Diagnostic Role of Mean-Platelet Volume in Acute Pulmonary Embolism: A Meta-analysis and Systematic Review

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ABSTRACT

BACKGROUND: Acute pulmonary embolism (PE) is the third most fatal cardiovascular disease. PE is frequently misdiagnosed due to its clinical presentation's heterogeneity and the inexistence of biomarkers for its immediate diagnosis. Mean platelet volume (MPV) has shown a potential role as a biomarker in acute PE. In this analysis, we aimed to systematically compare the MPV in patients with and without definite diagnosis of PE, in emergency departments.

METHODS: Embase, PubMed and Medline were searched for relevant publications, in English. The main inclusion criteria were studies which compared MPV in patients with acute PEA versus a control group.

RESULTS: Thirteen studies consisting of a total number of 2428 participants were included. Of the participants included, 1316 were patients with confirmed acute PE, and 1112 were assigned to the control group. MPV was significantly higher in patients with acute PE than in controls (RR: 0.84, 95% CI: 0.76 – 0.92; $P < .00001$). There was a significant heterogeneity in the data.

CONCLUSIONS: This analysis showed higher MPV to be associated with acute PE immediate diagnosis. These data show promise for the use of MPV as a readily available biomarker for the diagnosis of acute PE at the emergency department.

KEYWORDS: MPV, mean platelet volume, thrombosis/embolism, biomarker, coagulation, pulmonary embolism

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Introduction

Pulmonary embolism (PE) is the third most fatal cardiovascular disorder. The main contributing factor is a persistently high and increasing incidence of PE cases in the general population, with around 0.4 symptomatic cases per 1.000 person-years.[1]

Fatality rates of PE are still unacceptably high and are responsible for a short-term case fatality rate of 3.9% to 12%[1-4] among clinically recognizable cases, not to mention the sudden death clinical presentation cases, that may represent 20% to 25% of all PE cases.[5,6] As these events can be silent and misdiagnosed, an early and accurate diagnosis of acute PE is vital for initiating emergent directed therapy and preventing deaths. The delay in the diagnosis of acute PE is a common feature of the disease as almost one third of patients are diagnosed only after 5 days from the onset of symptoms,[7] equally divided between patient delays in getting medical care and long time from medical assistance to diagnosis. The heterogeneity and lack of specific symptoms and signs of PE clinical presentation may contribute to the physicians' attributable delay to diagnosis alongside limited access to the definite diagnostic test, only assured by the pulmonary CT scanning.[8] The current diagnostic approach to acute PE, entailing a laborious and non-specific integration of clinical judgment, laboratory D-dimers results and diagnostic imaging, could be revolutionized by the discovery of new sensitive and readily available biomarkers.

In recent years, platelet indices have been studied on cardiovascular diseases, and an elevated mean platelet volume (MPV), in particular, has been associated with coronary artery disease and with cardiovascular risk factors, of which diabetes and metabolic syndromes gathered the most evidence.[9-11] Although MPV value is automatically available to the prescribing physician from any ordinary electronic blood cell count, this parameter is only exceptionally used in the clinical practice. Nevertheless, recent attentions have focused on MPV as a potential diagnostic and prognostic biomarker in several conditions.[12] A recent meta-analysis reported a higher value of MPV in deep vein thrombosis patients, compared to control groups, but it included studies with mixed deep vein thrombosis and pulmonary embolism populations, and heterogenous clinical presentations such as acute and non-acute phases of the diseases.[13] Contradictory results and shortness of studies justify why the role of MPV in diagnosing acute PE is still uncertain and, therefore, undervalued in clinical practice.

This study aims to systematically review publications on MPV determinations in acute PE patients and to conduct a meta-analysis on differences of MPV between acute PE

patients and controls. We hypothesized that MPV is increased in patients with acute PE.

Methodology

Protocol

This systematic review and meta-analysis were conducted by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendation[14] (Supplementary Material).

Clinical question

The PICO model was used to define our clinical question: **Population** – Clinical studies of patients with acute PE; **Intervention** – MPV detected by any laboratory method; **Comparison** – Control patients who are (1) Emergency department controls (ruled out for acute PE diagnosis after imaging tests), or (2) Non-emergency department controls (inpatient or outpatient clinic patients without acute PE suspicion, or healthy); **Outcome measure** – Primary outcome: effect size (MPV in acute PE patients compared to controls). Secondary outcomes: assessment of quality and heterogeneity between studies.

