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Role of PDW and MPV in stratification of heart failure severity in older adults

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Background & Aims. Stratification of heart failure (HF) severity in older adults may be difficult. We hypothesized that mean platelet volume (MPV) and platelet distribution width (PDW) may serve as inflammation markers and used for this purpose. The objective of the study is to analyze the association between MPV/PDW and HF severity in older adults.
Methods. in this retrospective cross-sectional study, we enrolled 415 patients aged ≥ 65 years admitted for acute HF to an Acute Geriatric Ward. Participants were stratified according to the diagnosis of HF with preserved (HFpEF, N: 250) or non-preserved (HFmrEF/HFrEF, N: 165) ejection fraction. The association with ejection fraction (EF), NT-proBNP, right ventricular function (TAPSE), and diastolic function was analyzed using linear or multinomial regression models.
Results. mean age of the participants was 83.1 years (SD 7), 41.2% were male. MPV was positively associated with NT-proBNP in the total sample (Adjusted b: 0.16, p = 0.008) and in the HFmrEF/HFrEF group (Adjusted b: 0.215, p = 0.015), but not in the HFpEF group; no association was found with EF (analyzed only in HFmrEF/HFrEF group), or TAPSE. Using type I diastolic disfunction as reference, MPV was associated with an increased risk of monophasic pattern (Adj.OR: 1.44, 95% CI: 1.08-1.92) and III grade disfunction (Adj.OR: 1.54, 95% CI: 1.01-2.35) in the total sample, and in the HFmrEF/HFrEF group (Monophasic Adj.OR: 2.51, 95% CI: 1.33-4.74; III grade Adj.OR: 4.77, 95% CI: 2.05-11.1). Similar results were found analyzing PDW.
Conclusions. MPV and PDW are inexpensive and simple potential markers of HFmrEF/HFrEF severity in older adults. Further studies are needed to clarify their classificatory and prognostic properties.

Key words: heart failure, mean platelet volume, older adults, platelet activation, platelet distribution width

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INTRODUCTION

Most of the patients affected by heart failure (HF) are older adults, a population often characterized by the coexistence of many comorbidities and by polypharmacy. Thus, the differential diagnosis and the severity stratification of HF in these patients might be difficult, given the overlapping symptoms of many diseases, the increasing prevalence of atypical symptoms and signs, and the difficulty in performing echocardiography in disabled and bedridden patients [1].
Platelet overactivation is a common feature of HF patients [2], and it may progressively increase during the natural history of the disease. Several

pathophysiologic characteristics of HF contribute to this phenomenon: high catecholamine concentration [3], activation of the renin-angiotensin system [4], and release of pro-inflammatory cytokines [5], all contribute to platelet activation. Activated platelet are implicated in increased risk of thromboembolism [2], but also contribute to inflammation by producing a wide range of pro-inflammatory cytokines, such as IL-1 and CC chemokines [6]. Thus, platelet activity may be associated with the severity of HF.

Recently, mean platelet volume (MPV) and platelet distribution width (PDW) have been proposed as a simple, inexpensive and widely available markers of platelet activation [7,8]: activated platelets change their morphology, becoming larger (affecting the MPV), and of different size due to pseudopodia formation (affecting the PDW) [6]. An elevation of these markers has been associated with diagnosis of coronary artery disease and with increased cardiovascular risk in patients with ischemic cardiopathy and acute coronary syndromes [9,10], and some studies documented an association with ejection fraction [11] and diastolic function [12].

Only few studies on the association between MPV and outcomes are available among HF patients, all with a small sample size and focused on patients with reduced ejection fraction only; furthermore, no information is available on PDW as indicator of platelet activity. These studies showed that acute HF (AHF) patients have higher MPV values with respect to patients with chronic HF or without HF [13-15]. The association between MPV and severity of HF, however, has been poorly investigated: to our knowledge, only two studies have been published, showing an inverse association with ejection fraction [16] and a positive association with natriuretic peptides [14]. Once again, no information is available on PDW.

