Am J Blood Res 2025;15(4):61-79
www.AJBlood.us /ISSN:2160-1992/AJBR0165890

Review Article

Prognostic value of platelet volume indices in heart failure: a systematic review and meta-analysis

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Received May 8, 2025; Accepted July 29, 2025; Epub August 15, 2025; Published August 30, 2025

Abstract: Objectives: Heart failure (HF) is a complex condition with a substantial global prevalence and clinical burden. Prognostic biomarkers are essential for effective management. This study systematically reviews and synthesizes the prognostic value of mean platelet volume (MPV) and platelet distribution width (PDW) in HF patients. Methods: A comprehensive search was conducted in Medline, Scopus, Web of Science, and Embase databases. Eligible studies were identified, screened, and selected according to pre-defined criteria. Data extraction and quality assessment were performed by independent reviewers. Meta-analyses were conducted using random-effects models, and heterogeneity was assessed using I^2 statistics. Publication bias was assessed using Egger's regression and Begg's tests. Results: From 12471 records, 21 studies were included. MPV showed significant predictive value, with pooled hazard ratios (HR) of 1.49 (0.67-3.32) and odds ratios (OR) of 1.71 (1.5-1.91) for mortality and morbidity. The pooled mean difference in MPV values between the affected and unaffected subjects was 0.66 (0.21-1.1, P=0.008). MPV was positively correlated with NT-proBNP levels (pooled coefficient: 0.13, P=0.028). The pooled area under the curve for MPV in prognosticating adverse outcomes was 0.75 (0.69-0.82). However, PDW did not show significant prognostic value (HR: 1.56, OR: 1.11). Conclusions: MPV is a useful prognostic marker in HF, associated with increased mortality and morbidity. Prognostic significance of PDW remains unclear, requiring additional research. The application of MPV can improve risk stratification and management of HF, but further research with larger populations and diverse settings is essential to confirm these findings and establish clinical reference ranges.

Keywords: Heart failure, mean platelet volume, platelet distribution width, prognostic biomarkers

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by the inability of the heart to adequately pump blood to meet the physiologic metabolic demands. This pathological state stems from various etiologies, such as myocardial infarction, hypertension, valvular disease, and cardiomyopathies. Hence, HF is considered the end-stage of numerous cardiovascular diseases (CVDs) [1]. Based on a 2017 estimate, HF is thought to affect more than 64.3 million people worldwide, representing a 34% increase from 1990 and a 16% increase from 2007. The prevalence is expected to increase by 46% by 2030, considering the aging of the general population [2]. Clinical manifestations of HF encompass a range of symptoms, namely dyspnea, fatigue, fluid retention, and exercise intolerance, which can significantly diminish the quality of life of the affected ones [3]. With respect to the increasing prevalence and severity of the symptoms and despite recent advancements in therapy, HF remains a substantial burden on global healthcare systems. Accordingly, proper management of the

https://doi.org/10.62347/XUXB3631

disease is of crucial importance in reducing this burden. In this regard, prognostic biomarkers play a pivotal role in the treatment of patients.

Several cellular and molecular biomarkers have been identified as having prognostic value in heart failure (HF), including the N-terminal prohormone of brain-type natriuretic peptide (NT-proBNP), the mid-region of N-terminal prohormone of atrial-type natriuretic peptide (MR-proANP), and heart-type fatty acid-binding protein (hFABP) [4, 5]. However, high costs and limited availability of these indices have prompted clinicians to seek more accessible factors capable of prognosticating HF. Inflammation is considered the major contributor to heart failure (HF) pathophysiology, and several inflammatory markers have been identified that can accurately predict both short-term and long-term HF outcomes [6]. Respectively, accumulating evidence has demonstrated potentially high prognostic value of hematologic indices obtained from a simple complete blood count (CBC) test, such as absolute neutrophil and lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), red blood cell distribution width (RDW), and platelet volume indices, including mean platelet volume (MPV) and platelet distribution width (PDW), which reflects platelet activation [7]. MPV, the average platelet size and PDW, the variability in platelet size are calculated by automated hematology analyzers in conjunction with platelet count during routine blood tests. Platelet volume indices could not only indicate the inflammatory aspect of HF but also can point out to the thrombotic aspect of HF pathophysiology and have been an active area of research in the recent years. As such, in this study, we aimed to systematically review and conduct meta-analysis on the existing literature to further enlighten the prognostic value of MPV and PDW in HF.

Methods

Protocol and registration

This systematic review was conducted in accordance with the instructions outlined in the Cochrane Handbook of Systematic Reviews of Interventions. We further report this systematic review study using the Preferred Reporting Items For Systematic Reviews and Meta-Analyses (PRISMA) statement. The review protocol was registered on the international prospective register of systematic reviews (PROSPERO) database (CRD42024507103).

Search strategy

To conduct a comprehensive online search of published papers up to December 28, 2024, we carried out a systematic search in the Medline (PubMed), Scopus, Web of Science (WOS), and Embase databases without recourse to publication country, date, or language. The following search terms were used to identify and extract the compatible studies: ("platelet" OR "platelet volume index" OR "platelet volume indices" OR "mean platelet volume" OR "MPV" OR "platelet distribution width" OR "PDW") AND ("cardiac failure" OR "heart failure" OR "cardiac insufficiency" OR "cardiac decompensation" OR "acute heart failure" OR "acute decompensated heart failure" OR "acute cardiac failure" OR "AHF" OR "ADHF" OR "chronic heart failure" OR "congestive heart failure" OR "CHF"). Our search line was limited to the use of these terms in the title, abstract, and keywords. The reference lists of relevant papers were also reviewed to find undetected citations. After eliminating duplicate records, we screened the titles of the remaining articles and assessed their abstracts to determine their relevance. Subsequently, we obtained and evaluated the full text of the relevant studies to determine their eligibility. If the full text was not accessible, we reached out to the corresponding author of the study to ask for the manuscript, if feasible. The process included removing duplicates and storing the search records, which was implemented using EndNote version 20.

Eligibility criteria and study selection

We performed a systematic review of the literature and assessed all English peer-reviewed studies reporting the impact of the MPV and PDW on mortality and morbidity in patients with HF. We incorporated the PICO framework in screening and selecting the eligible studies. Based on this approach, our study focused on patients with heart failure (HF) as the defined population. Exposure and comparator items were not applicable, as our primary objective was to assess the potential prognostic value of MPV and PDW among all HF cases. For out-

comes, we considered several factors, including all-cause and cardiovascular mortality, rehospitalization, extended hospital stay, pulmonary hypertension, atrial fibrillation (AF), developing renal disease, and decreased functional capacity. Regardless of the designs, all studies evaluating the predictability of MPV and PDW in HF were considered eligible, except meeting abstracts, editorials, case reports, case series, animal studies, in vivo and in vitro investigations, and non-English records.

Quality assessment

Two independent reviewers assessed the methodological quality of the included records using the Quality in Prognostic Studies (QUIPS) tool. The QUIPS tool comprises six bias domains: study participation, study attrition, study confounding, outcome measurement, prognostic factor measurement, and statistical analysis and reporting. Each bias domain in this tool consists of 3 to 7 different items. The risk of bias for a specific study can be categorized as low, moderate, or high.

Data extraction

To minimize the likelihood of reporting and data collection bias, information from the included articles was gathered by two separate reviewers. A structured table consisting of the first author's name, publication date, study location, participants' demographics (including age and gender distribution), study design, sample size, follow-up period, outcome along with the measure effects and analyses used to quantify the outcome was designed to aid in the extraction process. Oversight of the extraction process was provided by a third reviewer. In the case that data were incomplete, efforts were made to contact with the corresponding authors of the studies.

