	0.365 (0.185, 0.721)	
Li	2019	China	Retrospective	266	50.5±9.6	Breast cancer	Mixed	8	ROC	60	OS	1.107 (0.548, 2.237)	
39	Huang2018	2018China	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)
Gu[21]	2015	China	Retrospective	170	51.6	Breast cancer	Mixed	8.45	Median	NA	OS	1.786 (1.031, 2.941)	
Wang	2017	China	Retrospective	218	63.2 (31–82)	Bladder cancer	Mixed	9.1	ROC	60	OS	0.44 (0.237, 0.816)	

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

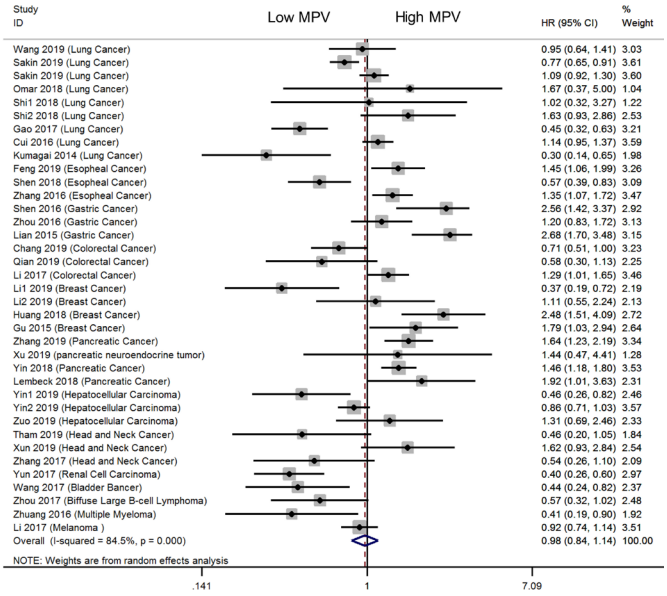

Figure 2 The forest plot between MPV level and OS in patients with cancer. Results are presented as individual and pooled HRs with 95% CIs. HR >1 indicates worse overall survival for the group. MPV, mean platelet volume; OS, overall survival.

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 9894 patients were included in our meta-analysis.[7–24 34–53] In one of these studies, patients with tumour were divided into two groups according to pathological classification,[38] and according to whether patients with tumour had type 2 diabetes, the subjects in two other studies were also, respectively, divided into two groups.[20 44] Therefore, a total of six subsets were extracted. The selection process of the included studies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 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 haematological malignancies were investigated in the eligible studies. Among solid tumours, the most frequently evaluated cancer was upper gastrointestinal cancer (including patients with oesophageal, 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 (n=1) and diffuse large B-cell lymphoma (n=1) were the two haematological 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, 10 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 9238 patients were analysed for OS. The pooled HRs of high MPV level was 0.98 (95% CI 0.84 to 1.14; figure 2), indicating no association between MPV level and OS in cancer patients. Table 2 shows the results for subgroup analysis, which was performed and stratified by six factors including tumour type, tumour stage, age, country of origin, cut-off value and method of defining the cut-off value. In solid tumours, gastric cancer with high MPV had the strongest relationship with poor OS (HR 2.01, 95% CI 1.18 to 3.41; online supplemental figure 1), followed by pancreatic cancer (HR 1.54, 95% CI 1.31 to 1.82; online supplemental figure 2). Whereas other cancers with higher MPV were not associated with worse OS (NSCLC: HR 0.85, 95% CI 0.64 to 1.15; oesophageal cancer: HR 1.05, 95% CI 0.63 to 1.77; breast cancer: HR 1.19, 95% CI 0.54 to 2.16; CRC: HR 0.86, 95% CI 0.52 to 1.42; HCC: HR 0.80, 95% CI 0.51 to 1.27; HNC: HR 0.77, 95% CI 0.33 to 1.77). In addition, neither advanced nor mixed-stage tumour patients showed significant relationship between high MPV and poor OS (HR 1.36, 95% CI 0.96 to 1.94; HR 0.90, 95% CI 0.74 to 1.09). There were considerable variations in the methodologies used to define cut-off values. ROC analysis was used widely to define cut-off values and low MPV was significantly related to poor OS in the subgroup of ROC-based cut-offs (HR 0.78, 95% CI 0.64 to 0.95). However, the other subgroup did not show a significant correlation between MPV and poor OS (HR 1.51, 95% CI 0.92 to 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 (figure 3).

Thirteen studies with 3014 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 to 1.73; figure 4).

