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Feasibility of mean platelet volume as a biomarker for chronic obstructive pulmonary disease: A systematic review and meta-analysis

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Abstract

Objective: To evaluate the feasibility of mean platelet volume (MPV) as a biomarker for chronic obstructive pulmonary disease (COPD).

Methods: A systematic search for studies published up to March 2019 was performed in the PubMed and Web of Science databases. Three independent investigators screened the titles and abstracts of including studies according to eligibility criteria. The Newcastle–Ottawa Scale was used to assess the quality of eligible studies, and statistical analyses were performed using Review Manager version 5.3.

Results: A total of eight studies with 1230 COPD patients and 443 healthy controls were included in our meta-analysis. No significant differences in MPV level were identified in pairwise comparisons of the acute exacerbations of COPD (AECOPD), stable COPD, and control groups. Furthermore, no significant correlation was observed between MPV level and systemic inflammatory biomarkers.

Conclusions: MPV does not appear to represent a suitable biomarker of disease phase or inflammatory burden in COPD. However, future large-scale studies should be performed to further investigate the relationship between MPV and COPD.

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Keywords
Chronic obstructive pulmonary disease, mean platelet volume, biomarker, inflammation, acute exacerbations, meta-analysis

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation attributable to airway and/or alveolar abnormalities, and is typically caused by significant exposure to noxious particles or gases.[1] Given that its high prevalence, morbidity, and mortality present a formidable challenge to health-care systems, COPD is in high focus worldwide.[2] COPD has been reported to represent the third leading global cause of death, and affected approximately 63 million individuals during 1990–2010.[3] COPD can be further aggravated by acute exacerbations (AECOPD), particularly in patients with severe disease, and up to 78% of AECOPD cases are attributable to bacterial and/or viral infection.[4]

Mean platelet volume (MPV) is an important component of routine blood analysis and correlates highly with platelet activation,[5] which is linked to the pathophysiology of diseases prone to inflammation.[6] Inflammation plays an important role in COPD, and the degree of inflammation increases with the severity of disease as classified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[7] Moreover, platelet activation is a high-risk factor for cardiovascular disease (CVD), which is regarded as a common comorbidity of COPD. Previous studies have shown that MPV may represent an inflammatory marker for multiple conditions such as CVD, cerebrovascular disease, rheumatoid disease, and diabetes mellitus.[8–11] Although several studies have explored the relationship between MPV and COPD, the conclusions of these studies are not aligned. We therefore performed a meta-analysis among relevant studies to clarify the relationship between MPV and COPD. Our findings may provide a reference for the use of MPV as a biomarker for COPD.

Methods

Database and literature search strategy

A systematic search of all papers published up to March 2019 was performed in the PubMed and Web of Science databases. We used key words and free text to search with the following terms: ('pulmonary disease, chronic obstructive' or 'chronic obstructive pulmonary disease' or 'COPD' or 'COAD' or 'chronic obstructive airway disease' or 'chronic obstructive lung disease' or 'airflow obstruction, chronic' or 'airflow obstructions, chronic' or 'chronic airflow obstructions' or 'chronic airflow obstruction') and ('mean platelet volume' or 'MPV'). Language restrictions were not applied during the database search.

Eligibility criteria

Studies that met the following criteria were included: (1) observational studies which the full-text manuscript was available; (2) diagnosis of COPD according to the GOLD criteria; (3) inclusion of at least one COPD group (stable COPD group

and/or AECOPD group) and one healthy control group; (4) MPV evaluation during the stable phase of COPD or after admission for AECOPD; (5) inclusion of the specific value of MPV as mean ± standard deviation (SD).

Data extraction and quality assessment

Three independent investigators screened the titles and abstracts of studies according to the eligibility criteria, and the full texts of potentially eligible studies were subsequently reviewed. Disagreements among the investigators were resolved by discussion. The following characteristics were extracted for eligible studies: first author, publishing year, country/territory, study type, study group, sample size, age, sex, MPV level and forced expiratory volume in the first second (FEV1). Primary outcomes included MPV level in the AECOPD group compared with the healthy control group, MPV level in the stable COPD group compared with the healthy control group, and MPV level in the stable COPD group compared with the AECOPD group. Secondary outcomes were correlations between MPV level and levels of systemic inflammatory biomarkers such as white blood cells (WBC), C-reactive protein (CRP), high-sensitivity C-reactive protein (hsCRP), and neutrophils. The Newcastle–Ottawa Scale (NOS) was used to assess the quality of included studies.[12] Studies with a total score of 6 or more were considered of high quality, and only high-quality studies were included in this meta-analysis.