None of the above-mentioned studies provide specific information on older adults, a population in which many other factors may influence platelet activation, such as comorbidities, pharmacological therapy and inflamm-aging [17,18] and in which, consequently, the association between platelet activation and severity of HF might be different compared to younger people. Furthermore, no studies evaluated the role of platelet activation both in patients with HF with preserved ejection fraction (HFpEF), mild reduced ejection fraction (HFmrEF), and reduced ejection fraction (HFrEF).

The objective of this study was to analyze the association between MPV/PDW and severity indicators of HF in a population of older adults admitted to an Acute Geriatric Ward with a diagnosis of AHF, stratified according to diagnosis of HFpEF, HFmrEF, or HFrEF.

PATIENTS AND METHODS

Study design and population

In this retrospective study, we reviewed medical records of all the patients admitted to the Geriatric Acute Care Ward of Campus Bio-Medico Teaching Hospital in Rome from 1st December 2009 to 30th June 2018. Inclusion criteria were age ≥ 65 years and a diagnosis of acute HF, performed according to the latest ESC guidelines [19]. We excluded patients with acute coronary syndrome during the hospital stay, active cancer, end-stage kidney disease, or any history of platelet disorders, because these conditions can influence platelet activation [20-22].

Measurements

Demographic characteristics, medical history, discharge diagnosis, and main comorbidities were systematically collected from the hospital medical records. We considered the results of the analysis of venous blood sampling performed within 24 hours from admission. For platelet count, the blood samples were collected into commercial tubes containing dipotassium ethylenediaminetetraacetic acid at room temperature and were analyzed within 4 hours of venipuncture on an automated blood cell counter (Sysmex Serie XN, DASIT S.p.A., Milan, Italy). Renal function was estimated using the CKD-EPI formula.

Echocardiography was performed to all patients during the hospital stay by a qualified trained physician. Left ventricular ejection fraction was calculated using the Simpson method (monoplane in patients without segmental systolic disfunctions, or biplane for those with segmental systolic disfunctions); diastolic function was evaluated calculating the E and A waves and the E deceleration time through the mitral valve; right ventricular systolic function was evaluated using the tricuspid annular systolic excursion (TAPSE). Quantification of valvular dysfunction, chambers dimensions, and systolic pulmonary artery pressure (sPAP) were also systematically collected.

Diagnosis and classification of HF (HFrEF, HFmrEF, and HFpEF) were performed according to the ESC guidelines for the diagnosis and treatment of acute and chronic HF [19].

Outcomes

Severity indicators of HF taken into account were left ventricular ejection fraction, calculated using the modified Simpson's method, right ventricular systolic function, evaluated using the tricuspid annular plane systolic excursion (TAPSE), diastolic function (degree of diastolic dysfunction), and NT-proBNP, that has a prognostic role also in older people [23].

Statistical analysis

We enrolled 415 patients; 250 were affected by HFpEF, 56 by HFmrEF, and 109 by HFrEF. Due to the relatively small sample of HFmrEF, these patients were analyzed in the same group of HFrEF (HFrEF/HFrmEF group). The characteristics of the study sample were reported using descriptive statistics (mean and standard deviation for continuous variables, proportion for categorical variables), according to HF classification. The comparison between groups was performed using Student t-test for continuous variables and chi-squared test for categorical ones. NT-proBNP was log-transformed to obtain a normal distribution.

The association between MPV/PDW and ejection fraction, right ventricular systolic function, and NT-proBNP, was evaluated using Pearson's correlation test and linear regression models, both in whole population and in the different classes of HF (the association with ejection fraction was not analyzed in the HFpEF subgroup). The association with diastolic function was assessed using multinomial regression models, using grade I diastolic disfunction as a reference (physiologically evident in older adults [24]). The models were then adjusted for potential confounders, selected on the basis of the clinical significance and prior knowledge (age, sex, anti-platelet drugs, ESR, platelet number, eGFR, hemoglobin, ACE-inhibitors or ARBs treatment).