Statistical analysis

We described the results quantitatively and qualitatively. Pooled effect sizes were reported as hazard ratios (HR) and odds ratios (OR) for mortality and morbidity, along with the mean value and 95% confidence interval (CI). To avoid skewness in the distribution of the ORs and HRs, we logit-transformed these values before pooling them. To enhance the accuracy of our results and reduce the heterogeneity of the included studies in the analyses, we further implemented sensitivity analysis by only including studies with either mortality or morbidity as the primary outcomes. Moreover, we pooled the mean difference (MD) of the MPV values between the survived subjects and those with rehospitalization, acute pulmonary edema (APE), cardiovascular events, HF decompensation, or deceased ones. To further investigate the prognostic value of these indices, we planned to implement meta-analysis on the correlation coefficients yielded from correlation analysis between MPV and PDW and NT-proBNP. Since all the analyses were performed with R version 4.2.3, we did not manually utilized fisher r-to-z transformation to convert our measure effects into standard normal metrics (metacor function does this transformation automatically). We used Wan et al.'s method to convert median and interquartile range (IQR) to mean ± standard deviation (SD) for continuous variables [8]. I^2 statistics were used to assess the heterogeneity among the included studies, however, the included studies were substantially heterogonous in terms of methodology, setting, and outcome and hence, random effect meta-analysis method was employed for pooling the measure effects. Egger's regression asymmetry test, and Begg's test were used to explore any potential source of publication bias. In case of at least 10 included studies in the analyses, funnel plot was depicted to further strengthen the relevant results. Meta-regression analysis was conducted to look for any potential variable affecting the outcome, however, since a majority of the included studies had not provided the intended demographic and clinical data, this analysis was carried out only for certain measure effects. The statistical level of significance was set at P-value <0.05.

Results

Study selection process

According to the aforementioned search strategy, 16855 records were found in the primary search. Upon removing duplicates, 12471 records remained. After title and abstract screening, 89 articles were gone for full-text review. Two studies were found in the grey literature of the relevant papers. One study was excluded because the manuscript was written in a non-English language. Eventually, 21 studies were included in the systematic review as presented in **Tables 1** and **2** (the following stud-

Table 1. Characteristics of the included studies investigating the prognostic value of MPV

Author (year)	Location	Population	Condition	Mean age (Mean [SD])	Male percentage	Study design	Follow-up period	MPV (Mean [SD])	Outcome	Measure effect
Angkananard et al. (2021)	Thailand	321	Acute HF	67.4 (14.9)	144 (44.9%)	Retrospective cohort	3 years	10.4 (0.9)	CVD events	Univariate Cox proportional hazards regression (HR: 1.31 [1.08-1.58])
Hammadah et al. (2015)	USA	1536	HF patients undergoing coronary angiography	66 (11)	983 (64%)	Prospective cohort	5 years	8.1 (0.9) MPV tertiles: T1: <7.6 T2: 7.6-8.3 T3: >8.3	All-cause mortality	Multivariate Cox regression (HR for highest vs lowest tertile: 1.3 [1.04-1.6])
Kaya et al. (2017)	Turkey	197	chronic HFrEF	65 (13)	140 (71%)	Retrospective cohort	1 year	MPV categories: MPV ≤9.1 MPV >9.1	HF-related hospitalization	Multivariate Cox regression (HR for MPV >9.1: 2.89 [1.77-4.7])
Kalcik et al. (2015)	Turkey	96	Decompensated HF	NA	NA	Prospective cohort	NA	14.7 (6.9)	Decompensation	A significant difference in MPV during decompensation and compensation before discharge
Menghoum et al. (2023)	Belgium	228	HFpEF	79 (9)	77 (34%)	Prospective cohort	2 years (median follow-up of 26 months)	10.7 (1.1)	all-cause mortality or HF hospitalization	Multivariate cox regression (HR for MPV >75th percentile: 1.70 [1.08; 2.67])
Sato et al. (2022)	Japan	400	HF patients with CHD	34 years [range:12-76]	196 (49%)	Retrospective cohort	28 months	NA	HF-related hospitalization and thrombus formation	Multivariate Cox regression (HR for hospitalization: 2.48 [1.51-4.2] and HR for thrombus formation: 4.2 [2.02-9.8]) Multivariate logistic regression (OR for hospitalization: 1.47 [1.05-2.05] and OR for thrombus formation: 1.79 [1.15-2.78])
Shore et al. (2012)	USA	14648	HFpEF	71	5860 (40%)	Prospective cohort	NA	NA	All-cause mortality	Multivariate Cox regression (HR: 1.19 [1.15-1.22])
Siedlecki et al. (2019)	Poland	367	advanced HF and diabetes mellitus	63.3 (10.8)	278 (75.7%)	Retrospective cohort	4.4±1.3 years	11.9 (0.71)	All-cause mortality	Univariate Cox proportional hazard regression (HR: 2.15 [1.87-2.47])
Kandis et al. (2011)	Turkey	136	decompensated HF	70 (9)	77 (56.6%)	retrospective cohort	18±12 months	10.5 (1.5)	All-cause mortality	Logistic regression (OR= 1.55 [1.02-2.35])
Jacob et al. (2011)	Spain	404	Acute HF	NA	NA	Prospective cohort	1 month	9.32 (4.13)	30-day mortality and readmission	A significant difference in MPV between patients with regard to 30-day mortality and readmission
Pachon et al. (2020)	Spain	55	Patients with pleural effusion due to HF	79 (11.8)	34 (62%)	Retrospective cohort	NA	8.78 (0.87)	Mortality upon thoracentesis	Insignificant difference in MPV between survivors and deceased ones
Mongirdienė et al. (2021)	Lithuania	185	CHF	54.3 (12)	154 (83%)	Prospective observational	NA	9.8 (1.1)	NYHA classification	Correlation analysis between MPV values and NYHA functional class (r=0.31, P=0.0001)
Dahlen et al. (2021)	Germany	3250	HF	64.6 (11)	2066 (63%)	Prospective cohort study	Median of 2.24 years	8.27 (0.86)	cardiac function and worsening of HF, reduced left ventricular ejection fraction, hospitalization, and cardiac death	Univariate and multivariable linear regression analyses for LVEF (beta estimate =-0.05 [-0.09; -0.02]), Cox regression demonstrated an increased risk for worsening of HF in subjects with MPV >75th percentile (HR=1.47 [1.16-1.87])

Catana et al. (2024)	Romania	260	CHF	NA	110 (42%)	Retrospective cohort	NA	NA	AF and reduced LVEF	Multivariate logistic regression (OR for AF=1.7 [SE of 0.29]; OR for LVEF reduction =1.73 [SE of 0.3])
Lelli et al. (2022)	Italy	415	HFpEF, HFmrEF, and HFrEF	83.1 (7)	171 (41%)	Cross-sectional	NA	11 (1.1)	NT-proBNP level	Significant correlation between NT-proBNP and MPV level (r=0.1, P=0.03) which was confirmed by multivariate linear regression (P=0.008)
Andrei et al. (2022)	Romania	130	Decompensated CHF	72.5 (10.8)	51 (39%)	Retrospective cohort	1 year	8.86 (0.21)	Rehospitalization and 1-year mortality	A significant difference between MPV values among patients categorized in terms of APE, AF, rehospitalization, and mortality
Catana et al. (2023)	Romania	260	CHF	NA	110 (42%)	Retrospective cohort	NA	NA	APE, 3-month rehospitalization, 6-month rehospitalization, 1-year mortality, and in-hospital mortality	Multivariate logistic regression (OR for APE=2.12 [SE of 0.43]; for 3-M rehospitalization=2.3 [SE of 0.46]; for 6-M rehospitalization =3.26 [SE of 0.7]; for 1-Y mortality =2.1 [SE of 0.52]; for hospital mortality =1.6 [SE of 0.8])
Zhang et al. (2019)	China	336	HF	62.4 (10.6)	188 (56%)	Cross-sectional	NA	10.3 (1.3)	Renal dysfunction	Multivariate logistic regression (OR: 1.96 [1.22-3.13])

Abbreviations: CVD, cardiovascular; HR, hazard ratio; OR, odds ratio; NA, not available; AHF, acute heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; CHD, congenital heart disease; NYHA, New York heart association; AF, atrial fibrillation; SE, standard error; CHF, congestive heart failure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; HFmrEF, heart failure with mid-range ejection fraction; LVEF, left ventricle ejection fraction; APE, acute pulmonary edema.