Statistical analysis

We expressed continuous variables as mean ± SD with 95% confidence interval (CI) and categorical variables as number (N) or percentage (%). To assess heterogeneity among the studies, Cochrane's Q statistic and the I^2 statistic were calculated. Studies with $P < 0.10$ for Cochrane's Q statistic or $\geq 50\%$ for the I^2 statistic were regarded as having high heterogeneity. A random-effects model was used when heterogeneity was high. Fisher's z transformation was used to transform correlation coefficients (r) between MPV levels and systemic inflammatory biomarkers to z, which is considered as the normal distribution.[13] Subgroup analysis was conducted based on whether self-control existed in each study. To evaluate whether overall outcomes were significantly affected by an independent study, a sensitivity analysis was carried out by analyzing the remaining studies after eliminating those with the highest or lowest weight. Evaluation of publication bias was not performed because of the limited number of studies included. All statistical analyses were performed using Review Manager version 5.3 (Cochrane Collaboration, Baltimore, MD, USA).

Results

Literature search

Our initial search yielded a total of 106 articles with 28 duplications. After screening the titles and abstracts of the 78 unique manuscripts, 64 were excluded for lack of relevance (60) or inappropriate publication type (conference abstracts (2) and letters (2)). Five studies were rejected during further full-text review; two studies were excluded because the full text was unavailable, two studies had no healthy control group, and in one study the specific value of MPV was not expressed as mean ± SD. The eight remaining studies were included in this meta-analysis. The flow diagram of study identification, inclusion, and exclusion is shown in Figure 1.

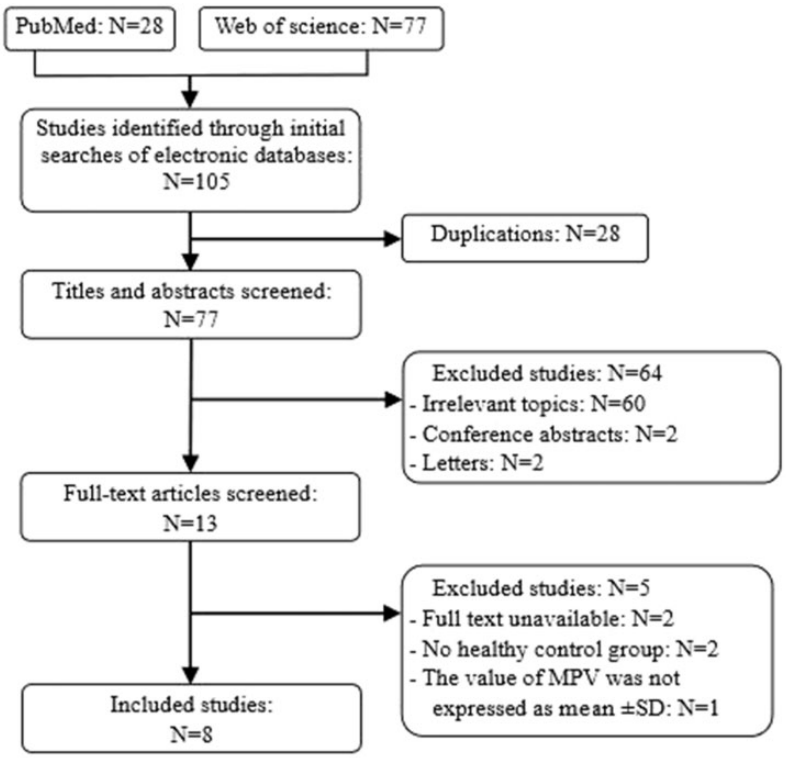

Figure 1. Flow diagram of the identification, inclusion, and exclusion of studies. MPV, mean platelet volume; SD, standard deviation.

