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Heart Failure

Mean Platelet Volume as a Predictor of Heart Failure-Related Hospitalizations in Stable Heart Failure Outpatients with Sinus Rhythm

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Background: In this study, we investigated the relationship between the mean platelet volume (MPV) with mortality and heart failure (HF)-related hospitalization in stable chronic HF outpatients with reduced ejection fraction (HFrEF) and with sinus rhythm (SR).

Methods: This retrospective cohort study included 197 consecutive stable chronic HFrEF outpatients with SR, who were admitted to our cardiology outpatient clinics for examination between January 2014 and January 2015. According to the receiver-operating characteristic curve analysis, the optimal cut-off value of MPV to predict HF-related hospitalization was > 9.1 fL. Patients were classified into two categories according to threshold MPV levels, as group I with MPV ≤ 9.1 fL and group II with MPV > 9.1 fL.

Results: The mean age of patients was 65 ± 13 years. The mean follow-up duration was 10 ± 3 months, and 44 patients (22%) succumbed to cardiovascular (CV) death. The rate of CV mortality was similar between the two groups (21% vs. 24%, p = 0.649). However, the rate of patients who experienced HF-related hospitalization was lower in group I compared with group II (41% vs. 87%, p < 0.001, respectively). Univariate analysis demonstrated associations of many clinical factors in addition to increased MPV > 9.1 fL with HF-related hospitalization; however, In the multivariate Cox proportional-hazards model, only increased MPV > 9.1 fL (HR: 2.895, 95% CI: 1.774-4.724, p < 0.001), systolic pulmonary artery pressure level (HR: 1.018, 95% CI: 1.001-1.036, p = 0.048) and pre-admission beta blocker use (HR: 0.517, 95% CI: 0.305-0.877, p = 0.014) remained associated with a risk of HF-related hospitalization.

Conclusions: The mean platelet volume might be a useful parameter for risk stratification with regard to HF-related hospitalization in HFrEF outpatients with SR.

Key Words: Cardiovascular mortality • Heart failure • Hospitalization • Mean platelet volume

INTRODUCTION

Although there have been advances in the treatment of heart failure (HF) in recent years, it remains a condition with a poor prognosis. Chronic HF patients are often admitted to the hospital with acute symptoms. Although various mechanisms have been proposed, the reasons for the development of acute decompensation in stable chronic HF patients are still unclear.[1,2]

The mean platelet volume (MPV) is an inexpensive and easy-to-use parameter, and its elevation shows an increase in the size and activity of platelets.[3] Previously, MPV has been shown to be elevated in many cardiovascular pathologies and increased MPV levels in atrial fibrillation (AF), acute myocardial infarction, and cerebral infarction have been associated with increased platelet activity.[4,5] In addition, it has also been demonstrated

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that MPV increases in decompensated HF patients and is an independent predictor of six-month mortality following decompensation, and correlated with disease severity in acute HF patients.[6,7]

According to our research, there have been no previous studies assessing the relationship of MPV levels with follow-up cardiovascular mortality and HF-related hospitalization in stable chronic HF outpatients without AF or acute decompensation leading to MPV elevation. In this study, we aimed to evaluate the relationship of MPV and HF-related outcome in stable patients with chronic heart failure with reduced ejection fraction (HFrEF).