Table 2. Characteristics of the included studies investigating the prognostic value of PDW

Author (year)	Location	Population	Condition	Mean age (Mean [SD])	Male percentage	Study design	Follow-up period	PDW (Mean [SD])	Outcome	Measure effect
Marques et al. (2023)	Portugal	394	Acute HF	79.1 (9.4)	38.1	Retrospective cohort	One year	13.7 (0.6)	All-cause mortality and rehospitalization	Multivariable Fine and Gray model for rehospitalization (event of interest) and death without rehospitalization (competing event) due to AHF: Rehospitalization: HR of (1.02 [0.95-1.1]) Mortality: HR of (0.89 [0.81-0.97])
Marques et al. (2023)	Portugal	429	Acute HF	79 (10)	37.5	Retrospective cohort	One year	13.7 (2.6)	All-cause mortality	Multivariable logistic regression: OR of 0.88 (0.80-0.97)
Sato et al. (2022)	Japan	400	HF patients with CHD	34 (16)	49	Retrospective	Three years	NA	HF-related hospitalization and thrombus formation	Multivariate logistic regression (OR for hospitalization: 1.36 [1.05-1.76] and OR for thrombus formation: 1.99 [1.46-2.63]) Multivariate Cox regression (HR for hospitalization: 3.74 [2.19-6.77] and HR for thrombus formation: 9.17 [3.65-30.7])
Zhang et al. (2019)	China	336	HF	62.33 (10.6)	56	cross-sectional	One year	16.30 (2.07)	Renal dysfunction	Logistic regression: OR of 0.65 (0.47-0.88)
Sato et al. (2020)	Japan	1746	HF	68.67 (14.7)	59.6	Prospective cohort	Ten years	15.98 (1.14)	All-cause death, cardiac death, CVD events	Multivariate Cox regression: HR for all-cause death 1.04 (1-1.09); HR for cardiac death 1.08 (1.02-1.15)
Siedlecki et al. (2019)	Poland	367	HF + DM	62.6 (11.6)	75.7	Retrospective cohort	Four years	13.45 (1.96)	All-cause death	Univariate Cox proportional hazard regression analysis: HR of 0.94 [0.88-1.01]
Ishino et al. (2018)	Japan	205	CHF	NA	NA	Prospective cohort	Two years	15.8 (0.6)	CVD events and mortality	Multivariate Cox proportional hazard analysis: HR of 1.576, *P*-value <0.05
Lelli et al. (2022)	Italy	415	HFpEF, HFmrEF, and HFrEF	83.1 (7)	171 (41%)	Cross-sectional	NA	13.3 (2.7)	NT-proBNP level	Significant correlation between NT-proBNP and MPV level (r=0.09, P=0.04) which was confirmed by multivariate linear regression (P=0.004)

Abbreviations: CVD, cardiovascular; HR, hazard ratio; OR, odds ratio; NA, not available; AHF, acute heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; CHD, congenital heart disease; DM, diabetes mellitus; CHF, congestive heart failure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

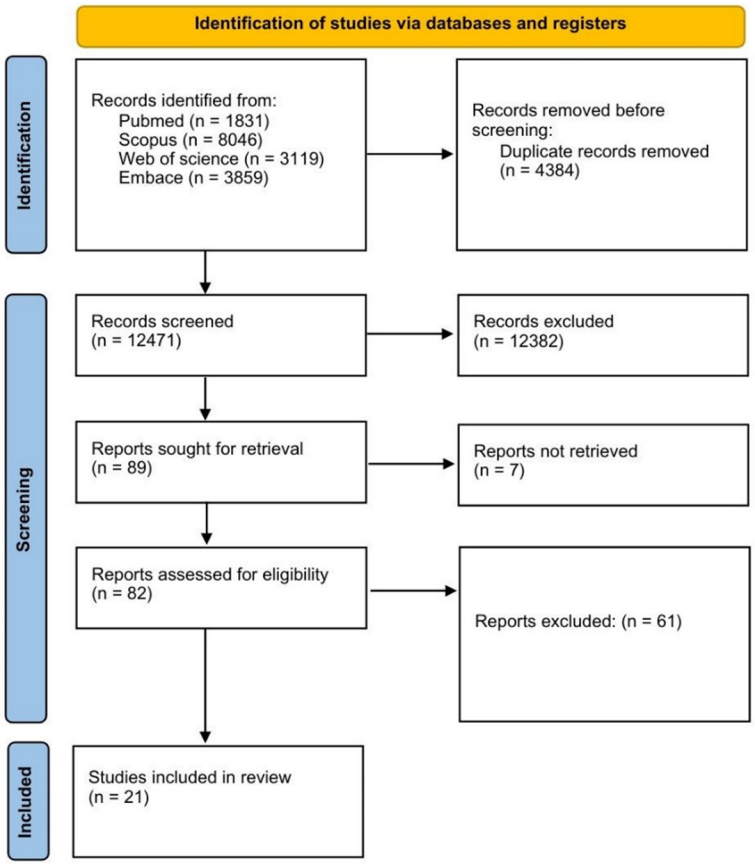

Figure 1. Flow diagram of the study selection process.

ies are not mentioned in the manuscript but are present in the table [9-16]). The flow diagram of the study selection process is demonstrated in **Figure 1**.

Study characteristics

Of the 21 total included studies, 18 studies had investigated the prognostic value of MPV. Twelve studies had reported the mean ± SD of MPV. Five studies provided the HR of MPV for all-cause mortality and cardiovascular events. Sato et al. provided two separate HRs for hospitalization and thrombus formation; therefore, two HRs were applied in the analysis [17]. Four studies reported ORs for all-cause mortality, in-hospital mortality, AF, APE, reduced left ventricular ejection fraction (LVEF), and renal dysfunction. Eight studies provided mean ± SD of MPV in the survived/unaffected subjects and deceased/affected patients. The outcomes are represented in **Table 1**. Three studies investigated the correlation between MPV value and NT-proBNP level, two of which found statistically significant correlations, while Andrei et al. failed to show this association (*P*-value of 0.1) [18]. Budak et al. conducted a correlation analysis between MPV and BNP levels, displaying a significant correlation [19]. Eight studies were not incorporated in the meta-analysis. Hammadah et al. reported a significantly increased mortality risk in the highest tertile compared to the lowest one, with a hazard ratio (HR) of 1.3 (1.04-1.6) [20]. In another study on 197 stable CHF patients with sinus rhythm, an MPV >9.1 was found to be an independent predictor of HF-related hospitalization (HR 2.89 [1.77-4.7]) [21]. Consistent with these findings, Dahlen et al. revealed worsening of HF in subjects within the MPV >75th percentile group with HR of 1.47 (1.16-1.87, *P*-value: 0.001). Furthermore, they found a negative association between MPV and LVEF, as derived from a multivariable linear regression model [22]. Similarly, Menghoum et al. indicated that an MPV greater than the 75th percentile is an independent predictor for all-cause mortality and HF hospitalization. They furthered their findings by showing an additional prognostic value of MPV >75th percentile compared to the MAGGIC (meta-analysis global group in chronic) score [23]. This score is a validated predictive tool to anticipate mortality in HFPEF which integrates various demographics and clinical and laboratory variables [24]. In 2011, Jacob et al. revealed significant difference in MPV values between patients with regard to 30-day mortality and readmission [25]. On the contrary, Pachon et al. and colleagues failed to reach significant results in this regard [26]. In a study by Mongirdienė et al., MPV was significantly correlated with the New York Heart Association (NYHA) functional class (r=0.31) [27]. For PDW, seven studies were identified as eligible for inclusion. Sato et al. (2020) showed their results by categorizing PDW into tertiles and comparing them in terms

