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Review Article

Evaluating the connection between mean platelet volume (MPV) and peripheral arterial disease risk: a meta-analysis

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ABSTRACT

Background: Numerous studies have been conducted to evaluate the role of Mean Platelet Volume (MPV) in relation to Peripheral Artery Disease (PAD). However, the results of these studies have been inconsistent regarding the significance of MPV as an indicator for PAD.
Objective: This meta-analysis aimed to clarify the role of MPV in PAD by collecting and analyzing data from various studies. The goal was to provide a more definitive assessment of whether MPV levels could serve as a reliable indicator for PAD
Methods: We conducted a meta-analysis from July to August 2024, utilizing data from three major databases: Scopus, Embase, and PubMed. We gathered data on MPV levels from studies comparing PAD patients with control groups. The meta-analysis included cumulative effect estimates, with analysis performed using the inverse variance method to synthesize data and evaluate the overall effect of MPV on PAD.
Results: Nine studies were included in this meta-analysis, comprising 1,214 PAD cases and 6,568 controls. Our analysis demonstrated that MPV was a significant marker in PAD, with PAD patients having higher MPV levels compared to controls (MD: 0.46; 95%CI: 0.25, 0.66; p Egger: 0.0911; p Heterogeneity <0.0001; p <0.0001).
Conclusion: Our findings support that MPV is an important indicator in the context of PAD. Further study is needed to explore the clinical applications of MPV in PAD and to establish standardized thresholds for its use in clinical practice.

1. Introduction

Peripheral artery disease (PAD) continues to be a significant global health issue. The prevalence of PAD varies widely and depends on factors such as age, gender, ethnicity, and geographic location. However, it generally ranges from 3% to 4.5% among individuals aged 40 and older.[1] PAD has a severe impact, with the average amputation rate related to PAD being around 11 per 100,000 annually for individuals aged 25 and older. This amputation rate is higher in patients with diabetes mellitus.[2] Furthermore, the mortality rate associated with PAD also presents a stark picture. Studies report that mortality rates due to PAD vary from about 0.13% of total global deaths to approximately 49% of PAD patients dying within 10 years of diagnosis.[3] The high rates of amputation and mortality in PAD are often due to the disease being diagnosed at advanced stages or delays in seeking medical attention.[3] Effective management of PAD requires comprehensive diagnostic evaluations.[4,5] Therefore, there is an urgent need for simpler and more accessible diagnostic indicators to facilitate earlier detection and intervention. Addressing this need could significantly improve outcomes for PAD patients.

The Mean Platelet Volume (MPV) reflects the average size of platelets in the blood. MPV is typically measured in femtoliters (fl), with a normal range generally between 7.2 and 11.7 fl.[6] MPV is frequently assessed in patients who present to the Emergency Department. MPV is a simple valuable indicator of platelet function. Theoretically, MPV is an important parameter as it provides insights into platelet production and activity. A higher MPV indicates that the average platelet size is larger, which can be associated with increased platelet activation and a higher risk of thrombotic events, such as blood clots.[7] Studies have extensively evaluated the role of MPV in various conditions, including varicocele,[8] obstructive sleep apnea syndrome,[9] cardiovascular risk,[7] and coronary artery disease.[10] Given that coronary artery disease and PAD have similar pathogenesis, involving significant atherosclerosis, it is crucial to examine the role of MPV in PAD.[11] Although studies have reported on the role of MPV in PAD, their results have been inconsistent and varied.[12-20] This uncertainty underscores the need for a comprehensive meta-analysis to provide a cumulative evaluation of MPV's role in PAD. Such a meta-analysis could clarify the actual impact of MPV on PAD incidence and help establish MPV as an important indicator for diagnosing and monitoring PAD.

2. Methods

Design

This meta-analysis study was conducted between July and August 2024. To achieve the objectives of this study, we extracted data from each article and then compiled the data for the calculation of cumulative mean differences (MDs) along with 95% confidence intervals (95%CIs). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist to guide the protocols and ensure that each protocol in this study adhered to a systematic and transparent review process.[21] The study has been registered under the Prospero number 582460.

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Eligibility criteria

Articles included in our study analysis had to meet the predetermined inclusion and exclusion criteria. The inclusion criteria for this study were: the study design had to be observational, the study context focused on evaluating the relationship between mean platelet volume levels and the occurrence of peripheral arterial disease, and the articles had to have complete data for calculating cumulative effect estimates. Meanwhile, the exclusion criteria were defined as follows: irrelevance in the title and/or abstract, article types such as reviews or commentaries, and poor article quality based on the assessment using the Newcastle-Ottawa Scale.