MATERIAL AND METHODS

Patients

This retrospective cohort study initially comprised a total of 886 consecutive HF patients who were admitted to our cardiology outpatient clinics for examination between January 2014 and January 2015. A total of 197 patients who had stable HFrEF with sinus rhythm (SR) were included in the study. Patients with acute decompensated HF and those with cardiac rhythm other than SR were excluded. Other exclusion criteria were as follows: acute coronary syndromes or cerebrovascular accidents within the past three months, the use of warfarin or other anticoagulants for any reason, the use of antiplatelet medications other than aspirin, existing pregnancy, and overt/active hematological, renal, hepatobiliary, respiratory, immunological, inflammatory, infectious, and malignant disorders (Figure 1). Outcomes concerning cardiovascular (CV) death and HF-related hospitalization were assessed by an independent study coordinator who gathered and reviewed the hospital's medical records and made necessary phone calls for outcome data. Demographic data, medical history, clinical characteristics, and laboratory test results were collected from the hospital database. Hypertension was defined as blood pressure of ≥ 140/90 mmHg on more than two occasions during office measurements, or receiving an anti-hypertensive medication. Diabetes mellitus was defined as a fasting blood glucose of ≥ 126 mg/dL or receiving an anti-diabetic medication. Coronary artery disease (CAD) was recorded to be present if there was a clinical history of CAD, abnormal stress test results with evidence of ischemia, or documented coronary stenosis > 50%. Stable systolic heart failure was defined as the New York Hear Association (NYHA) Functional Class I-III patients with an ejection fraction (EF) of < 50%, who were followed at the cardiology outpatient clinics and in whom the NYHA Class remained unchanged in the previous month. Heart failure-related hospitalization was defined as the presence of clinical signs or symptoms of HF requiring the use of intravenous diuretics of at least 40 mg furosemide on admission and hospitalization in either a ward or coronary care unit (CCU) or intensive care unit (ICU) lasting more than three days. Cardiovascular death was defined as mortality due to acute coronary syndrome (ACS), sudden death, HF, or stroke. The patients were divided into two groups: those with a MPV level of ≤ 9.1 fL (Group 1; n = 91) and those with a MPV level of > 9.1 fL (Group 2; n = 106).

Written informed consent was obtained from each patient, and the study protocol was approved by the Institutional Review Board. The study was performed in accordance with the principles of the Declaration of Helsinki for Human Research.

Laboratory measurements

After an overnight fasting, blood samples were drawn in the morning from the antecubital vein using a sterile 21-gauge needle syringe without stasis. For platelet count and MPV measurements, blood samples were collected in 2 mL tubes (Vacutainer®, Becton, Dickinson and Company, Franklin Lakes, NJ, USA) containing 3.6 mg of dry dipotassium ethylenediaminetetraacetic acid (EDTA). These whole blood samples were then analyzed within 30 minutes of venipuncture on an automated blood cell counter (Coulter® Gen. STM, Beckman Coulter, Inc., Brea, CA, USA). Both intra- and inter-assay coefficients of variation for all measurements were < 5%.

Echocardiographic measurements

Using the Vivid 7 system (GE Medical System) with 2.5-5 MHz probes, experienced echocardiographers performed the examinations, and digital records of the echocardiographic examinations were evaluated offline. The left ventricular ejection fraction (LVEF) was calcu-