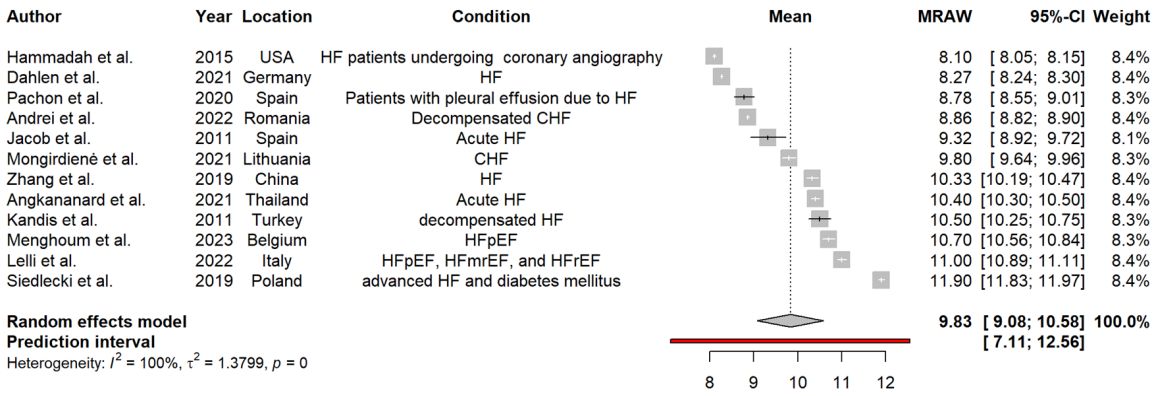

Figure 2. Pooled mean values of the MPV in the included studies.

Table 3. Meta-regression results of the studies investigating prognostic value of MPV

Variable	Estimate	*P*-value
Age	0.01	0.8
Male percentage	-0.007	0.78
Body mass index	0.22	0.24
NT-proBNP	0.24	0.51
Systolic blood pressure	0.03	0.27
Diastolic blood pressure	-0.02	0.56

of all-cause death and cardiac death. However, they had provided their dataset; hence, we carried out multivariable Cox regression with PDW as a continuous variable and found slightly significant HRs of 1.04 (1-1.09) and 1.08 (1.02-1.15) for all-cause and cardiac death, respectively. Marques et al. and colleagues, conducted multivariable cox analysis with Fine and Gray model for rehospitaliazation and mortality without rehospitalization and found HRs of 1.02 (0.95-1.1) and 0.89 (0.81-0.97), respectively [28]. Similarly, Siedlecki et al. showed insignificant predictive performance of PDW for all-cause death (HR of 0.94 [0.88-1.01]) [29]. On the other hand, Sato et al. (2022), reveal significant predictive value of PDW for hospitalization (HR: 3.74 [2.19-6.77]) and thrombus formation (HR: 9.17 [3.65-30.7]) [17]. They also ran logistic regression analysis for these outcomes and reported ORs of 1.36 (1.05-1.76) for hospitalization and 1.99 (1.46-2.63) for thrombus formation. Two more studies reported ORs yielded from logistic regression with different defined outcomes. One of these studies by Zhang et al., demonstrated OR of 0.65 (0.47-0.88) for renal dysfunction in a cohort of 336 Chinese HF patients [30]. The other study, by Marques et al., showed an OR of 0.88 (0.80-0.97) for all-cause mortality in 429 patients hospitalized with acute HF [31].

Results of data synthesis for MPV

We performed separate meta-analyses according to the measure effects. For mean MPV values, as demonstrated in **Figure 2**, the pooled mean value of the 12 included studies is 9.83 (9.08-10.58, 95% CI). We conducted a meta-regression to identify potential factors affecting the pooled MPV, but neither of the items was a significant predictor of the outcome. The detailed results are represented in **Table 3**. For pooling HRs, we had logit-transformed the values, and as shown in the relevant forest plot (**Figure 3**), the pooled log-HR is 0.52 (0.08-0.97), which after taking the exponential function of this value, yields a pooled HR of 1.68 (1.08-2.63). Meta-regression results revealed age as a significant factor associated with the outcomes, with an estimate of -0.02 and a *P*-value of 0.003. To reduce the bias of pooling various outcomes, we repeated the analyses on only studies with mortality being the study outcome. The results showed an insignificant but positive association between increasing MPV and HR of demise (pooled HR 1.49 [0.67-3.32]) (**Figure 4**). Similarly, for ORs, we had a pooled log-OR of 0.54 (0.44-0.65) or pooled OR of 1.71 (1.55-1.91) (**Figure 5**). We further conducted the meta-analysis separately for studies with mortality as the primary outcome (pooled OR 1.63 [1.16-2.29]) (**Figure 6**) and studies assessing morbidity (1.75 [1.5-2.01]) (**Figure 7**). As displayed in the figures, the ORs for both mortality and morbidity were statisti-

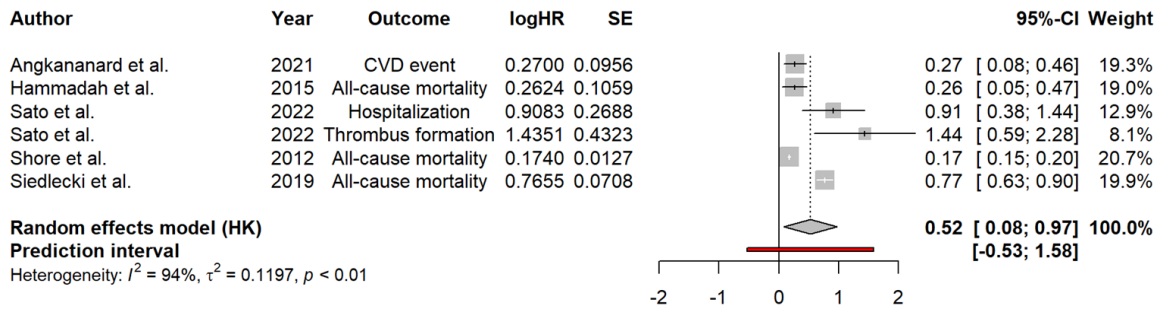

Figure 3. Pooled log-HRs of the MPV in the included studies.

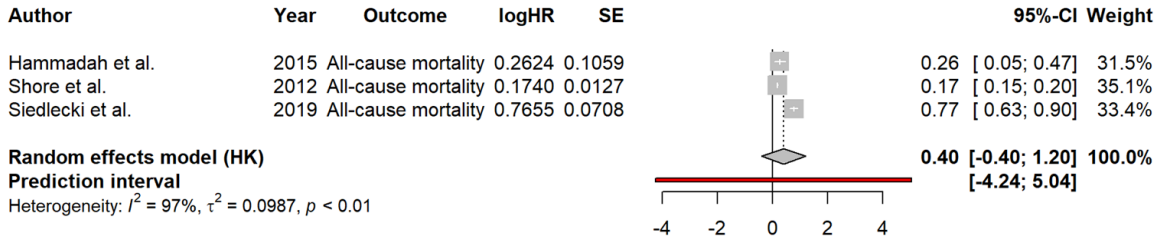

Figure 4. Pooled log-HRs of the MPV in the included studies assessing mortality as the primary outcome.