All the analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

General characteristics of the population

The mean age of the study sample was 83.1 years (SD: 7), 41.2% were male. Compared to HFrEF/HFrmEF, participants in the HFpEF group were older (84.1 years, SD 6.6 *vs* 81.5 years, SD 7.3, $p < 0.001$), less frequently male (30 *vs* 58.2%, $p < 0.001$), had lower serum hemoglobin concentration (11.9 g/dl, SD 2.1 *vs* 12.3 g/dl, SD 1.8, $p = 0.021$), PDW (12.9 fl, SD 2.6 *vs* 13.9 fl, SD 2.8, $p < 0.001$), MPV (10.8 fl, SD 1.1 *vs* 11.2 fl, SD 1.1, $p < 0.001$), and higher PLT concentration (236.900/ul, SD 87.000 *vs* 212.000/ul, SD 80.900, $p = 0.003$), and erythrocyte sedimentation rate (ESR) (73.1 mm/h, SD 37.3 *vs* 62 mm/h, SD 34.4, $p = 0.003$) (Tab. I).

Table I. General characteristics of the population according to HF class.

	HFpEF N: 250	HFrEF/HFmrEF N: 165	All N: 415	P
Age (years), mean(SD)	84.1 (6.6)	81.5 (7.3)	83.1 (7)	< 0.001
Male sex, %	75 (30)	96 (58.2)	171 (41.2)	< 0.001
BMI (kg/m^2), mean(SD)	27.8 (7.7)	26.9 (5.2)	27.4 (6.8)	0.280
Hypertension, %	188 (75.2)	104 (63)	292 (70.4)	0.011
IHD, %	66 (26.4)	66 (40)	132 (31.8)	0.005
Atrial fibrillation, %	146 (58.4)	92 (55.8)	238 (57.3)	0.666
Dyslipidemia, %	35 (14)	31 (18.8)	66 (15.9)	0.243
Type II Diabetes, %	74 (29.6)	58 (35.2)	132 (31.8)	0.280
COPD, %	51 (20.4)	43 (26.1)	94 (22.7)	0.219
Never smoking, %	133 (58.1)	65 (42.5)	198 (51.8)	0.006
Previous smoking, %	87 (38)	75 (49)	162 (42.4)	
Current smoking, %	9 (3.9)	13 (8.5)	22 (5.8)	
eGFR (ml/min/1.73m^2), mean (SD)	53.5 (20.2)	52.8 (20.5)	53.2 (20.3)	0.743
Hemoglobin (g/dl), mean (SD)	11.9 (2.1)	12.3 (1.8)	12 (2)	0.021
MCV (fl), mean (SD)	88.5 (7.6)	89.5 (6.6)	88.9 (7.2)	0.193
PLT (*1.000/uL), mean (SD)	236.9 (87)	212 (80.9)	227 (85.4)	0.003
PDW (fl), mean (SD)	12.9 (2.6)	13.9 (2.8)	13.3 (2.7)	< 0.001
MPV (fl), mean (SD)	10.8 (1.1)	11.2 (1.1)	11 (1.1)	< 0.001
ERS (mm/h), mean (SD)	73.1 (37.3)	62 (34.4)	68.7 (36.6)	0.003
INR, mean (SD)	1.4 (0.8)	1.4 (0.8)	1.4 (0.8)	0.792
Total cholesterol (mmol/l), mean (SD)	4.01 (1)	3.70 (1.05)	3.9 (1.03)	0.002
LDL (mmol/l), mean (SD)	2.37 (0.79)	2.2 (0.78)	2.3 (0.79)	0.030
HDL (mmol/l), mean (SD)	1.24 (0.38)	1.16 (0.41)	1.2 (0.39)	0.048
Triglycerides (mmol/l), mean (SD)	1.19 (0.62)	1.12 (0.48)	1.16 (0.57)	0.178

Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; ERS: erythrocyte sedimentation rate; INR: international normalized ratio; MCV: mean corpuscular volume; MPV: mean platelet volume; PLT: platelet; PDW: platelet distribution width

Table II. Echocardiographic characteristics and cardiologic pharmacologic treatment according to HF class.