Quality assessment

The tool used to assess the quality of the articles was the Newcastle-Ottawa Scale. This scale evaluates three main components: selection of study groups, comparability of the groups, and the ascertainment of the outcome of interest. The minimum score on the scale is 0, while the maximum score is 9. Articles with a score of 0-3 were classified as low quality, scores of 4-6 were considered moderate quality, and scores of 7-9 were deemed high quality.[22] The quality assessment of the articles was conducted by AD and AB.

Search strategy

The data sources used for the article search strategy in this study included PubMed, Embase, and Scopus. The article search was conducted up to 5 August 2024. Only articles published in English were considered for inclusion in our study. The keywords used in the article search were "mean platelet volume" or "MPV" and "peripheral arterial disease" or "PAD," which align with the Medical Subject Headings (MESH). In addition to the database searches, articles were also identified by reviewing the reference lists of related studies.

Data extraction and study covariates

Information extracted from each article included the name of the first author, year of publication, country where the study was conducted, study design, age of participants, predictors, outcomes, sample size of cases and controls, and the Newcastle-Ottawa Scale score. The data extraction process was carried out by AD and AB. In this study, the predictor covariate was the MPV levels, while the outcome covariate was the occurrence of PAD.

Statistical analysis

Data in this study were presented as mean ± standard deviation (SD). To assess potential publication bias, we used Egger's test and funnel plots. A p-value from Egger's test of <0.05 and an asymmetrical funnel plot indicate potential publication bias. If potential publication bias was detected, effect estimates were adjusted using the Trim and Fill method.[23] Heterogeneity in this study was assessed using the Q statistic, with a heterogeneity p-value <0.10 indicating the presence of heterogeneity. If heterogeneity was found, effect estimates were calculated using a random-effects model; if no heterogeneity was detected, we used a fixed-effects model.[24] The association between MPV levels and the occurrence of PAD was assessed using the inverse variance method. Cumulative effect estimates were presented using MD and 95%CI in forest plots.[25] The software used for this study was Review Manager Version 5.4 (RevMan, Cochrane, UK).

3. Results

Article selection

In the initial selection process, we identified 10,497 articles from the database and 7 articles from the reference lists of related articles. From this total, we excluded 23 articles due to duplication and 10,448 articles because their titles and/or abstracts did not align with the study's objectives. Subsequently, 33 articles were moved to the full-text evaluation stage. Of these, 2 articles were excluded because they lacked data for calculating cumulative effect estimates, and 22 articles were excluded as they were reviews. The final sample included in the study comprised 9 articles.[12-20] Figure 1 provides a detailed flowchart of the article selection process in this study according to PRISMA guidelines. The baseline characteristics of the articles included in the study are presented in Table 1.

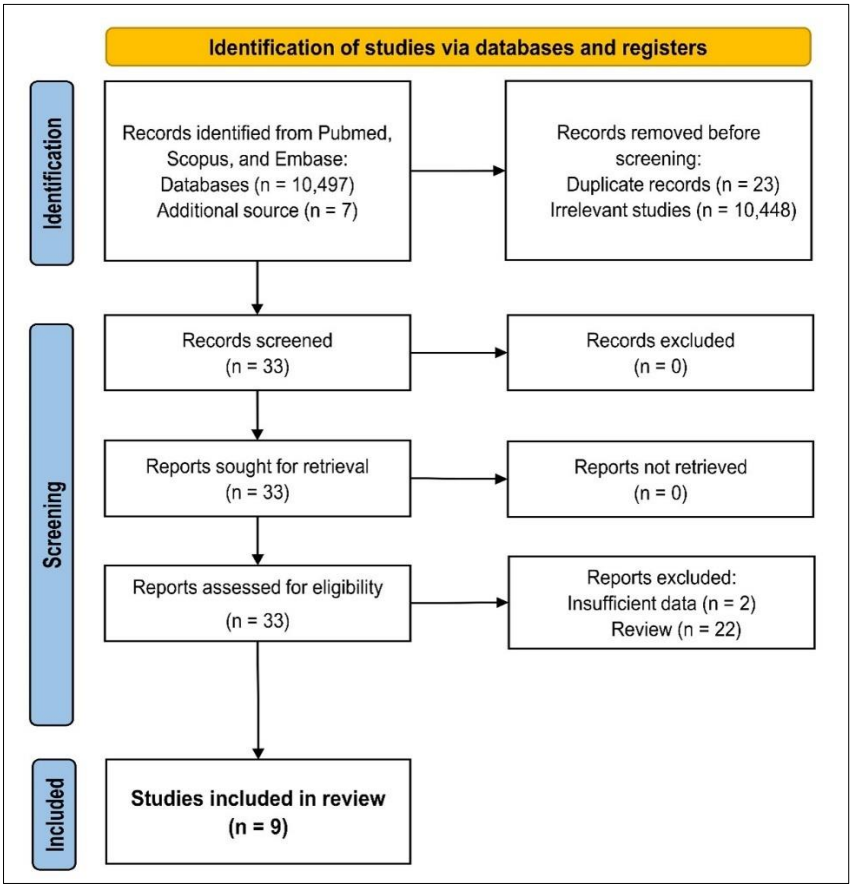

Figure 1. A flowchart of article selection in our study.