Characteristics of included studies

The eight eligible studies included 1230 COPD patients and 443 healthy controls, were published from 2012 to 2016, and were conducted in Turkey, China, Greece, and Italy.[14–21] All studies had a observational design and four were self-controlled, meaning that the AECOPD and stable COPD groups came from the same population.[14,15,17,18] One study reported MPV values only in a stable COPD group and a healthy control group,[16] while the other studies reported MPV values in three groups (AECOPD, stable COPD, and control). Basic characteristics such as sample size, age, sex, and FEV1 are shown in Table 1.

Quality assessment

Quality assessment using the Newcastle–Ottawa Scale (NOS) is shown in Table 2. The total score for each included study was at least 6 and the average score was 7.25, meaning that the quality of studies included in this meta-analysis was high.

Primary outcomes

MPV level in the AECOPD group vs the stable COPD group. Figure 2 shows a forest plot for MPV level in the AECOPD group compared with the stable COPD group. The MPV level was lower in AECOPD patients than in stable COPD patients, although the difference was not statistically significant

Table 1. Summary of basic characteristics of studies included in the meta-analysis.

First author	Year	Country	Study group	Sample size	Age (mean ± SD, years)	Sex (male %)	MPV level (fl)	FEV1 (% predicted)
Ulasli [17]	2012	Turkey	AECOPD/Stable COPD/Control	47/47/40	70.6 ± 10/70.6 ± 10/ 68.7 ± 9.2	78.7/78.7/65	8.5 ± 1.03/ 9.3 ± 1.3/ 9.3 ± 0.8	54.5 ± 24.5/ 54.5 ± 24.5/ 123 ± 14.2
Wang [18]	2013	China	AECOPD/Stable COPD/Control	70/70/70	69 ± 4/69 ± 4/ 68 ± 5	60/60/57	9.5 ± 0.9/ 9.8 ± 0.9/ 10.4 ± 1.1	34.5 ± 12.6/ 45.6 ± 16/88 ± 9.9
Steiropoulos [19]	2012	Greece	Stable COPD/ Control	NA/85/34	NA/71.5 ± 9.8/ 60 ± 5.5	NA/90.6/50	NA/10.69 ± 1/ 9.96 ± 1.1	NA/42.2 ± 17.66/ 98.57 ± 16.66
Zhang [20]	2015	China	AECOPD/Stable COPD/Control	90/90/90	63 ± 7/63 ± 7/ 62 ± 7	78.9/78.9/77.8	11.4 ±1.45/ 10.3 ± 1.24/ 9.89 ± 1.19	NA/50.3 ± 13.2/ 85.7 ± 5.75
Agapakis [21]	2015	Greece	AECOPD/Stable COPD/Control	81/81/37	65.3 ± 11.1/69 ± 4/ 68 ± 5	78.7/78.7/72.4	8.5 ± 0.9/ 9.3 ± 1.3/ 9.1 ± 0.9	47.5 ± 15.9/ 54.7 ± 17.7/ 121.1 ± 11.3
Karadeniz [22]	2016	Turkey	AECOPD/Stable COPD/Control	50/60/50	66.9 ± 11.05/ 68.42 ± 9.74/ 67.6 ± 7.8	88/66.7/76	8.36 ± 0.72/ 9.56 ± 1.07/ 10.06 ± 0.84	39.12 ± 17.03/ 55.62 ± 18.24/NA
Malerba [23]	2016	Italy	AECOPD/Stable COPD/Control	75/403/72	74.26 ± 7.8/ 74.26 ± 7.8/ 75.83 ± 9.19	60/64/60	8.9 ± 1/8.7 ± 1/ 8.44 ± 0.78	26.3 ± 16.9/ 48.6 ± 16.9/ 98 ± 1.2
Gunay [24]	2013	Turkey	AECOPD/Stable COPD/Control	91/178/50	67.26 ± 9.49/ 65.06 ± 7.92/ 64.96 ± 5.46	65.9/70.8/60	8 ± 2.2/8.8 ± 2.1/ 10.1 ± 1.9	48.5 ± 29/ 54.5 ± 27 /NA

Note: SD, standard deviation; MPV, mean platelet volume; FEV1, forced expiratory volume in the first second; COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; NA, not available.

Table 2. Quality assessment of studies included in the meta-analysis according to the Newcastle–Ottawa Scale.