	HFpEF N: 250	HFrEF/HFmrEF N: 165	All N: 415	P
Ejection fraction (%), mean (SD)	57.6 (5)	33.5 (9.2)	48 (13.7)	< 0.001
Left ventricular end diastolic diameter (mm), mean (SD)	45.8 (7.3)	55.1 (8.5)	49.4 (9)	< 0.001
Left ventricular diastolic function				
Diastolic Monophasic pattern, %	121 (53.1)	97 (68.3)	218 (58.9)	0.002
Diastolic disfunction, grade I, %	70 (30.7)	19 (13.4)	89 (24.1)	
Diastolic disfunction, grade II, %	23 (10.1)	16 (11.3)	39 (10.5)	
Diastolic disfunction, grade III, %	14 (6.1)	10 (7)	24 (6.5)	
TAPSE (mm), mean (SD)	19.1 (4)	16.1 (3.7)	18.1 (4.2)	< 0.001
Normal PAPS, %	75 (33.6)	37 (25.9)	112 (30.6)	0.027
Mild pulmonary hypertension, %	71 (31.8)	39 (27.3)	110 (30.1)	
Moderate pulmonary hypertension, %	39 (17.5)	44 (30.8)	83 (22.7)	
Severe pulmonary hypertension, %	38 (17)	23 (16.1)	61 (16.7)	
ASA, %	67 (26.8)	71 (43)	138 (33.3)	< 0.001
Other antiplatelet agents, %	32 (12.8)	24 (14.5)	56 (13.5)	0.717
Oral anticoagulants, %	82 (32.8)	47 (28.5)	129 (31.1)	0.412
Subcutaneous LMWH, %	81 (32.4)	49 (29.7)	130 (31.3)	0.636
ACE-inhibitors or ARBs, %	132 (52.8)	93 (57.1)	225 (54.5)	0.455
Potassium channel blockers, %	0.4 (0.5)	0.5 (0.5)	0.4 (0.5)	0.280
Furosemide, %	239 (96.8)	160 (97)	399 (96.8)	1
B-blockers, %	152 (60.8)	111 (67.3)	263 (63.4)	0.217
HMG-inhibitors, %	65 (26)	61 (37)	126 (30.4)	0.023

Abbreviations: ARB: angiotensin II receptor blocker; ASA: acetylsalicylic acid; HMG: 3-hydroxy-3-methylglutaryl; LMWH: low molecular weight heparin; TAPSE: tricuspid annular plane systolic excursion

Mean ejection fraction was 57.6% (SD 5) in HFpEF participants and 33.5% (SD 9.2) in HFmrEF/HFrEF. Patients affected by HFpEF had less frequently a diastolic monophasic pattern (53.1 *vs* 68.3%, p = 0.002) (in the whole sample, no patients had a normal diastolic function), and a higher TAPSE (19.1 mm, SD 4 *vs* 16.1 mm, SD 3.7, p < 0.001). Regarding cardiologic pharmacological treatment, there were no differences between groups, with the exception of acetylsalicylic acid and HMG-inhibitors, that were administrated less frequently in the HFpEF group (26.8 *vs* 43%, p < 0.001 and 26 *vs* 37%, p = 0.023, respectively) (Tab. II).

MPV and outcomes

Total HF population

There was a positive correlation between MPV and the log-transformed NT-proBNP (r: 0.136, p = 0.034) (Fig. 1). This association was confirmed in a linear regression model adjusted for potential confounders (b 0.16, p = 0.008) (Tab. III). There was no association between MPV and TAPSE (Adj. b 0.13, p = 0.664).

With respect to I grade diastolic dysfunction, increase in MPV was associated with a higher risk of monophasic pattern (Adj. OR 1.44, 95% CI 1.08-1.92), and of grade III diastolic disfunction (Adj. OR 1.54, 95% CI 1.01-2.35), but not with grade II diastolic function (Adj. OR 1.25, 95% CI 0.87-1.79) (Tab. III).

HFrEF/HFmrEF subsample

There was a negative association between MPV and ejection fraction (b -1.33, p = 0.050), that was not confirmed after adjustment for potential confounders (b -1.12, P = 0.154) (Tab. III).

There was a slight positive association with log-transformed NT-proBNP (r: 0.128, P = 0.126) (Fig. 1), that became more evident after adjustment for potential confounders (b 0.215, p = 0.015) (Tab. III).

Using grade I disfunction as a reference, for increasing MPV values, an increased risk of monophasic pattern and of grade III disfunction was evident (Adj. OR 2.51, 95% CI 1.33-4.74 and Adj. OR 4.77, 95%CI 2.05-11.1, respectively) (Tab. III).