Study design

All study types in which MPV was measured and compared to a control.

Search strategy and data extraction

A highly sensitive search strategy was conducted in EMBASE, PubMed and Medline without date restrictions. The keywords used for systematic searches were deep vein thrombosis, pulmonary embolism (PE), and MPV. Search terms were (Pulmonary Embolism [MeSH] OR Venous Thrombosis [MeSH] OR Venous Thromboembolism [MeSH]) AND (Mean Platelet Volume [MeSH] OR Blood Platelets [MeSH]). The last search was performed on 02/03/2020 and we re-ran the searches at final analyses' procedures.

Study selection and inclusion criteria

We looked for studies assessing the measurement of MPV for acute PE in adult patients. Two independent reviewers (the authors) conducted title and abstract screening procedures of the initial search results and independently evaluated eligibility of the retrieved articles. Only those in which MPV was measured at the exact moment of the acute PE provisional diagnosis and whose PE diagnosis was confirmed by contrast thoracic angiographic tomography were finally included for analysis. This review was limited to studies comparing acute PE patients with control individuals, and only included studies where the association of MPV and acute PE was explicitly investigated.

Study selection and data collection process

The titles of publications were independently reviewed by the authors and eligible abstracts were evaluated, in a standardized manner. The studies fulfilling the inclusion criteria were full-text read and finally selected for inclusion in the analysis. Further studies identified through references were equally evaluated. Lack of consensus between authors were solved through discussion and there was no need of a third reviewer's moderation.

Data items

Data extracted from each study included: authors, year of publication, type of population (emergency department patients, or other clinical settings), type of study, number of patients and controls, characterization of controls (recruitment and inclusion criteria), age of patients and controls, MPV measurement method, and values of MPV for patients and controls.

Quality assessment

Quality assessment of the observational retrospective and prospective studies was carried out by the Newcastle-Ottawa scale (NOS)[15] where scores were attributed in number of stars quantitatively related to positive parameters.

Risk of bias and applicability were evaluated in Review Manager (RevMan 5.3, The Cochrane Collaboration, Oxford, UK). Domains were graded as low risk, high risk, or uncertain risk respecting biases. The studies were stratified in terms of risk of bias: low risk, when a maximum of 1 domain was "uncertain" or "high"; moderate risk when 2 or 3domains were "uncertain" or "high"; and high risk when at least 4 domains were "uncertain" or "high."[16]

Statistical analysis

Standardized mean differences (SMDs) were considered for MPV within each study. SMD > 0 demonstrates an increased level of MPV.

Heterogeneity across studies was quantified using the I^2 statistics and an $I^2 \geqslant 50\%$ pointed to significant heterogeneity.[17] Publication bias was analyzed trough Egger's Regression test and bias visualization was assessed using funnel plot.

Statistical analysis was carried out by the RevMan (software version 5.3) and R (software version 3.6.1, package "metaphor" and "PRROC"). The data are expressed as a value (95% confidence interval [CI]). $P < .05$ was considered statistically significant.

Results

Study selection

From a total of 42 studies, we isolated 13 studies which fulfilled all the inclusion criteria and had complete data on MPV values