Relationship between MPV level and clinicopathological parameters

To further explore the association between MPV and the clinicopathological parameters in cancer, we extracted

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 to 1.15)	0.295	83.90	0
ESCC	3	981	Random	1.05 (0.63 to 1.77)	0.844	88.40	0
Gastric cancer	3	767	Random	2.01 (1.18 to 3.41)	0.01	82.60	0.003
CRC	3	926	Random	0.86 (0.52 to 1.42)	0.549	81.50	0.004
Breast cancer	3	971	Random	1.19 (0.54 to 2.61)	0.672	85.90	0
Pancreatic cancer	3	1095	Fixed	1.54 (1.31 to 1.82)	0	0.00	0.645
HCC	2	600	Random	0.80 (0.51 to 1.27)	0.35	66.60	0.05
HNC	3	392	Random	0.77 (0.33 to 1.77)	0.543	77.20	0.012
Cancer stage							
Mixed	25	6401	Random	0.9 (0.74 to 1.09)	0.278	83.40	0
Advanced	8	2287	Random	1.36 (0.96 to1.94)	0.082	87.90	0
Age							
<60	18	4691	Random	1.05 (0.88 to 1.26)	0.557	82.50	0
≥60	9	1969	Random	0.83 (0.54 to 1.28)	0.409	91.40	0
Ethnicity							
Asian	32	8542	Random	0.97 (0.83 to 1.14)	0.753	84.90	0
Non-Asian	2	477	Random	0.97 (0.24 to 3.89)	0.962	86.00	0.007
Cut-off value							
<10	19	5436	Random	0.84 (0.68 to 1.04)	0.103	84.10	0
≥10	13	3166	Random	1.23 (0.88 to 1.72)	0.235	87.90	0
Definition of cut-offs							
ROC	21	6181	Random	0.78 (0.64 to 0.95)	0.014	83.30	0
Median	6	852	Random	1.51 (0.92 to 2.47)	0.103	82.20	0

CRC, colorectal cancer; ESCC, oesophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; HNC, head and neck cancer; MPV, mean platelet volume; NSCLC, non-small cell lung cancer; OS, overall survival; ROC, receiver operating characteristic.

parts of included studies based on age, sex, depth of cancer invasion and tumour stage. As shown in table 3, MPV was not shown to be associated with age (n=13, OR 0.96, 95% CI 0.90 to 1.02), sex (n=17, OR 1.04, 95% CI 1.00 to 1.09), depth of cancer invasion (n=10, OR 0.90, 95% CI 0.77 to 1.04) and tumour stage (n=11, OR 0.91, 95% CI 0.78 to 1.07).

Publication bias

We detected no evidence of obvious asymmetry by the inspection of the Begg's funnel plot (figure 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) (see online supplemental figure 3) and pancreatic cancer subgroup (p=0.255) (see online supplemental figure 4).

DISCUSSION

The 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, tumour size, depth of cancer invasion and tumour 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 patients with cancer.

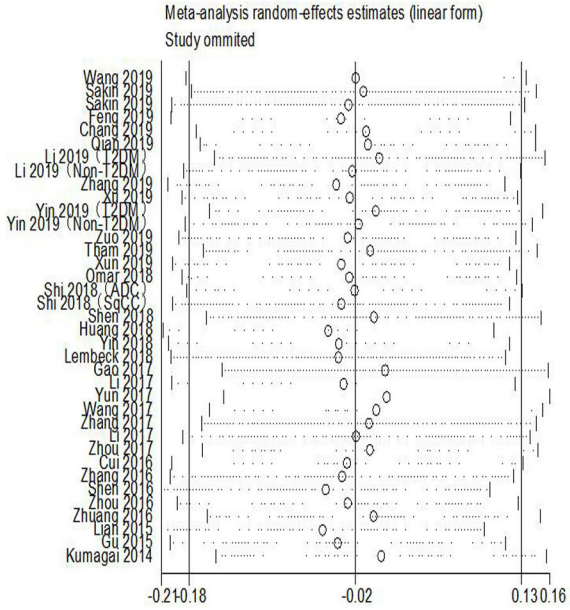

Figure 3 Sensitivity analysis of MPV for OS in patients with cancer. No significant change in the corresponding combined HR was observed, which indicated that our meta-analysis results were stable and robust. MPV, mean platelet volume; OS, overall survival.

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, tumour stage and tumour 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 unfavourable OS in subgroups with cut-off values ≥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 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 OS 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 unfavourable OS. But we believe this result requires to verify prognostic significance of an 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 unfavourable OS 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 cut-off 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 (eg, 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 tumours. We believe there may be some biological reasons behind this. Literatures indicated that MPV level could be influenced by a number