HFpEF subsample

There was no association between MPV and NT-proBNP (r: 0.002, p = 0.980) (Fig. 2); the lack of association was confirmed also after adjustment for potential confounders (b 0.063, p = 0.389). Similarly, a lack of association with TAPSE was observed (b Adjusted 0.583, p = 0.113) (Tab. III).

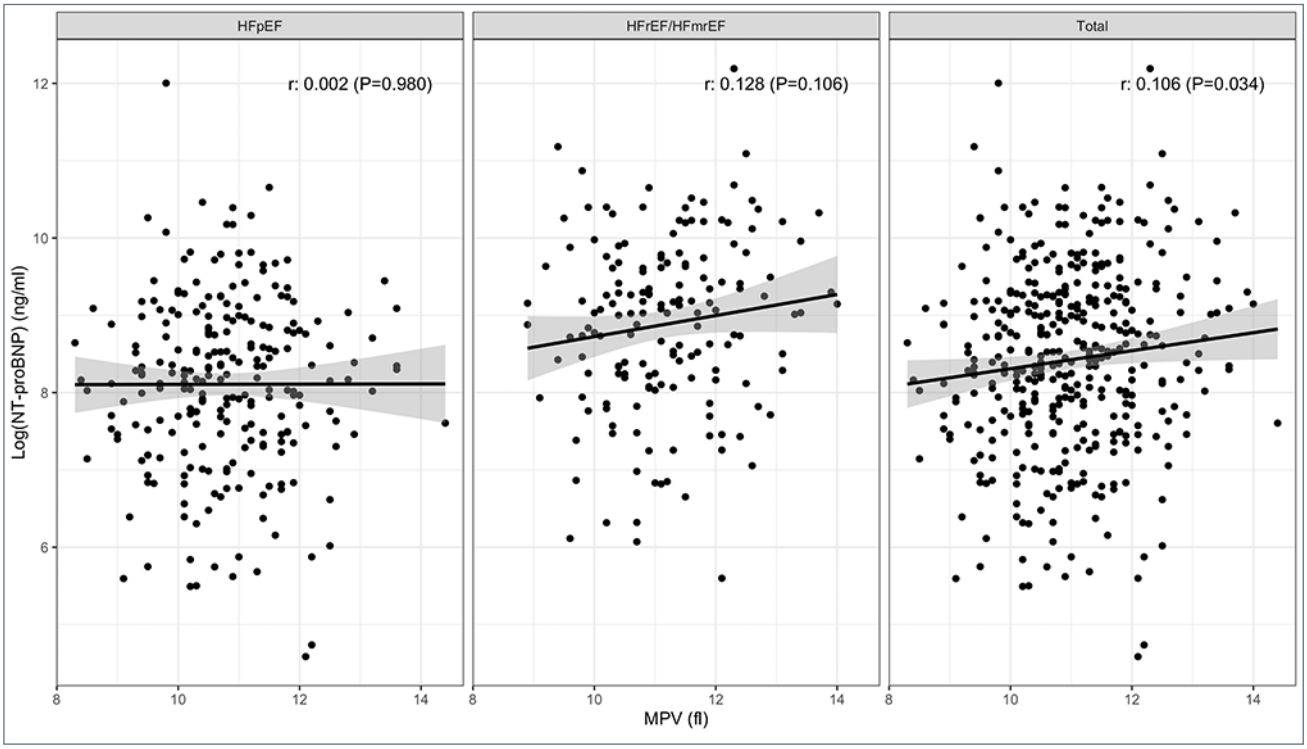

Figure 1. Correlation between MPV and NT-proBNP. The association between MPV and log-transformed NT-proBNP is showed according to heart failure class and for the overall population.

Table III. Linear regression models of the association between MPV and cardiac function.