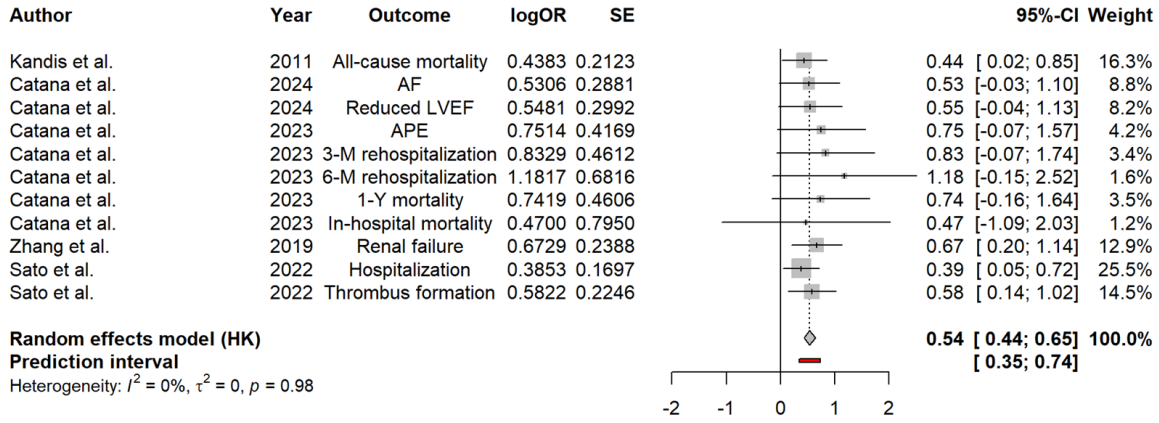

Figure 5. Pooled log-ORs of the MPV in the included studies.

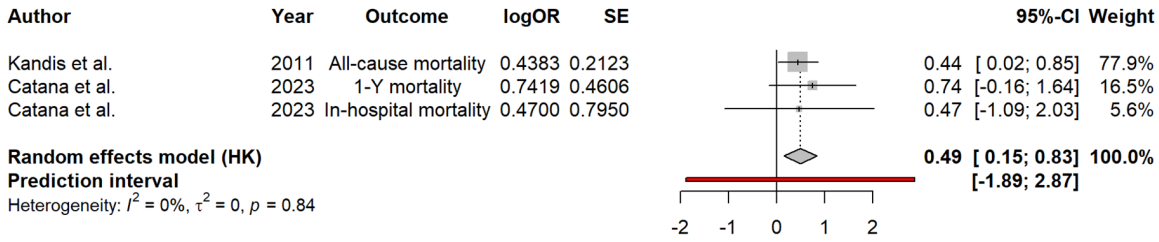

Figure 6. Pooled log-ORs of the MPV in the included studies assessing mortality as the primary outcome.

cally significant. Meta-analysis of the MDs showed a significant reduction or difference of MPV value in the survived/unaffected patients and those with rehospitalization, APE, cardiovascular events, HF decompensation, or deceased ones. As demonstrated in **Figure 8**, the

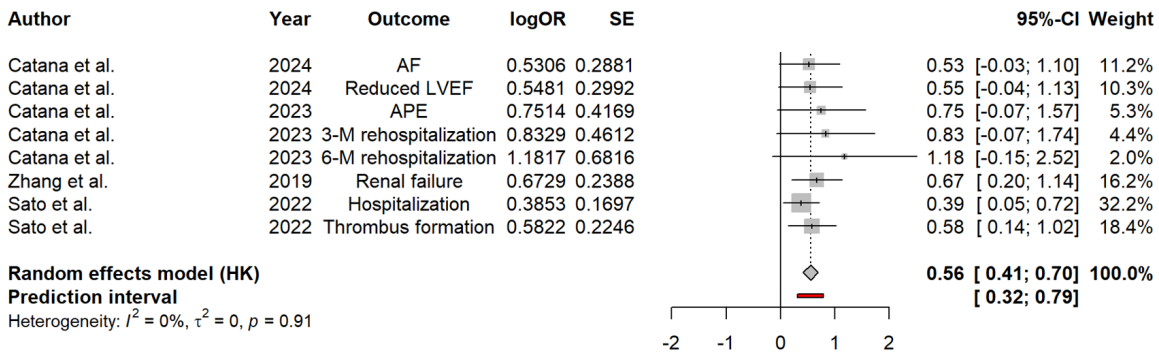

Figure 7. Pooled log-ORs of the MPV in the included studies assessing morbidity as the primary outcome.

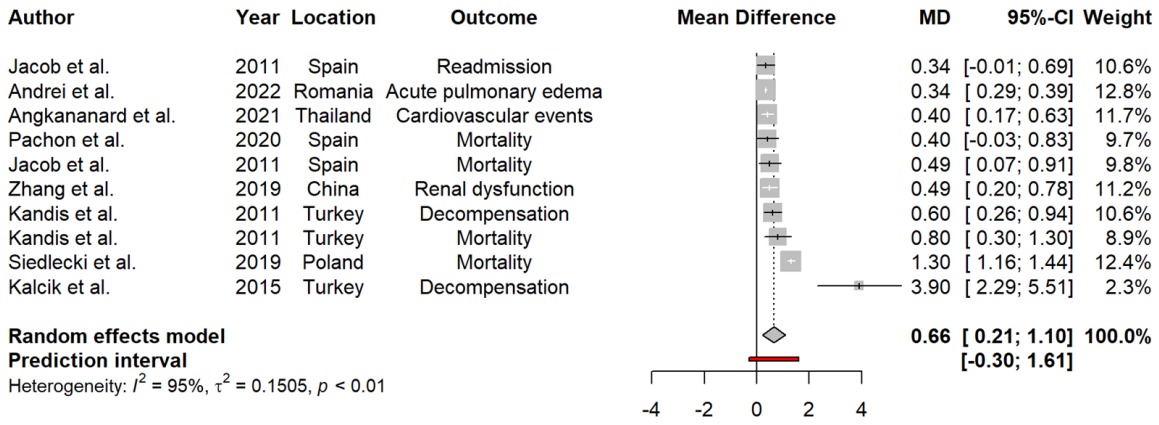

Figure 8. Pooled mean differences of the MPV value among the unaffected/survived ones and the affected/deceased subjects.

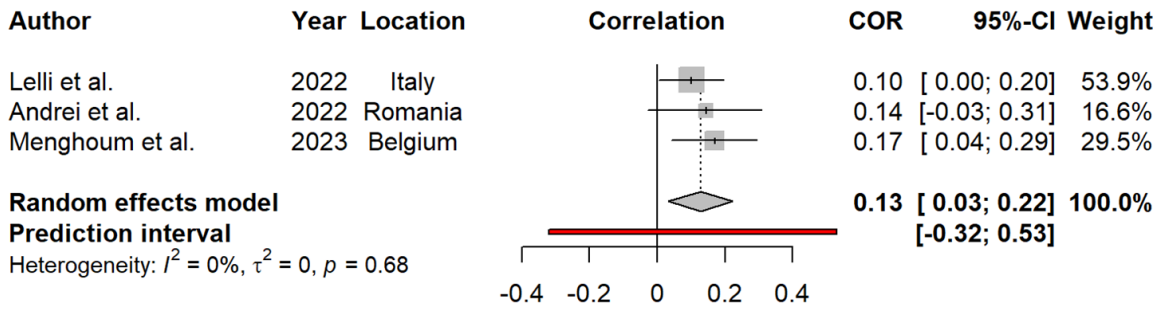

Figure 9. Pooled coefficients of the correlation between MPV value and NT-proBNP.

pooled MD was 0.66 (0.21-1.1, *P*-value of 0.008). To further strengthen these findings, we pooled the correlation coefficients from the three studies that evaluated the correlation between MPV and NT-proBNP levels. As shown in **Figure 9**, the pooled coefficient is 0.13 (0.03-0.22, *P*-value of 0.028). In all the included studies, MPV was reported with femtoliters (fl) unit.