Table 1. Baseline characteristics of studies included in our analysis

Study	Country	Design	Age	Sample size	Other predictors	Outcomes	Quality assessment
Alan 2015	Turkey	Retrospective	42.83 ± 10.49	427	NLR, PLR	PAD, severity	Moderate
Arican-Ozluk 2015	Turkey	Retrospective	59.00 ± 10.00	84	Hemogram parameters	PAD	Moderate
Berger 2010	US	Retrospective	67.80 ± 0.70	6354	Platelet count	PAD, CVD	Moderate
Caliskan 2022	Turkey	Retrospective	61.50 ± 14.30	215	MPV/platelet ratio	PAD	Moderate
Hudzik 2018	Poland	Retrospective	63.00 ± 8.00	277	Comorbidities	PAD, diabetes, CVD	Moderate
Soydinc 2014	Turkey	Retrospective	51.67 ± 13.49	95	Valentini score	PAD, Systemic sclerosis	Moderate
van-Geffen 2015	Switzerland	Retrospective	67 (65 - 72)	80	Fibrinogen, p-selectin	PAD, thrombus formation	Moderate
Velioglu 2019	Turkey	Retrospective	58.48 ± 7.91	150	Hemogram parameters	PAD	Moderate
Zeiger 2000	Germany	Retrospective	52.90 ± 9.10	100	P-Selectin, platelet-derived microparticle	PAD	Moderate

Note, NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MPV, mean platelet volume; PAD, peripheral artery disease; CVD, cardiovascular disease.

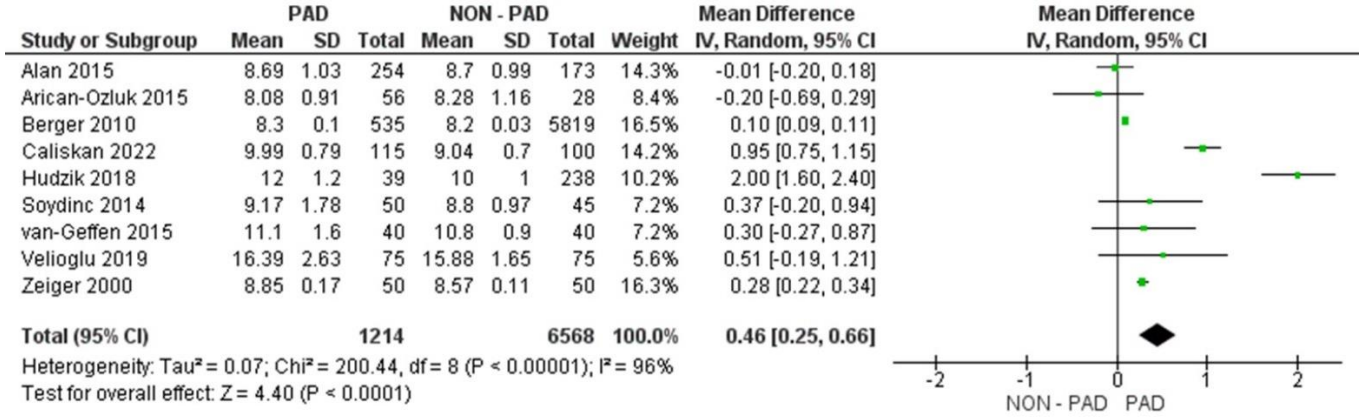

Figure 2. A forest plot of the association between MPV levels and the risk of PAD (MD: 0.46; 95%CI: 0.25, 0.66; p Egger: 0.0911; p Heterogeneity <0.0001; p <0.0001).

The association between MPV levels and the occurrence of PAD

To determine the relationship between MPV levels and the occurrence of PAD, we analyzed data from 9 articles, comprising 1,214 PAD cases and 6,568 controls.[12-20] Our results indicated that patients with PAD had higher MPV levels compared to controls (MD: 0.46; 95% CI: 0.25, 0.66; p Egger: 0.0911; p Heterogeneity <0.0001; p <0.0001) (Figure 2).