	Total		HFrEF/HFmrEF		HFpEF	
	Crude b (P)	Adjusted† b (P)	Crude b (P)	Adjusted† b (P)	Crude b (P)	Adjusted† b (P)
Ejection fraction	-	-	-1.33 (P = 0.050)	-1.12 (P = 0.154)	-	-
Log(NT-proBNP)	0.12 (0.034)	0.16 (0.008)	0.136 (P = 0.106)	0.215 (P = 0.015)	0.002 (P = 0.98)	0.063 (P = 0.389)
TAPSE	-0.12 (0.655)	0.13 (0.664)	-0.178 (P = 0.667)	0.255 (P = 0.575)	0.422 (P = 0.189)	0.583 (P = 0.113)
Diastolic function						
	OR crude (95%CI)	OR adjusted* (95%CI)	OR crude (95%CI)	OR adjusted* (95%CI)	OR crude (95%CI)	OR adjusted* (95%CI)
Grade I	Reference	Reference	Reference	Reference	Reference	Reference
Monophasic pattern	1.33 (1.04-1.69)	1.44 (1.08-1.92)	1.45 (0.87-2.41)	2.51 (1.33-4.74)	1.22 (0.89-1.68)	1.19 (0.89-1.58)
Grade II	1.22 (0.85-1.74)	1.25 (0.87-1.79)	1.23 (0.63-2.40)	1.18 (0.56-2.48)	1.24 (0.78-1.97)	1.16 (0.74-1.82)
Grade III	1.30 (0.84-1.99)	1.54 (1.01-2.35)	2.02 (0.95-4.28)	4.77 (2.05-11.1)	0.95 (0.54-1.68)	0.89 (0.51-1.57)

†Models adjusted for age, sex, eGFR, antiplatelet drugs, treatment with ARBs/ACE-inhibitors, platelet number, ERS, hemoglobin

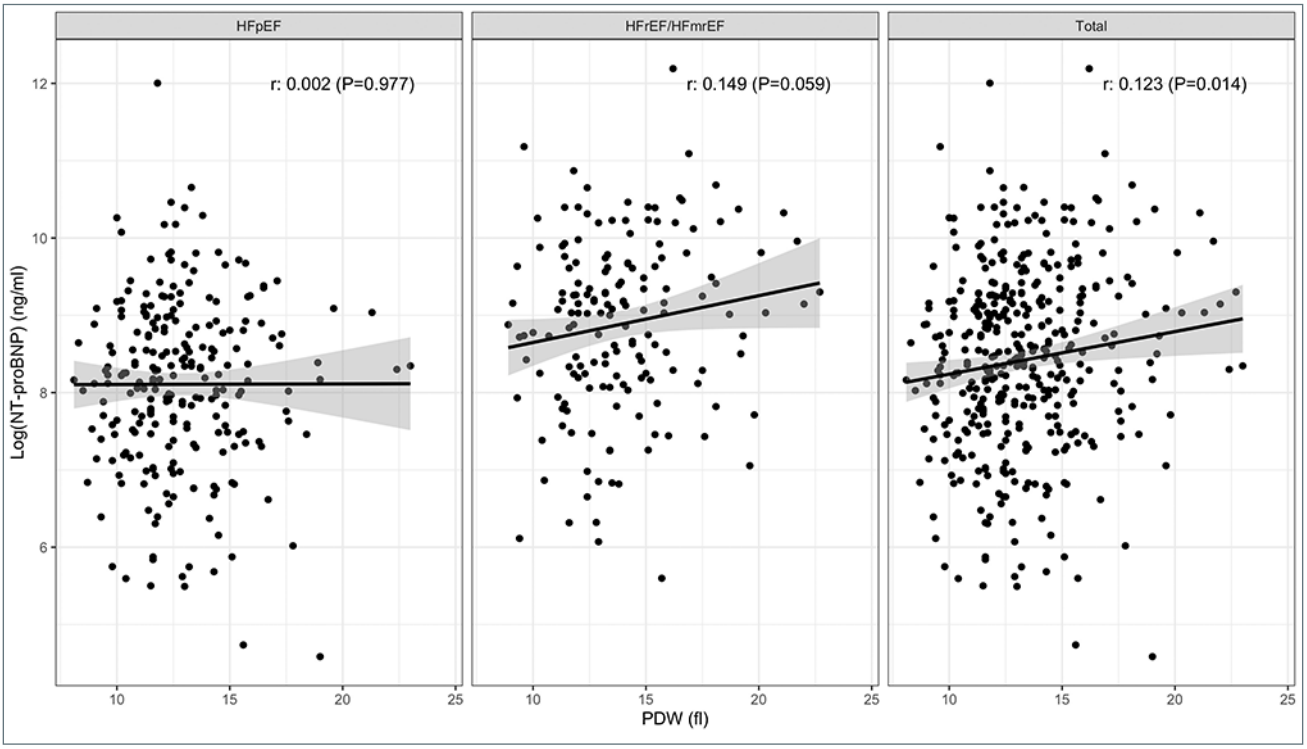

Figure 2. Correlation between PDW and NT-proBNP. The association between PDW and log-transformed NT-proBNP is showed according to heart failure class and for the overall population.