Results of data synthesis for PDW

A meta-analysis of the six studies reporting the mean value of PDW reveals a pooled mean of 14.82 (13.42-16.22) (**Figure 10**). No demographic or clinical feature capable of affecting the pooled mean was identified by the meta-regression analysis. Strikingly, the results yielded from the pooling of HRs and ORs were con-

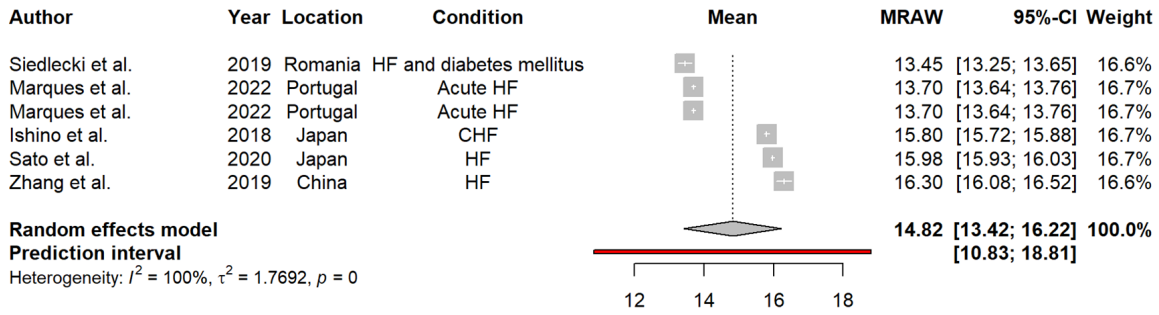

Figure 10. Pooled mean values of the PDW in the included studies.

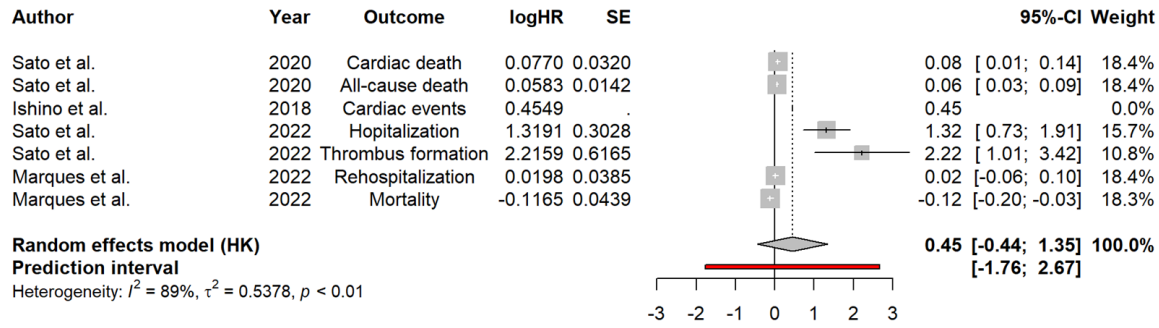

Figure 11. Pooled log-HRs of the PDW in the included studies.

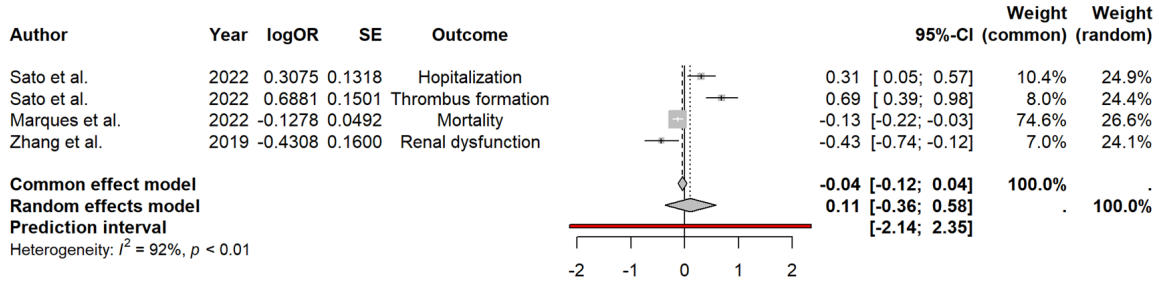

Figure 12. Pooled log-ORs of the PDW in the included studies.

tradictory to those of MPV, as insignificant pooled HRs and ORs of the PDW were 1.56 (0.64-3.85) and 1.11 (0.69-1.78), respectively (**Figures 11**, **12**). Respecting the heterogeneous outcomes, we pooled the HRs of studies evaluating the risks of mortality according to the PDW values, which yielded similar insignificant results (pooled HR of 1.01 [0.77-1.3]) (**Figure 13**).

Results of AUC synthesis for MPV

To further enrich our results regarding the prognostic value of MPV, we pooled the areas under the curve (AUCs) yielded from receiver operating characteristic (ROC) analyses. To perform this analysis, we should have utilized the standard error of the AUC, which was obtained either from the confidence interval or through contact with the relevant corresponding author. A meta-analysis of the three studies reporting the AUC of MPV for hospitalization, thrombus formation, in-hospital mortality, and 6-month mortality yielded a pooled value of 0.75 (0.69-0.82) (**Figure 14**). Since, each study had used a distinct cut-off value of MPV for ROC analysis, we conducted meta-regression, which revealed a non-significant impact on the pooled value.

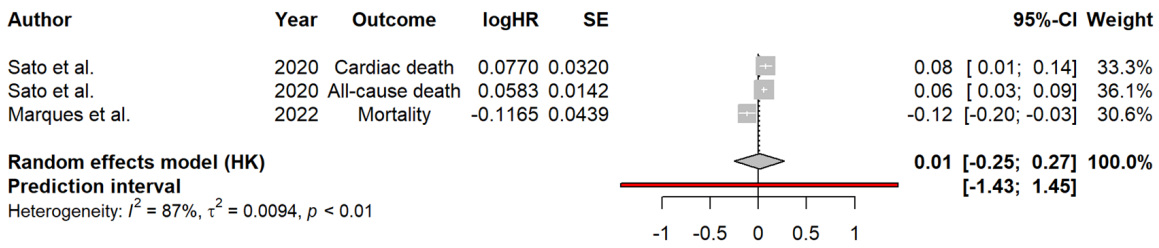

Figure 13. Pooled log-HRs of the MPV in the included studies assessing mortality as the primary outcome.