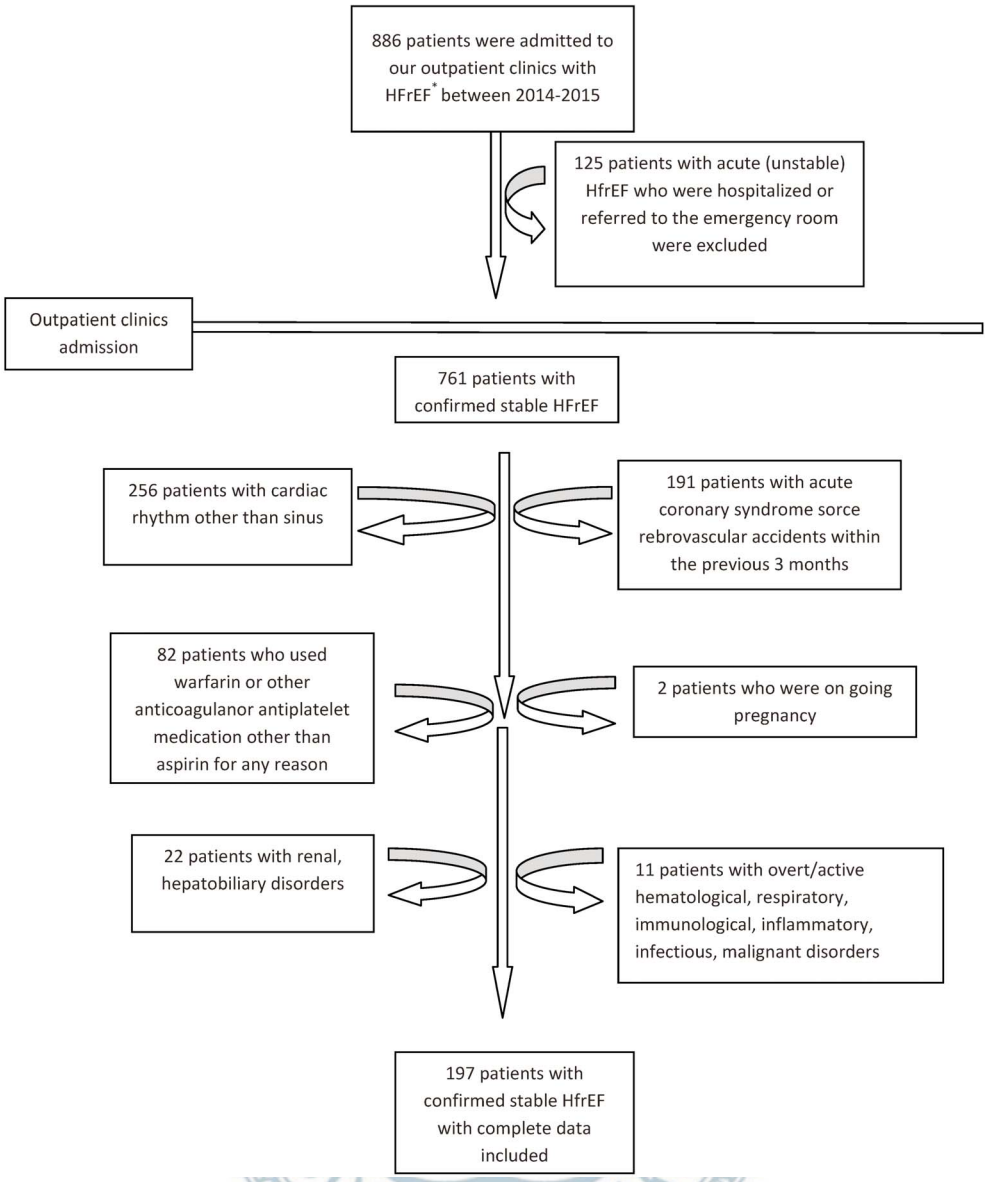

Figure 1. *Patient flow chart. * HfrEF, heart failure with reduced ejection fraction.*

lated using the Modified Simpson's method. The chamber sizes were defined according to the recent guidelines. The right ventricular (RV) dimensions were evaluated according to the most recent guideline[8] and, hence, midcavity and/or basal RV diameters above and below the reference range in the apical 4-chamber view at the end diastole were considered.[9] The LA size was measured at the endventricular systole by M-mode linear dimensionfrom the parasternal long axis view. Systolic pulmonary artery pressure (sPAP) was estimated from the velocity of tricuspid regurgitation.[9]

Statistical analysis

Statistical analysis was performed using the SPSS version 14.0 software (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to confirm the normality of the distribution of continuous variables. Continuous variables were expressed as mean ± SD or median (min-max) in the presence of abnormal distribution, and categorical variables as percentages. Comparisons between the groups were made using the chi-square or Fisher's exact tests for categorical variables, independent samples t test for normally distributed con-

tinuous variables, and Mann-Whitney U test when the distribution was skewed. A p value of 0.05 was considered as statistically significant. The receiver operator characteristic (ROC) was calculated as a measure of discrimination ability of MPV for HF-related hospitalization. The cumulative re-hospitalization rates were estimated by Kaplan-Meier curves in two patient subgroups, as defined as having no increased or increased MPV based on a cut off value of 9.1 fL. Univariate Cox proportional hazard model was used to quantify the association of variables with HF-related hospitalization. Variables found to be statistically significant ($p < 0.1$) in univariate analysis and variables, which were significantly different between two groups, were used in a multivariate Cox proportional-hazards model with forward stepwise method in order to determine the independent prognostic factors of HF-related re-hospitalization in HFrEF outpatients with SR.