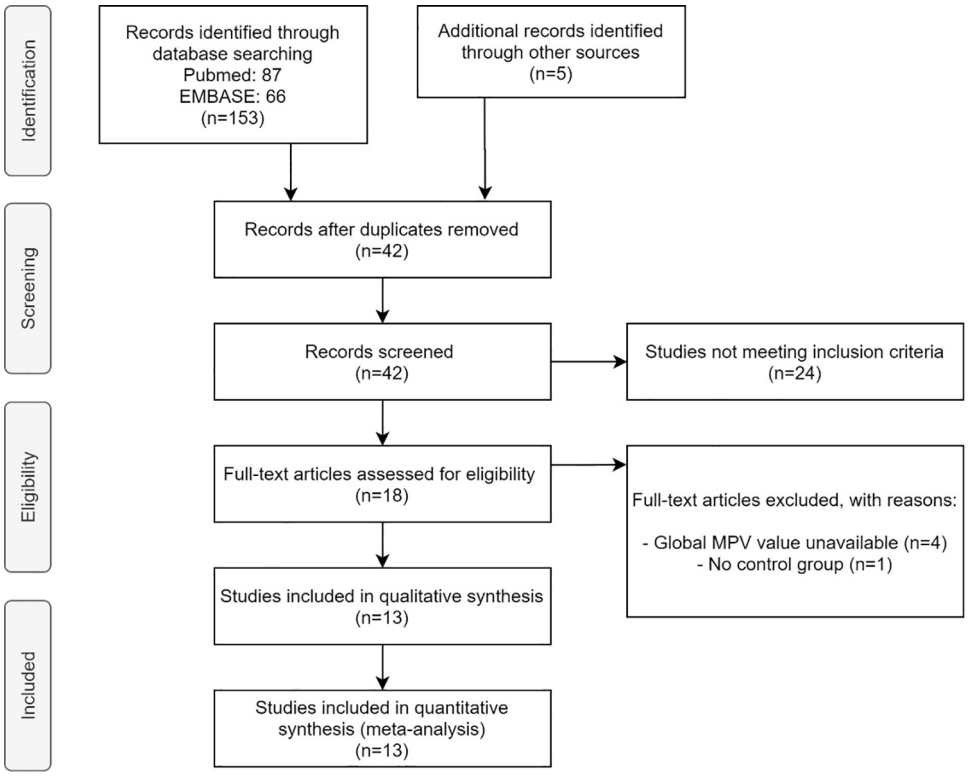

Figure 1. Search process.

at the time of acute PE diagnostic hypothesis for a patients' group. The complete searching process is shown in Figure 1.

Study characteristics

A total of 13 studies were included in the meta-analysis[18,19,20-30]. There were 4 prospective cohort studies and 9 retrospective case-control studies for a total of 2428 participants, including 1316 patients and 1112 controls. In 7 studies, controls were specified as patients presenting suspected pulmonary embolism, although not confirmed after imaging tests results, which represented 576 individuals of the control group. The other control sub-groups were represented by healthy adults (229 individuals) or other emergency department patients (307 patients). 11 studies were performed in an emergency department and 1 study was conducted in the hospital ward. Only 1 study did not specify the clinical department.

Risk of bias within studies

No publication bias was identified through Egger's test (P = .696), and low evidence of publication bias was observed through a funnel plot, as shown in Figure 2.

Quality assessment

The overall assessment of the 13 studies revealed a classification of 5 or more stars in 11 studies (Table 1), but only 2 studies included healthy and community controls (the same studies) and none was blinded to cases.

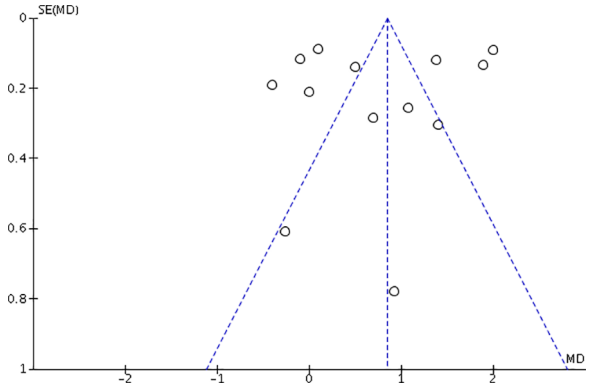

Figure 2. Begg's funnel plot – Publication bias.

Results for MPV

Meta-analysis of acute PE versus controls using standard mean difference found an effect estimate of 0.84 (95% CI: 0.76–0.92) and a Z-score of 20.25 ($P < .00001$) demonstrating a significant increase in MPV of patients with acute PE compared to controls (Figure 3). However, Chi^2 was 439.06 and I^2 was 97%, showing significant heterogeneity in this dataset.

ROC curve analysis

The ROC curve analysis of MPV when predicting acute PE were constructed on an exploratory basis (Supplementary Material). The optimal cut-off values for MPV when predicting acute PE was 8.5 fl (sensitivity 80%; specificity 60%).

Table 1. General properties and MPV features of the studies.