	Selection				Comparability	Exposure			
Study	Case definition adequate	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total score
Ulasli [17]	–	–	0	0	–	–	–	–	6
Wang [18]	–	–	0	0	2	–	–	–	7
Steiropoulos [19]	–	–	0	–	2	–	–	–	8
Zhang [20]	–	–	0	0	2	–	–	–	7
Agapakis [21]	–	–	0	0	2	–	–	–	7
Karadeniz [22]	–	–	0	–	2	–	–	–	8
Malerba [23]	–	–	0	–	2	–	–	–	8
Gunay [24]	–	–	0	0	2	–	–	–	7

(MD=−0.37, 95%CI [−0.93, 0.20]). The random-effects model was used as high heterogeneity was observed among the studies.

MPV level in the AECOPD group vs the control group. MPV level in the AECOPD group was lower than that in the control group, but the difference between the two groups was not statistically significant (MD = −0.58, 95%CI [−1.43, 0.27]; random-effects model). The result was demonstrated in Figure 3.

MPV level in the stable COPD group vs the control group. Figure 4 shows a forest plot for MPV level in the stable COPD group compared with the control group. No significant difference was found between the two groups (MD = −0.08, 95%CI [−0.45, 0.30]; random-effects model).

Secondary outcomes

Table 3 illustrates the correlation coefficient (r) and Fisher's Z value between MPV level and systemic inflammatory biomarkers. Five studies reported the correlation between MPV and WBC. The Z value in the AECOPD group was −0.16 (95%CI [−0.51, 0.20]; random-effects model), and the r value using reverse Fisher's z transformation was −0.159 [Figure 5]. The Z value in the stable COPD group was 0.10 (95%CI [−0.08, 0.29]; random-effects model) and the r value using reverse Fisher's z transformation was 0.10 [Figure 6]. The results indicate that there was no significant correlation between MPV and WBC in either the AECOPD or the stable COPD group.

Among the included studies, Wang et al.[15] reported a negative correlation between MPV level and log- transferred CRP in both an AECOPD and a stable COPD group. Zhang et al.[17] reported that MPV levels were positively correlated with hsCRP in both AECOPD and stable COPD groups. Agapakis et al.[18] showed that there

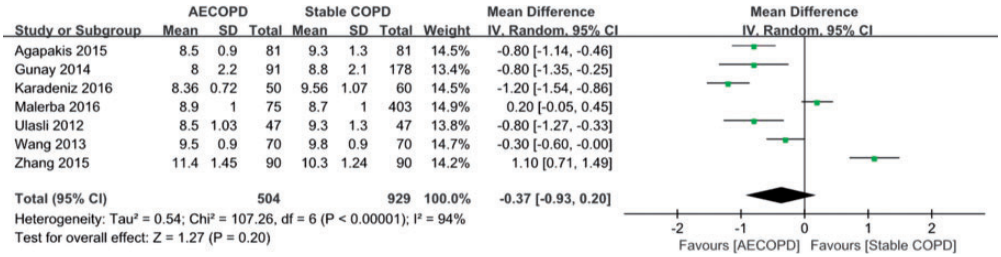

Figure 2. Forest plot for mean platelet volume (MPV) level in the AECOPD group compared with the stable COPD group.

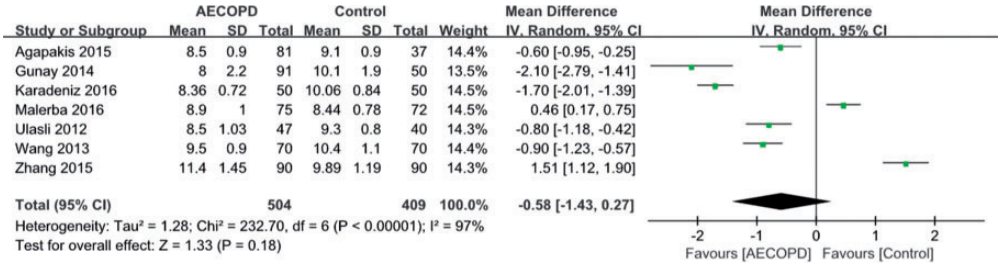

Figure 3. Forest plot for mean platelet volume (MPV) level in the AECOPD group compared with the healthy control group.