RESULTS

Of all patients, 29% were females and 71% were males, with a mean age was 65 ± 13 years. The mean follow-up was 10 ± 3 months. The ROC curve analysis of MPV is shown in Figure 2. According to the ROC curve, the optimal cut-off value of MPV to predict HF-related hospitalization was > 9.1 fL. Area under curve (AUC) was 0.777 with 95% confidence interval 0.713 to 0.834.

Baseline characteristics, laboratory, echocardiographic parameters, and concomitant medications of the patient groups are listed in Table 1. The history of DM was more frequent in those with a higher MPV level (Group 2). Also, the patients with a higher MPV level were older and they had higher blood urea nitrogen (BUN) and creatinine levels, compared to Group 1.

Of the patients, 44 (22%) were lost due to CV death. Of these, 19 (21%) were in Group 1 and 25 (24%) were in Group 2 ($p = 0.649$, Table 1). However, 129 (65%) patients experienced HF-related hospitalization. Of these patients, 37 (41%) were in Group 1 and 92 (87%) were in Group 2 ($p < 0.001$, Table 1).

In the Kaplan-Meier analysis, there was a significant difference in the HF-related hospitalization rates after six months, particularly between Group 1 and Group 2 ($p < 0.001$) (Figure 3).

The results of the univariate Cox proportional hazard model for HF-related hospitalization are listed in Table 2. Age, MPV > 9.1 fL on admission, the presence of DM, blood urea nitrogen (BUN), creatinine and hemoglobin levels on admission, presence of RV dilatation, SPAP, and pre-admission beta-blocker use were found to have prognostic significance in the univariate analyses. In the multivariate Cox proportional hazard model, while elevated MPV > 9.1 fL levels and higher SPAP levelson admission found to beassociated with an increased risk for HF-related hospitalization, pre-admission beta-blocker use was found to be associated with a decreased risk for HF-related hospitalization. This was following adjustment for the variables which were statistically significant in the univariate analysis and for the variables which were significantly different between Group 1 and Group 2 (Table 3).

DISCUSSION

To the best of our knowledge, our study is the first to show that a MPV level of > 9.1 fL is an independent predictor of HF-related hospitalization in the short to midterm in stable HFrEF outpatients with SR.

Although parameters, such as P-selectin, CD62P

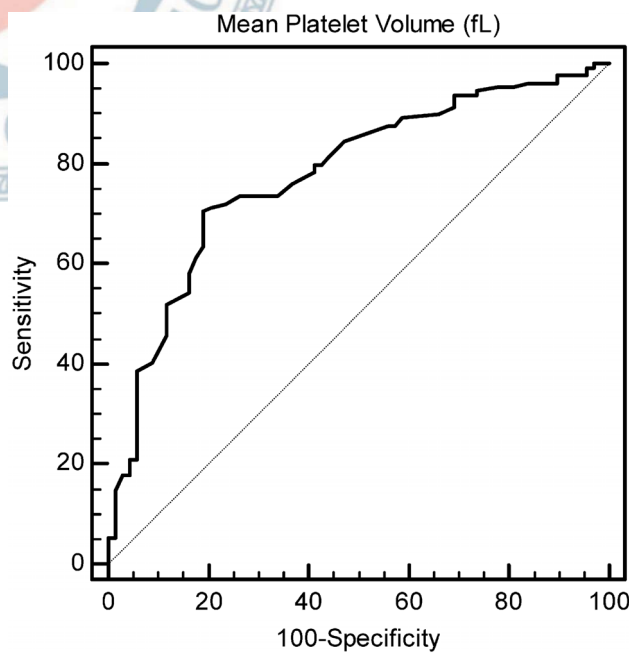

Figure 2. *ROC curve for heart failure-related rehospitalization.*

Table 1. Baseline characteristics, echocardiographic parameters, laboratory parameters, chronic medications and outcomes