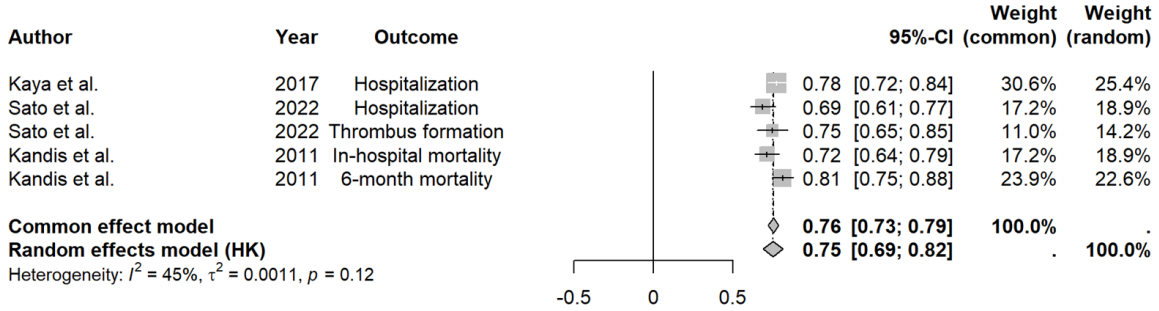

Figure 14. Pooled values of area under the curve for MPV.

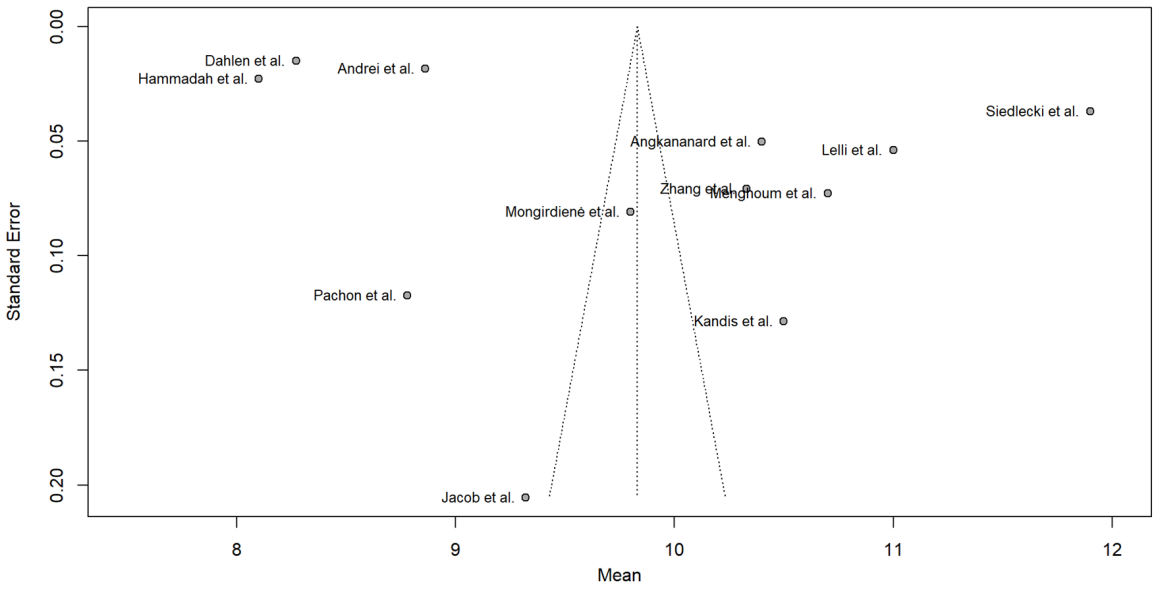

Figure 15. Funnel plot for the publication assessment of the studies pooling MPV values.

Publication bias

As mentioned earlier, Egger's regression and Begg's test were utilized to assess publication bias. In line with the symmetrical funnel plots (**Figures 15** and **16**), no publication bias was detected for studies pooled in terms of mean MPV value and MDs between survived/unaffected and deceased/affected subjects. Regarding the limited number of studies reporting the prognostic value of PDW, publication bias tests were not conducted for these studies.

Quality assessment

Results from a quality assessment using the QUIPS tool are summarized in **Table 4**. We

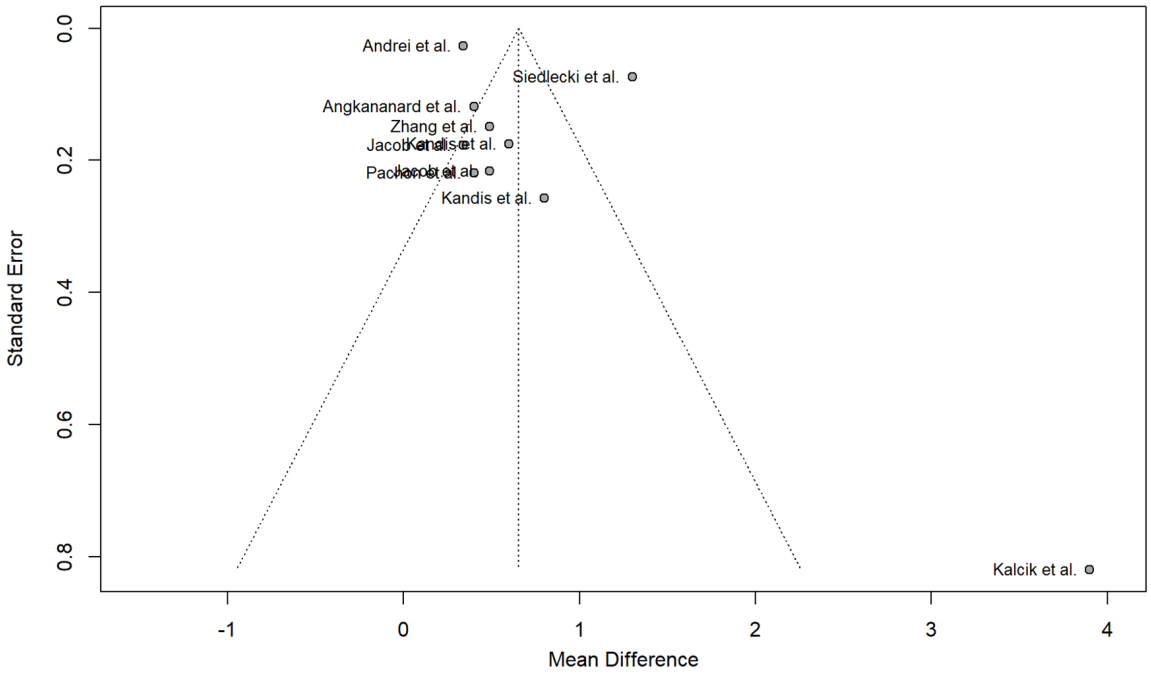

Figure 16. Funnel plot for the publication assessment of the studies pooling mean differences of the MPV values among the unaffected/survived ones and affected/deceased subjects.

Table 4. Quality assessment of the included studies using the QUIPS tool

Study	Study participation	Study attrition	Prognostic factor measurement	Study confounding	Outcome measurement	Statistical analysis and reporting	Overall assessment
Kalcik et al. (2015)	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Siedlecki et al. (2019)	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Mongirdienė et al. (2021)	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Kandis et al. (2011)	Moderate risk	Low risk	Moderate risk	Moderate risk	Low risk	Low risk	Low risk
Pachon et al. (2020)	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Andrei et al. (2022)	Moderate risk	Low risk	Moderate risk	Moderate risk	Low risk	Low risk	Low risk
Sato et al. (2022)	Moderate risk	Low risk	Moderate risk	Moderate risk	Low risk	Low risk	Low risk
Sato et al. (2022)	Moderate risk	Low risk	Moderate risk	Moderate risk	Low risk	Low risk	Low risk
Dahlen et al. (2021)	Moderate risk	Low risk	Moderate risk	Moderate risk	Low risk	Low risk	Low risk
Marques et al. (2023)	Low risk	Low risk	Low risk	moderate risk	Low risk	Moderate risk	Low risk
Zhang et al. (2019)	Low risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Moderate risk
Kaya et al. (2017)	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Moderate risk
Marques et al. (2023)	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Low risk	Moderate risk
Menghoum et al. (2023)	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Moderate risk
Angkananard et al. (2021)	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Moderate risk
Shore et al. (2012)	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Low risk	Moderate risk
Jacob et al. (2011)	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Low risk	Moderate risk
Hammadah et al. (2015)	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Moderate risk
Lelli et al. (2022)	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Catana et al. (2024)	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Catana et al. (2023)	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk

found that the majority of the studies exhibited a low risk of bias in the outcome measurement, statistical analysis, and reporting domains. For the remaining domains, the included studies had a moderate risk of bias. For the study by Lelli et al. and colleagues, we detected a high

risk of bias in the study attrition and confounding domains.