MPV was not associated with increased risk of diastolic dysfunction different from grade I, both in a crude and adjusted multinomial regression model (Tab. III).

PDW AND OUTCOMES

Total HF population

PDW was positively correlated with NT-proBNP (r: 0.123, p = 0.014) (Fig. 2); the association was confirmed after adjustment for potential confounders (b 0.07, p = 0.004). No association was evident with TAPSE (b adjusted -0.09, p = 0.485) (Tab. IV).

With respect to association with type I disfunction, increasing PDW values were associated with a slight increased risk of monophasic pattern (adj. OR 1.12, 95% CI 0.99-1.26) and III grade disfunction (adj. OR 1.18, 96% CI 0.97-1.43), but not of grade II disfunction (Tab. IV).

HFrEF/HFmrEF subsample

PDW was not associated with ejection fraction (Adj. b -0.126, p = 0.462). Similarly, it was not associated with TAPSE (adjusted b 0.02, p = 0.875) (Tab. IV).

A positive correlation with NT-proBNP was observed (r: 0.149, p = 0.059) (Fig. 1); the association was confirmed after adjustment for potential confounders (b 0.079, p = 0.015) (Tab. IV).

With respect to association with grade I disfunction, increasing PDW values were associated with an increased risk of monophasic pattern (adj. OR 1.40, 95% CI 1.05-1.86) and III grade disfunction (adj. OR 1.67, 96% CI 1.15-2.42) (Tab. IV).

HFpEF subsample

PDW was not associated with NT-proBNP (Fig. 1), also after adjustment for potential confounders (b 0.03, p = 0.345), nor with TAPSE (Adj. b 0.127, P = 0.490) or with diastolic function (Tab. IV).

DISCUSSION

In our sample of older adults affected by AHF we found no association between MPV or PDW and left or right systolic function, while both MPV and PDW were associated with diastolic function and NT-proBNP concentration. Stratifying for classification of HF, this association was not evident in patients with HFpEF.

To the best of our knowledge, this is the first study focused on older adults analyzing the association between MPV/PDW and severity of HF, and the first analyzing separately patients with HFpEF. In fact, the association between platelet activation and echocardiographic characteristics or natriuretic peptides has

Table IV. Regression models of the association between PDW and cardiac function.

	Total		HFrEF/HFmrEF		HFpEF	
	Crude b (P)	Adjusted† b (P)	Crude b (P)	Adjusted† b (P)	Crude b (P)	Adjusted† b (P)
Ejection fraction	-	-	-0.182 (P = 0.416)	-0.176 (P = 0.462)	-	-
Log(NT-proBNP)	0.05 (0.014)	0.07 (0.004)	0.061 (P=0.059)	0.079 (P = 0.015)	0.001 (P = 0.977)	0.030 (P = 0.345)
TAPSE	-0.16 (0.139)	-0.09 (0.485)	-0.122 (P = 0.408)	0.02 (P = 0.875)	0.074 (P = 0.594)	0.127 (P = 0.490)
Diastolic function						
	OR crude (95%CI)	OR adjusted* (95%CI)	OR crude (95%CI)	OR adjusted* (95%CI)	OR crude (95%CI)	OR adjusted* (95%CI)
Grade I	Reference	Reference	Reference	Reference	Reference	Reference
Monophasic pattern	1.08 (0.98-1.19)	1.12 (0.99-1.26)	1.13 (0.92-1.38)	1.40 (1.05-1.86)	1.02 (0.91-1.15)	1.02 (0.88-1.19)
Grade II	1.04 (0.90-1.21)	1.08 (0.91-1.28)	1.04 (0.79-1.36)	1.04 (0.73-1.49)	1.03 (0.86-1.24)	1.10 (0.89-1.36)
Grade III	1.10 (0.93-1.30)	1.18 (0.97-1.43)	1.29 (0.98-1.70)	1.67 (1.15-2.42)	0.92 (0.71-1.19)	0.91 (0.68-1.23)