	All patients n = 197	MPV ≤ 9.1 n = 91	MPV > 9.1 n = 106	p
Baseline Characteristics				
Mean age (y)	65 ± 13	63 ± 14	67 ± 13	0.036
Women	57 (29%)	24 (26%)	33 (31%)	0.463
Presence of HT	73 (38%)	32 (36%)	41 (39%)	0.579
Presence of DM	55 (29%)	18 (20%)	37 (36%)	0.015
Presence of CAD	92 (48%)	45 (50%)	47 (47%)	0.579
Presence of COPD	61 (32%)	29 (32%)	32 (32%)	0.894
NYHA class I-II	114 (58%)	57 (63%)	57 (54%)	0.209
Heart rate (min)	77 ± 16	79 ± 19	76 ± 14	0.204
Echocardiographic parameters				
LA diameter (mm)	44 ± 7	43 ± 8	44 ± 7	0.517
LV diastolic diameter (mm)	57 ± 9	56 ± 8	58 ± 10	0.092
Ejection fraction (%)	32 ± 8	32 ± 8	32 ± 7	0.944
RV dilatation (%)	103 (53%)	43 (47%)	60 (59%)	0.108
sPAP (mmHg)	42 ± 13	40 ± 15	43 ± 12	0.369
Laboratory parameters				
Hemoglobin (gr/dl)	12.5 ± 2.2	12.8 ± 2.1	12.3 ± 2.2	0.115
RDW (%)	15.9 ± 3.3	15.9 ± 3.6	15.9 ± 3.0	0.901
Platelet (10^3/uL)	235 ± 66	240 ± 65	230 ± 68	0.288
WBC (10^3/uL)	7.8 ± 2.0	7.6 ± 1.8	7.9 ± 2.1	0.360
Neutrophil (10^3/uL)	5.0 ± 1.8	4.8 ± 1.7	5.2 ± 1.9	0.115
Lymphocyte (10^3/uL)	1.9 ± 0.9	1.8 ± 0.9	1.9 ± 0.9	0.461
Glucose (mg/dl)	106 (70-282)	101 (70-282)	108 (73-204)	0.304
BUN (mg/dl)	38 (11-95)	31 (11-86)	42 (11-95)	0.008
Creatinine (mg/dl)	1.2 ± 0.3	1.1 ± 0.3	1.2 ± 0.2	< 0.001
Sodium (mmol/L)	138 ± 4	138 ± 4	138 ± 4	0.288
Potassium (mmol/L)	4.5 ± 0.5	4.5 ± 0.5	4.5 ± 0.5	0.944
Chronic medications				
Beta blocker (%)	139 (75)	65 (75)	74 (75)	0.996
ACEI/ARB (%)	148 (81)	73 (84)	75 (78)	0.421
MRA (%)	98 (54)	50 (58)	48 (50)	0.312
Ivabradine (%)	32(18)	13 (16)	19 (20)	0.682
Diuretics (%)	141 (77)	62 (71)	79 (82)	0.111
Digoxin (%)	37 (20)	15 (17)	22 (23)	0.441
Statin (%)	84 (46)	45 (53)	39 (41)	0.097
Aspirin (%)	135 (75)	65 (76)	70 (74)	0.903
Outcomes				
Cardiovascular mortality (%)	44 (22)	19 (21)	25 (24)	0.649
HF related hospitalization (%)	129 (65)	37 (41)	92 (87)	< 0.001

ACEI, angiotensinogen converting enzyme inhibitor; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HF, heart FAILURE; HT, hypertension; LA, left atrium; LV, left ventricle; MPV, mean platelet volume; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RDW, red cell distribution width; RV, right ventricle; SPAP, systolic pulmonary artery pressure; WBC, white blood cell.