Discussion

Despite advances in medical knowledge and technologies, HF remains a major health burden and is anticipated to increase in prevalence in the upcoming years [2]. Risk stratification based on prognostic factors is crucial for implementing the most appropriate treatment and follow-up strategies and is a subject of growing interest in research. Therefore, this meta-analysis aimed to evaluate the potential prognostic value of MPV and PDW in HF.

Prior research has shown an association be tween platelet indices and numerous diseases, including diabetes, dyslipidemia, inflammatory bowel disease, rheumatoid arthritis, cardiovascular and cerebrovascular diseases, psoriasis, cancers, and even mental disorders [32-41]. MPV is the most commonly investigated platelet index and is known to indicate pro-inflammatory and pro-thrombotic states. It is reported to increase in cardiovascular disease, psoriasis, cerebrovascular disease, autoimmune thyroid disease, mood disorders, and malignant tumors [36-38, 40-42]. In contrast, decreased levels of MPV have been found in certain conditions, such as rheumatoid arthritis, ulcerative colitis, and attacks of familial Mediterranean fever [34, 35, 43]. Higher MPV is also reported in HF patients and has been investigated as a prognostic factor for short-term and long-term events in whether acute HF or chronic HF.

Our findings demonstrate that elevated MPV is consistently associated with adverse outcomes in HF, including mortality, cardiovascular events, hospitalization, AF, APE, renal failure, and thrombus formation (HR of 1.71 (1.24-2.36) and OR of 1.71 (1.44-2.03)). The pooled mean-difference analysis likewise demonstrated higher MPV levels in patients with rehospitalization, APE, cardiovascular events, HF decompensation, or death, compared to unaffected individuals, and ROC curves indicated good discriminatory ability (AUC of 0.75 (0.69-0.82)).

From a mechanistic perspective, we interpret the elevation in MPV as a marker of systemic inflammation and platelet activation. A higher MPV value indicates the presence of more giant platelets that contain more granules of pro-thrombotic factors, such as thromboxane A2, Adenosine Diphosphate, and Adenosine Triphosphate [23]. These platelets are more metabolically active, leading to greater adhesion and aggregation of platelets, which can contribute to the development of cardiovascular diseases. Tissue ischemia, platelet consumption within atherosclerotic plaques, and the secretion of inflammatory cytokines, such as IL-3 and IL-6, have a significant impact on megakaryocytes, leading to the release of larger, more active, and often deformed platelets [44, 45]. Platelets are known to secrete inflammatory agents, which can signal monocytes to enter the myocardial tissue and transform into macrophages [46]. This process can lead to impaired ventricular relaxation, which may have significant implications for cardiovascular health [47, 48]. Activated platelets release growth factors that promote the proliferation of smooth muscle cells, thereby reducing the elasticity of arteries [49]. On the other hand, medical treatments proven effective in HF patients, including beta-blockers, reduce MVP values and show the treatments' effectiveness in the long run [50].

In contrast, evidence for PDW was heterogeneous. PDW, a measure of variation in platelet size, is considered a specific marker for platelet activation and has been identified as an independent risk factor for coronary and peripheral artery disease [28, 51]. While several studies have evaluated the potential prognostic value of PDW in patients with HF, the findings have been inconsistent and inconclusive. In a survey by Marques et al., lower PDW values were associated with a higher risk of overall mortality after discharge and death without rehospitalization. In contrast, Sato et al. reported a positive correlation between higher PDW values and a higher risk of all-cause mortality [52]. Methodological variability (different cut-offs, endpoints, and follow-up durations) may explain the inconsistency. Until harmonized results emerge, PDW should be viewed as exploratory rather than definitive.

Some prognostic factors have been extensively evaluated in HF risk stratification. Natriuretic peptides, including BNP and NT-proBNP, are released in response to stretch and neurohormonal signals and are widely used as predictors of long-term prognosis [53]. MiRNAs play a

role in cardiac regulation and have recently been reported as biomarkers in HF [54]. hFABP is another marker for myocardial injury. Although it is considered highly specific for myocardial infarction, some studies have shown its value in predicting HF complications [55]. However, BNPs are still the most validated biomarkers in HF. In the present meta-analysis, MPV was positively correlated with NT-proBNP levels, suggesting that MPV may integrate information on both inflammatory load and neurohormonal stress. The key picture that emerges from these data is that MPV has the potential to be used as an indicator for HF prognosis.

Since BNP, miRNA, and hFABP tests are relatively expensive, alternative inflammatory markers were identified using the readily available CBC test. A CBC is one of the most easily accessible tests in the medical field and is reported to be about 150 times cheaper than an NT-proBNP test [56]. Hence, the prognostic role of markers, such as RDW, MPV, PDW, NLR, and PLR, is a topic of research interest. NLR is known to be indicative of worse prognosis in some conditions, such as sepsis, appendicitis, cirrhosis, Kawasaki disease, stroke, and malignancies [57-62]. A recent meta-analysis found an association between NLR and higher mortality rates in HF. Also, higher levels of NLR were reported in deceased patients in comparison to unaffected ones [63]. RDW was attributed to a worse prognosis in HF, as every 1% increase in RDW led to 10% higher mortality events based on another meta-analysis [64]. In contrast, the role of PLR as a prognostic factor in HF was investigated by Vakhshoori et al, showing no correlation with mortality risk [65].

Conclusion

To our knowledge, this study offers the most systematic insights yet into the prognostic value of platelet volume indices, namely MPV and PDW. A broad search strategy was employed to gather all relevant studies, and multiple statistical analyses were conducted to optimize accuracy. Our results suggest that MPV might be linked to key outcomes in HF, and through further research this simple parameter could be used in clinical practice to improve the care of HF patients. However, we failed to reach significant results regarding the predictive value of PDW. Notably, the findings of our study should be considered with caution, as we included studies with various outcomes and heterogeneous populations in the meta-analyses, which may introduce some bias into our results. Therefore, further studies need to be performed to clarify the significance of these indices in the prognosis of HF. More studies with advanced statistical analyses and meticulous designs are warranted so that future meta-analysis studies could generate more accurate results for clinical use.

Limitations

Our study should be interpreted in light of some limitations. First, the number of studies regarding this topic was limited, especially on PDW, as we could include only a few studies in the meta-analysis, particularly in the sensitivity analysis. Furthermore, since the demographic and clinical data of some of the included studies were inadequately described, we were unable to find the sources of heterogeneity in our meta-regression analyses. Another limitation of this meta-analysis is the use of random-effects model over multilevel approach, which might affect the pooled values. Future analyses should consider this method to enhance accuracy. Due to the aforementioned limitations, additional research with various settings and a large sample size is essential to draw definitive conclusions. We believe that future studies should focus on categorizing MPV and PDW values and determining reference ranges for these parameters to be used in clinical practice.

Disclosure of conflict of interest

None.

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