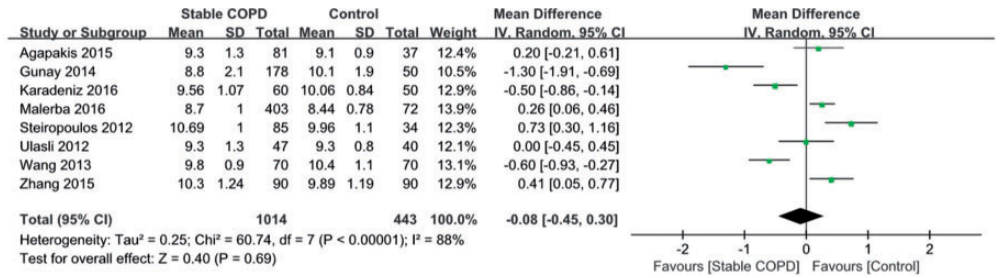

Figure 4. Forest plot for mean platelet volume (MPV) level in the stable COPD group compared with the healthy control group.

were negative correlations between MPV level and CRP/neutrophil levels in the AECOPD group.

Subgroup analysis

Four studies were self-controlled, with MPV levels evaluated during both stable periods and acute exacerbations in the same population. We divided all studies into two subgroups based on whether they were self-controlled or not and respectively analyzed studies from different subgroups. No significant difference was found for either subgroup (self-controlled: MD= −0.20, 95%CI [−1.02, 0.63]; random-effects

Table 3. Correlation coefficient and Fisher's Z value between MPV level and systemic inflammatory biomarkers.

First author	Study group	Sample size	r value of correlation	Fisher's Z value
Wang [18]	AECOPD	n = 70	r(MPV−WBC) = −0.265; r(MPV−logCRP) = −0.371	Z(MPV−WBC) = −0.271; Z(MPV−logCRP) = −0.39
	Stable COPD	n=70	r(MPV−WBC) = 0.018^{NS}; r(MPV−logCRP) = −0.177	Z(MPV−WBC) = 0.018; Z(MPV−logCRP) = −0.179
Steiropoulos [19]	Stable COPD	n = 85	r(MPV−WBC) = 0.312	Z(MPV−WBC) = 0.323
Zhang [20]	AECOPD	n = 90	r(MPV−WBC) = 0.265; r(MPV−hsCRP) = 0.498	Z(MPV−WBC) = 0.271; Z(MPV−hsCRP) = 0.546
	Stable COPD	n = 90	r(MPV−WBC) = -0.085^{NS}; r(MPV−hsCRP) = 0.317	Z(MPV−WBC) = −0.085; Z(MPV−hsCRP) = 0.328
Agapakis [21]	AECOPD	n = 81	r(MPV−WBC) = −0.5; r(MPV−CRP) = −0.4; r(MPV−N) = −0.4	Z(MPV−WBC) = −0.549; Z(MPV−CRP) = −0.424; Z(MPV−N) = −0.424
Karadeniz [22]	AECOPD	n = 50	r(MPV−WBC) = -0.06^{NS}	Z(MPV−WBC) =−0.06
	Stable COPD	n = 60	r(MPV−WBC) = 0.16^{NS}	Z(MPV−WBC) =0.161

MPV, mean platelet volume; r, correlation coefficient; Z, the value of r after Fisher's Z transformation; COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; WBC, white blood cell; CRP, C-reactive protein; logCRP, log-transformed C-reactive protein; hsCRP, high-sensitivity C-reactive protein; N, neutrophil; NS, no significance.