(platelet membrane bound P-selectin), CD63, glycoprotein IIb/IIIa, and platelet factor 4 have been used to evaluate the platelet activation, the measurement of these parameters is technically challenging and expensive and cannot be used in daily practice. However, a blood count parameter, namely MPV, can provide infor-

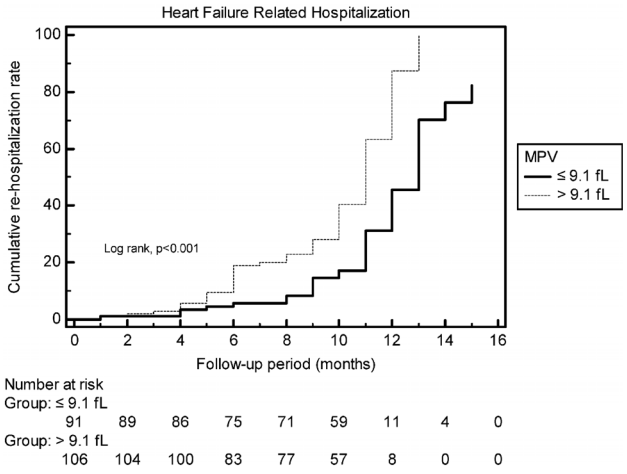

Figure 3. *Kaplan Meier curve for heart failure-related hospitalization.*

mation relating to the platelet size and activity, and it is more cost-effective and straight forward.[10,11] In previous studies, it has been shown that MPV can be elevated in acute HF and AF.[6,12,13] Furthermore, some authors have suggested that MPV can be used as a predictor of thrombogenic complications in AF patients.[14,15] In addition, as the major contribution of increased inflammatory activity and oxidative stress in AF pathogenesis is well-known, it can be considered that increased inflammatory activity may play a role in the MPV elevation in patients with AF.[16] In a study by Kandis et al.,[6] it was reported that MPV levels were higher in decompensated HF patients, compared to stable HF patients and MPV was an independent predictor of in-hospital mortality and over a six-month period in decompensated HF patients. Inconsistent with these findings, our study included stable HF outpatients without AF, rather than decompansated HF. During follow-up, 65% of our patients had HF-related hospitalization; however, 22% of our patients died due to CV reasons. The overall number of CV deaths may not be sufficient to find a possible correlation between MPV levels, as our study population consisted of only stable HF patients and the duration of follow-up was relatively short. Although the mechanism is unclear, a limited number of studies showed that platelet activation increased in acute HF patients.[17-23] In addition, there are studies showing an increase of MPV, which is an indicator of platelet activation, in acute HF patients, stable chronic HF patients, and patients with ischemic or idiopathic cardiomyopathy, compared to healthy controls.[19,21,24] Furthermore, in the study of

Table 2. Univariate cox-regression analysis for predicting HF-related hospitalizations

Variables	Univariate		
	p	HR	(95% CI)
Age (years)	0.077	1.013	0.999-1.029
MPV > 9.1	< 0.001	2.569	1.739-3.794
Presence of DM	0.022	1.545	1.066-2.241
BUN (mg/dl)	0.059	1.009	0.999-1.018
Creatinine (mg/dl)	0.018	2.500	1.167-5.357
Hemoglobin (g/dl)	0.088	0.930	0.856-1.011
Presence of RV dilatation	0.015	1.566	1.092-2.245
sPAP (mmHg)	0.038	1.017	1.001-1.032
Pre-admission beta blocker use	0.001	0.511	0.341-0.766

All the variables from Table 1 were examined and only those significant at p < 0.1 level are shown in univarite analysis. CI, confidence interval; HR, hazard ratio; Abbreviations in Table 1.

Table 3. Multivariate cox-regression analysis for predicting HF-related hospitalizations

Variables	Multivariate		
	p	HR	(95% CI)
MPV > 9.1	< 0.001	2.895	1.774-4.724
sPAP (mmHg)	0.048	1.018	1.001-1.036
Pre-admission beta blocker use	0.014	0.517	0.305-0.877

Multivariate cox-regression model with forward stepwise method. Including all the variables in univariate analysis and also variables found to be significantly different between groups in Table 1. CI, confidence interval; HR, hazard ratio, Abbreviations in Table 1.