Heterogeneity among studies & potential publication bias

Egger's test yielded a p-value of 0.0911, indicating that no potential publication bias was detected in our data. The Q statistic test produced a p-value of <0.0001, which suggests the presence of heterogeneity in our data. Therefore, effect estimates in this study were calculated using a random-effects model.

4. Discussion

Our study revealed that higher MPV levels were found in patients with PAD compared to controls, with PAD patients having MPV levels 0.46 units higher than controls. This is the first meta-analysis to evaluate the relationship between MPV levels and the occurrence of PAD. Therefore, we were unable to compare our results with previous studies. However, in a similar context, prior meta-analyses have reported on the role of MPV levels and the platelet-lymphocyte ratio in the occurrence of coronary artery disease.[10,26] Those studies found that MPV levels were higher in patients with coronary artery disease compared to controls.[10] Given that coronary artery disease and PAD share a similar pathogenesis involving significant atherosclerosis processes,[11] this study adds valuable information on the role of MPV levels in the atherosclerosis process across different disease settings.

The theoretical reasons underlying the results of this study remain a topic of debate. However, the following explanations may provide a basis for understanding these findings. First, platelet activation may play a role in our study. MPV reflects the average size of platelets in the blood. An increase in MPV indicates that platelets have become active and undergone faster aggregation. This process has been linked to increased thrombotic potential, where larger platelets have higher density and greater expression of glycoprotein Ib and IIb/IIIa receptors. Consequently, this facilitates quicker platelet aggregation and triggers the development of atherosclerosis, which forms the basis for PAD progression.[6] Second, vascular conditions may also contribute to the findings of this study. PAD is a vascular condition characterized by stenosis or occlusion of peripheral arteries, which can lead to increased blood pressure in the lower extremities. Hypertension is a common condition found in PAD patients and can trigger platelet activation and increased MPV, as high blood pressure induces more aggressive vascular reactions, including platelet activation.[27] Third, inflammatory processes may also play a role in this study. PAD is often accompanied by inflammatory processes that can affect platelet function. Inflammation can increase the production of thrombogenic factors, such as thromboxane A2, which may also elevate MPV levels.[28] Fourth, the comorbidities of PAD patients may also influence the study's findings. A study showed that PAD patients often have other risk factors such as hypertension, diabetes mellitus, and obesity.[29] These factors may directly or indirectly affect MPV through inflammatory processes, platelet activation, and vascular changes.[30]

This meta-analysis had several clinical implications. First, it was the first study to report the role of MPV in the occurrence of PAD. Therefore, these results could serve as an initial basis for future studies that would more specifically evaluate the role of MPV in PAD. Second, the study found that PAD patients had higher MPV levels compared to

controls. This emphasized that, moving forward, MPV could be used as an early indicator for clinicians to suspect patients with clinical symptoms of PAD. Third, these findings could have served as a preventive measure for PAD patients. Understanding that high MPV was associated with faster platelet activation and aggregation,[30] this study could have helped in developing more effective preventive strategies to reduce the risk of thrombosis in PAD patients. Fourth, these results could have formed the basis for better monitoring of PAD patients. The study might have enhanced clinical surveillance in PAD patients, particularly by monitoring MPV levels and taking appropriate preventive actions to reduce thrombosis risk.

This meta-analysis had several limitations. First, the study did not account for potential confounding factors such as comorbidities, glycoprotein levels, and thromboxane A2.[28] Second, the sample size in this study was limited, with only 9 articles available for analysis. Future study involving a larger sample size might be necessary to obtain more robust results. Third, the study population was not evenly distributed, as most studies were conducted in Turkey. Therefore, caution is needed when generalizing the results of our study. Fourth, all the studies included in this meta-analysis were observational. Future studies incorporating intervention designs may be required to achieve more comprehensive results.

5. Conclusion

This study revealed that MPV is an important indicator in PAD, with PAD patients exhibiting higher MPV levels compared to controls. These findings suggest that MPV could serve as a useful marker for diagnosing and monitoring PAD patients. However, future studies are needed to address the limitations of our study and further validate the role of MPV in PAD.

6. Declaration

6.1 Ethics Approval and Consent to participate
Not applicable.

6.2. Consent for publication
Not applicable.

6.3 Availibility of data and materials
Data used in our study were presented in the main text.

6.4 Competing interests
Not applicable.

6.5 Funding Source
Not applicable.

6.6 Authors contributions
Idea/concept: AD, AB. Design: AD, AB. Control/supervision: AD, AB. Data collection/processing: AD, AB. Analysis/interpretation: AD, AB. Literature review: AD, AB. Writing the article: AD, AB. Critical review: AD, AB. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

6.7 Acknowledgements
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