STUDY	DEPARTMENT	CONTROLS	TOTAL (N)	ACUTE PE (N)	CONTROLS (N)	MPV ACUTE PE (MEAN)	MPV CONTROLS (MEAN)	NOS
Gunay	ER and outpatient clinic	Healthy	113	63	50	10.92 ± 1.37	10.23 ± 1.61	✷✷✷✷✷
Hilal	ER	Other ER	371	209	162	8.0 ± 1.1	7.9 ± 0.59	✷✷✷✷✷✷
Huang	Non specified	Non specified	145	70	75	9.91 ± 1.4	8.84 ± 1.68	✷✷✷
Icli	ER and outpatient clinic	Suspected DVT, ruled out	293	98	98	9.9 ± 0.6	7.9 ± 0.7	✷✷✷✷✷✷✷✷
Kostrubiec	Wards	Ophtalmologic and HTN	292	192	100	10 ± 1.2	10.1 ± 0.8	✷✷✷✷✷✷✷✷
Moharamzadeh	ER	Suspected DVT, ruled out	173	125	48	10.38 ± 8.59	9.46 ± 1.11	✷✷✷✷✷
Talay	ER	Suspected DVT not confirmed	315	150	165	9.42 ± 1.22	8.04 ± 0.89	✷✷✷✷✷✷
Varol	ER and outpatient clinic	Suspected cardiac disease	177	107	70	9.9 ± 1.0	8.1 ± 0.8	✷✷✷✷✷✷
Abd El-Hady	ER and outpatient clinic	Suspected DVT, ruled out	70	50	20	8.9 ± 1	7.5 ± 1.2	✷✷✷✷✷
Çevik	ER	Suspected DVT not confirmed	128	61	67	9.73±1.19	10.13 ± 0.94	✷✷✷✷
Erdal In	ER	Healthy	187	108	79	8.9 ± 1.1	8.4 ± 0.8	✷✷✷✷✷✷✷
Farokhi	ER	Suspected DVT, ruled out	141	16	125	8.6 ± 2.39	8.86 ± 1.19	✷✷✷✷✷
Sunnetcioglu	ER	Suspected DVT, ruled out	120	67	53	8.4 ± 1.2	8.4 ± 1.1	✷✷✷✷✷✷

Abbreviations: DVT, deep vein thrombosis; ER, emergency room; HTN, hypertension; MPV, mean platelet value; NOS, NewcastIle-Ottawa scale; PE, pulmonary embolism.

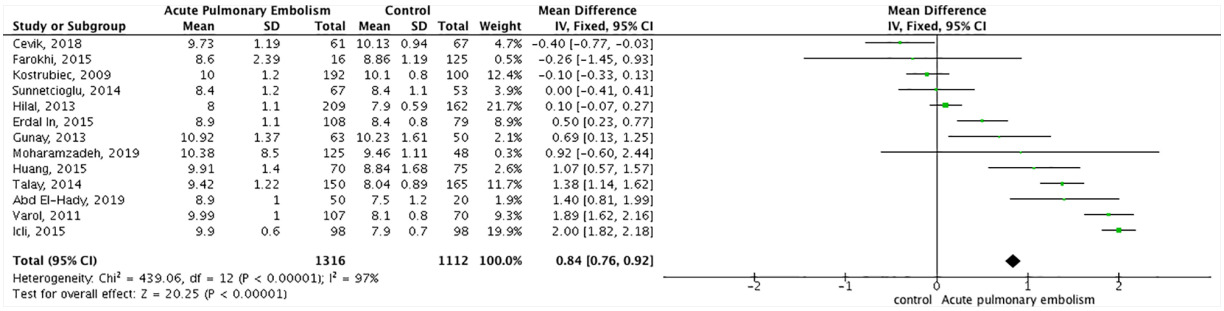

Figure 3. Forest plot for mean platelet volume: acute PE patients versus controls.

Discussion

To our knowledge, this is the first meta-analysis on the MPV values of acute PE at emergency department presentation. Our analysis showed significantly higher MPV in acute PE patients. However, likely due to diverse laboratory methods in MPV measurement, clinical manifestations' heterogeneity in acute PE, and diverse controls, we found substantial heterogeneity and risk of bias across the studies. Furthermore, different time-frames from sampling to storage – which were not documented – may have influenced MPV values. Nonetheless, diagnostic criteria for patient selection did not vary between studies.