Budak et al.,[25] MPV levels and brain natriuretic peptid (BNP) values were correlated among acute HF patients admitted to the emergency department. The authors concluded that MPV could be an indicator for the disease severity and clinical status in acute HF.

The MPV, as an independent predictor of HF-related hospitalization during follow-up in our study, may be explained by two possible causes. First, although it was evaluated as stable on admission, increased catecholaminergic activity, increased activation of the renin-angiotensin system, inflammatory activity, and, hence, increased release of cytokines in patients with high-risk of decompensation may have caused platelet activation and MPV elevation.[23,26-28] In a study investigating the effects of carvedilol and nebivolol treatment on MPV levels in non-ischemic HF patients, Karabacak et al.[29] reported that beta-blockers, which reduce the mortality

and hospitalization in HF by reducing high catecholaminergic activity,[30,31] decreased the MPV levels in HF patient. On the other hand, in the study by Alper et al.,[32] resynchronization therapy (CRT) in HF patients significantly reduced MPV levels. The authors reported that reduced MPV levels could be related to reverse remodeling, which is formed with CRT; however, reduced catecholaminergic and inflammatory activity as a result of reverse remodeling might contribute to the reduced MPV levels by decreasing the platelet activity. The second possible cause which may cause MPV elevation, as an independent predictor for HF-related hospitalizations, is paroxysmal AF episodes, which can occur during follow-up in hospitalized patients. It was previously shown that MPV is higher in patients with permanent and paroxysmal AF when compared with patients with SR.[12,15,33] Although patients with SR were included in our study, symptomatic and asymptomatic developed and spontaneously resolved AF episodes in these patients can cause MPV increase and elevate HF-related hospitalization ratios during follow-up by increasing the possibility of hemodynamic decompensation.

In our study, the ratio of DM patients in the higher MPV group was found to be highly consistent with previous studies, additionally showing that MPV levels were higher in patients with DM and that MPV was related to microvascular complications, such as peripheral neuropathy and microalbuminuria.[34-36] When nephropathy is considered as a microvascular complication of diabetes, it is not surprising that in our study BUN and creatinine values were higher in the group with higher MPV levels. Furthermore, in our study, SPAP levels and pre admission beta blocker use were found to be independent predictors of HF-related hospitalization in addition to MPV and these results are consistent with the results of previous studies.[37-42]

On the other hand, our study has some limitations. First, it is a single-center, retrospective cohort study with a small sample size. Therefore, these results should be supported by further multi-center, large-scale, prospective studies. In addition, the relatively short follow-up may have resulted in inadequate evaluation of prognosis-related with mortality in patients with stable HF without AF. In this patient population, long-term studies are required to evaluate the relationship between MPV levels and CV mortality. Although patients with SR were included in the study, there might be patients with asymptomatic or symptomatic paroxysmal AF episodes during follow-up and this may have affected the results. In addition, NT-Pro BNP, which is an indicator of HF severity and prognosis, was unable to be included in the analysis due to financial problems. The MPV measurements can be affected by the time of blood collection and the type of anticoagulants in the blood tubes during transportation.[43] It is known that MPV may increase, if the blood samples are left for more than one hour after collection and EDTA blood collection tubes are used.[44] However, in our study, all blood samples were collected in the morning and studied within 30 minutes; therefore, the possibility of such an effect is minimal.

CONCLUSIONS

Our study results show that in addition to pre-admission beta blocker use and SPAP level, a MPV level of higher than 9.1 fL is also an independent predictor for HF-related hospitalizations in stable, chronic HFrEF outpatients with SR. Further large-scale, prospective studies to confirm the value of MPV for the risk stratification of HF outpatients with SR in terms of HF-related hospitalizations are warranted.

CONFLICT OF INTERESTS

The authors report no declarations of conflict interest.

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