†Models adjusted for age, sex, eGFR, antiplatelet drugs, treatment with ARBs/ACE-inhibitors, platelet number, ERS, hemoglobin

been previously investigated in other populations, such as patients with ischemic heart disease or idiopathic cardiomyopathy [25], or patients admitted to a Cardiology Department for any cause [12], finding an association with ejection fraction and diastolic disfunction. Despite the evidence available on platelet activation documented in patients with HF compared to healthy controls [15,26], the association with severity of HF has been poorly investigated. In a sample of patients admitted to Emergency Department for dyspnea, Budak et al. found a correlation between MPV and BNP [14], but participants with AHF were not analyzed separately and the association was not adjusted for potential confounders. Karadag et al investigated the association between MPV and ejection fraction in a sample of 114 patients with stable HF and of 69 healthy controls, finding an inverse association between MPV and ejection fraction after adjustment for potential confounders [16].

Our study confirmed the available evidence on the association between MPV and natriuretic peptides in a sample of patients with AHF, but only in patients with reduced or mildly reduced ejection fraction. With respect to ejection fraction, in our sample there was no association with this outcome. To the best of our knowledge, only one study investigated this association in patients with HF, finding an inverse relationship [16]. However, this study was performed in a younger population: older adults have higher platelet activation [27], and the high number of comorbidities, that are common feature of this population, contribute to further platelet activation [28], thus potentially influencing the association between platelet activation and cardiac function.

We documented an association between MPV/PDW and diastolic function in patients with reduced or mildly reduced ejection fraction. To the best of our knowledge, this association has never been previously investigated in a population with HF, while evidence of such association was documented in a sample of patients admitted to a cardiology department for any cause [12].

The lack of association between MPV and PDW and severity indicators of HF in patients with preserved ejection fraction documented in our population might be related to a lower mechanical stress of blood stream in the heart of patients with preserved ejection fraction, that causes less platelet activation [29] and consequently a less evident relationship with outcomes. Instead, in patients with reduced or mild reduced ejection fraction, the larger ventricular diameters may cause a higher platelet mechanical stress and consequent further activation, that reflects to a stronger relationship between MPV/PDW values and diastolic function or natriuretic peptides. This hypothesis is supported also by the evidence of similar platelet activation in patients with ischemic or other cause HF with reduced ejection fraction, that was higher with respect to patients affected by coronary artery disease [30].

Our study has some limitations: first, it has a retrospective design; second, it included patients with AHF only, and therefore our results may not be generalizable to chronic HF. Furthermore, being the setting an acute care ward, other acute diseases may influence the platelet activation of patients with chronic HF, potentially introducing biases. Third, the NYHA class at admission was not available.

In conclusion, PDW ed MPV qualify as inexpensive and easily available indicators of diastolic dysfunction and HF severity in older adults with AHF with reduced or mild reduced ejection fraction. This testifies to their biologic plausibility, given multimorbidity and intrinsic complexity are the hallmark of this population. However, confirmatory studies are needed to verify whether and to which extent PDW and MPV could improve the classification

of HF patients. Finally, testing their prognostic implication with prospective studies will definitively clarify their role in the diagnostic armamentarium of HF even in the very old. If these results will be confirmed, MPV and PDW will be help to stratify heart failure severity, and may prove useful as a adjunctive information to provide a tailored treatment and disease management of older adults with physical or logistical difficulties in performing echocardiography.

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Conflict of interest
The Authors declare no conflict of interest.

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Author contributions
DL, CP, and RAI contributed to the study conception and design; DL, VA, GM, and IB contributed to the acquisition of data.
Data analysis were performed by DL, and were interpreted by all the Authors.
The first draft of the manuscript was written by DL, and all Authors commented on previous versions of the manuscript.
All Authors read and approved the final manuscript.

Ethical consideration
This study was approved by the Campus Bio-Medico University Ethic Committee (65/18 OSS ComEt CBM).
The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.
Written informed consent was obtained from each participant/patient for study participation and data publication.

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