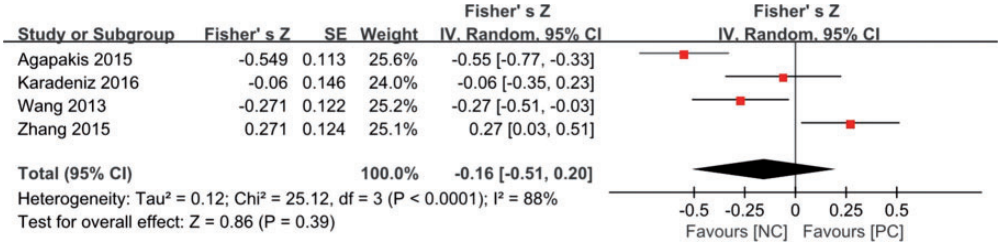

Figure 5. Forest plot for correlation coefficient (r) between mean platelet volume (MPV) level and white blood cells (WBC) in the AECOPD group. Z, value of r after Fisher's Z transformation; SE, standard error; NC, negative correlation; PC, positive correlation; r' = −0.159 (using reverse Fisher's Z transformation).

model; not self-controlled: MD= −0.59, 95%CI [−1.58, 0.39]; random-effects model). The results of this analysis are shown in Figure 7.

Sensitivity analysis

In contrast with our original results, the removal of studies with the highest or lowest weight had no effect in the sensitivity analysis, indicating that the overall outcomes of our meta-analysis were robust.

Discussion

We performed a meta-analysis in eight studies that included 1230 COPD patients and 443 healthy controls to explore the relationship between MPV and COPD. We found no significant differences in pairwise

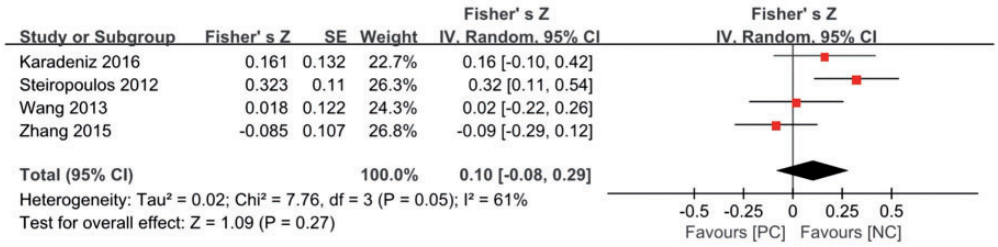

Figure 6. Forest plot for correlation coefficient (r) between mean platelet volume (MPV) levels and white blood cells (WBC) in the stable COPD group. Z, value of r after Fisher's Z transformation; SE, standard error; NC, negative correlation; PC, positive correlation; r' = 0.10 (using reverse Fisher's Z transformation).

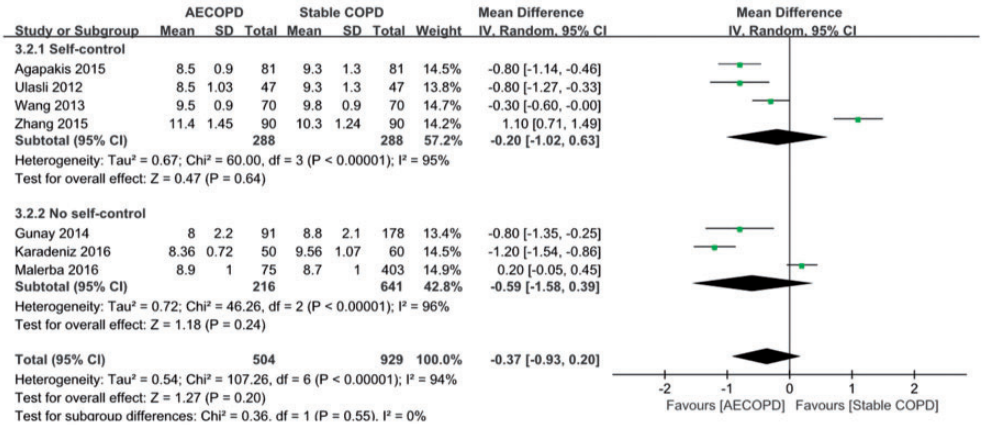

Figure 7. Forest plot for subgroup analysis of mean platelet volume (MPV) level in the AECOPD group compared with the stable COPD group based on whether studies were self-controlled.

comparisons of the three groups (AECOPD, stable COPD, and control). Furthermore, no significant correlation was observed between MPV and WBC, although a potential correlation may exist between MPV and CRP/hsCRP/neutrophils that warrants further investigation.