Data on the role of MPV in acute PE is misleading. We know that variation of platelet size occurs in different arterial and venous thrombotic conditions, but it is not clear whether the sizing changes are a cause of a pro-thrombotic status or the consequence of the presence of an intra-vascular thrombus, which may lead to an increase of younger and bigger platelets on blood samples. We found the best cut-off value for the predictive value of MPV for acute PE to be 8.5 fl and this can be interpreted as a consequence of increased platelet aggregation.

Along with evidence on the influence of genetic polymorphisms[31] and lifestyle factors[32] on MPV (although these being assumed to contribute to pathogenic mechanisms of cardiovascular diseases known to develop under their influence), studies on acute phases of venous thrombosis rise additional associative hypotheses. MPV has been shown to increase in acute thrombotic conditions after platelet consumption and accelerated platelet turnover,[33] making it a potentially good hyper-acute diagnostic marker for PE. Additionally, inflammatory mediators seem to give feedback to the bone marrow that results in changes towards a higher MPV and prothrombotic phenotype. This reinforces that higher MPV is a consequence of acute thrombosis and may be detected in the beginning of acute PE pathologic processes.[34,35]

The pragmatic question raised with this meta-analysis results is: how can we gather MPV to other variables in the early diagnosis of acute PE?

Some particular aspects deserve special considerations when it comes to biomarkers, and to MPV as an acute PE biomarker specifically. First, technical conditions for MPV determination represent a great amount of results variability. MPV values may be affected by venipuncture and sample storage conditions, indicated by significant different results in samples stored at room temperature for more than a 3-hour period,[36] which corresponds to an easily accepted time-frame of delayed refrigeration for real clinical conditions. Similarly, platelet exposure to EDTA, the uniformly used anticoagulant in clinical laboratories, results in an increase of up to 50% on MPV determinations.[37] In the analytical phase, several other factors contribute to differences in the MPV measurements by different automated analyzers, either impedance or optical counters,[38] and, in our opinion, the daily use of MPV as a diagnostic marker for acute PE shall not precede the optimization of guidelines for its quantification.

Second, we share Norris et al[12] concerns about the small difference on MPV absolute results between both arterial and venous thrombosis patients, and controls. The narrow diagnostic range of MPV for acute PE complicates the definition of unquestionable cut-off values for its use in clinical practice, although this being already the case for d-dimers, the only blood biomarker used to determine PE diagnostic probability before imaging exams. In our opinion, this points out that investigation on the diagnostic efficacy of well-defined MPV measurements for acute PE in an early stage of the disease is justifiable by the present evidence. In summary, we believe that MPV values should not be used as a single diagnostic tool of acute PE. However, this parameter deserves further investigation as a potential biomarker of this potential suddenly fatal event, in the light of clinical probability scores' validation efforts.

Our meta-analysis has certain limitations. First, the majority of studies included represent small and somewhat heterogeneous populations. Although we were very strict to select only absolutely clear acute PE events in the patient's group, we had to accept some heterogeneity of controls. In fact, while some controls were healthy individuals, others were acute patients who presented to an emergency department and were suspected of having acute PE at admission. Even though these varied controls may have had some impact on the studies' results, their exclusion would have implied a significant loss of patients included in the meta-analysis. Second, most of such studies were retrospective, which may have limited their conclusions. Moreover, missing information on counters and technical protocols, on some demographic variables, on risk factors to venous thrombosis, or on time from symptoms to MPV determination, limited our evaluation on clinical heterogeneity. Third, there

was no sufficient available information to conduct robust analyses of cut-off points of MPV for acute PE diagnosis.

The existence of a new biomarker like MPV for the immediate diagnosis of acute PE, available at all emergency departments and other acute and chronic care facilities, even in the prehospital setting, could help to support the clinical decision of immediate administration of anti-coagulants before imaging results become available, thus potentially saving thousands of lives every year, worldwide.

Conclusion

Our systematic review and meta-analysis reveal that MPV may be a promising biomarker for the immediate diagnosis of acute PE. Given the current gap of diagnostic biomarkers of acute PE, further research regarding MPV's utility in this context shall be pursued.

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Supplemental material

Supplemental material for this article is available online.

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