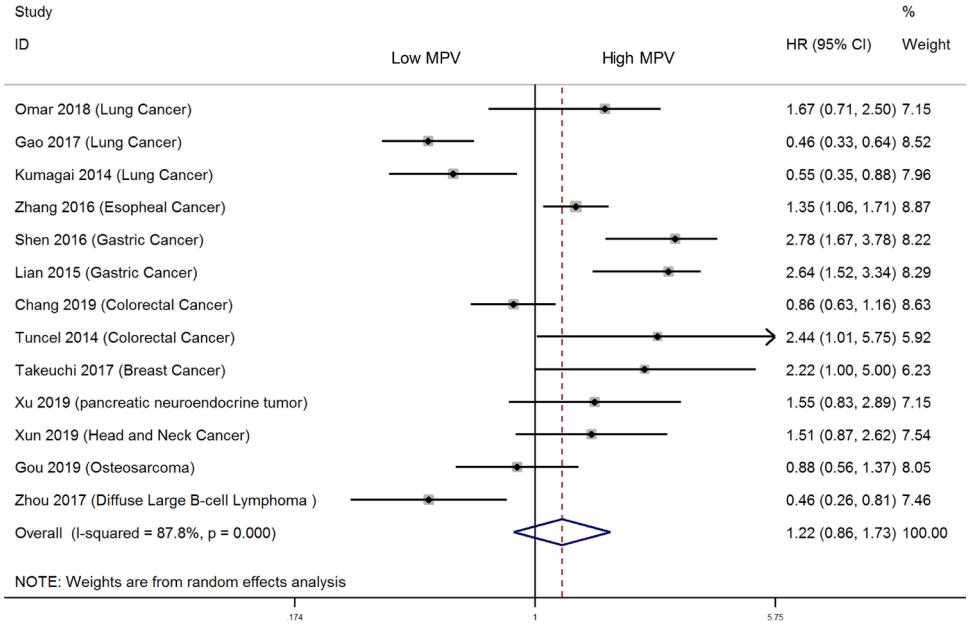

Figure 4 The forest plot between MPV level and DFS in patients with cancer. Results are presented as individual and pooled HRs with 95% CIs. HR>1 indicates worse overall survival for the group. DFS, disease-free survival; MPV, mean platelet volume.

Table 3 Association between MPV level and clinicopathological parameters

Clinical features	No of studies	No of patients	Model	OR (95% CI)	P value	Heterogeneity $I^{2,\%}$	Heterogeneity P_H value
Age (older vs younger)	13	2968	Fixed	0.96 (0.90 to1.02)	0.155	25.40	0.188
Sex (male vs female)	17	4077	Fixed	1.04 (1.00 to 1.09)	0.077	0.00	0.533
Depth of invasion (T1+T2 vs T3+T4)	10	2420	Random	0.90 (0.77 to 1.04)	0.149	78.10	0
Tumour stage (I/II vs III/IV)	11	2425	Random	0.91 (0.78 to 1.07)	0.257	78.90	0

MPV, mean platelet volume; P_H, p values of Q test for heterogeneity test.

of lifestyles and various diseases like smoking,[56 57] hypertension,[58 59] diabetes,[60 61] dyslipidaemia and obesity,[62 63] cardiocerebrovascular 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 tumours are accompanied by systemic inflammatory response.[68 69] Numerous inflammatory cytokines (eg, interleukin-1, IL-1, IL-6 and tumour necrosis factor-α, TNF-α) 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 tumour microcirculation and coat circulating tumour cells to protect tumour cells from shear stress and the host's immune response,[5] which promote tumour 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 proinflammatory 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, tumour cells release TNF-α, IL-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.

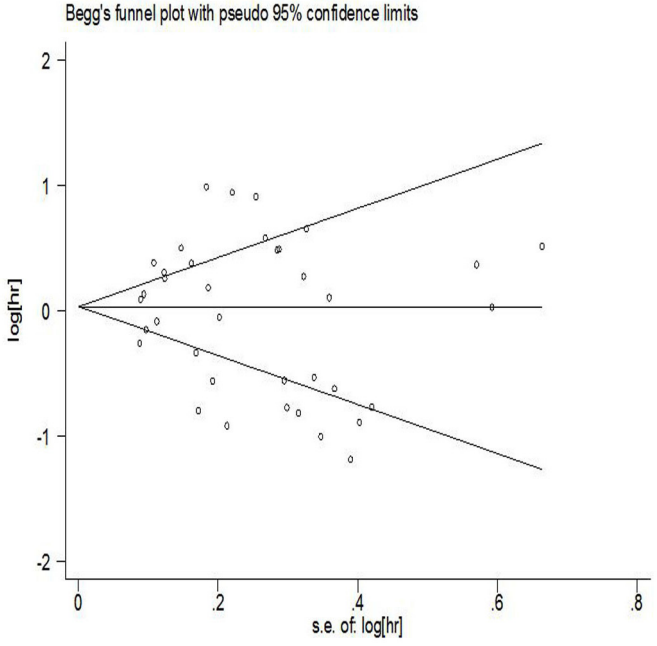

Figure 5 Begg's funnel plot of publication bias test for OS in patients with cancer. No significant publication bias for studies evaluating the association between MPV level and os was observed. MPV, mean platelet volume; OS, overall survival.

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 tumour 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 patients with cancer and no relation with age, sex, tumour size, depth of invasion and tumour 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 tumours 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 patients with cancer.

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Funding The work was supported by Youth Research Fund Project of the Health and Family Planning Commission of Nantong (QA2019028), Guiding Project of Nantong Municipal Science and Technology Plan (JCZ19110).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. 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'.

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