COPD is characterized by low-grade systemic inflammation, and selected inflammation biomarkers can be used to improve the ability of established clinical variables to predict exacerbation and mortality in COPD.[22] Previous studies have shown that an increased risk for exacerbation in patients with stable COPD is strongly associated with increased levels of inflammatory biomarkers such as CRP, tumor necrosis factor-alpha (TNF-alpha), interleukin 6 (IL-6), and interleukin 8 (IL-8).[23,24] Chronic inflammation is linked to platelet activation,[6] as overproduction of proinflammatory cytokines can promote the release of small-sized platelets by interfering with megakaryopoiesis and enhancing oxidative stress, which may lead to platelet activation.[25,26] MPV is a useful index to reflect platelet activation, and has been considered as an inflammatory biomarker in multiple diseases as correlations exist between MPV and CRP, erythrocyte sedimentation rate,

and other inflammatory biomarkers.[10,27–30] Kisacik et al.[10] reported that assessment of MPV may provide additional information about inflammation in ankylosing spondylitis and rheumatoid arthritis. Wang et al.[27] found that a decreased level of MPV was related to severe periodontal inflammation, and that MPV might reflect the disease activity of periodontitis. Furthermore, MPV may also be considered a marker of inflammatory burden in patients with type 2 diabetes mellitus and obesity.[28,29]

The findings of our meta-analysis, however, indicate that MPV is not an appropriate biomarker for discriminating between patients with stable COPD, those with acute exacerbations, and those who do not have COPD. Our study therefore draws different conclusions from those of previous independent studies. These differences may be attributable to the limited sample sizes of studies, meaning that the accuracy of conclusions may not be sufficiently robust. Furthermore, MPV can be affected by multiple factors and should be assessed in parallel with other inflammatory markers.[31] Risk factors including smoking, hypertension, dyslipidemia, and diabetes can also influence MPV,[6] as can comorbidities with inflammatory conditions.[8–11] Nevertheless, the interfering factors and comorbidities examined in previous studies have not been entirely consistent.

Some previous studies have reported a lack of significant correlation between MPV level and stage of stable COPD.[14,32] Ulasli et al.[14] also found no significant differences among various stages of COPD during exacerbation. These results indicate that MPV cannot distinguish disease severity among COPD patients and therefore might not represent a suitable biomarker for COPD.

Patients with COPD inevitably have comorbidities, the most common of which are CVD, lung cancer, metabolic disorder, osteoporosis, anxiety and depression, skeletal muscle dysfunction, and other respiratory conditions.[33] CVD in particular is a high-risk factor that may increase the mortality of COPD.[34] Patients with COPD are more likely to be diagnosed with CVD, including a two-to-five times higher risk of ischemic heart disease, cardiac dysrhythmia, heart failure, diseases of the pulmonary circulation, and diseases of the arteries.[35] There is thus a critical need to develop strategies to screen for and reduce cardiovascular risks that accompany COPD.[35] Platelets play an important role in the course of CVD, and the monitoring of platelet function in COPD patients is therefore necessary to evaluate cardiovascular risk. Moreover, thrombosis exists in many COPD patients in the form of pulmonary embolism or deep vein thrombosis, both of which are associated with platelet activation.[36] Taken together, MPV is a common clinical index and its level warrants close consideration in patients with COPD.

Our study had some limitations. First, the meta-analysis involved eight observational studies and no randomized controlled trials with a high level of evidence. Second, given the inclusion of few studies, heterogeneity among studies was high and publication bias was not evaluated. Furthermore, sample sizes within some of the studies were small, meaning that statistical power may have been insufficient. Additional studies with larger sample sizes and sufficient control of potential interfering factors (such as sex, age, pulmonary function, and smoking status) should be undertaken to further explore our findings.

To our knowledge, this study is the first meta-analysis to explore the relationship between MPV and COPD. We comprehensively searched the PubMed and Web of Science databases using appropriate eligibility criteria to ensure the quantity and quality of included studies. The quality of studies included in this meta-analysis was

high, and subgroup and sensitivity analysis were performed to minimize heterogeneity, resulting in robust outcomes of significant reference value.

Conclusion

Our findings show that there were no significant differences in pairwise comparison of the AECOPD, stable COPD, and control groups in this meta-analysis. MPV may not represent a suitable biomarker of disease phase or inflammation burden in patients with COPD. Further large-scale, well-designed studies are needed to further investigate the relationship between MPV and COPD.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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