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Hypertension

Long-Term Prognostic Value of Mean Platelet Volume in Patients with Hypertension

Hamdi Pusuroglu,[1] Ahmet Yaşar Cizgici,[1] Ali Rıza Demir,[1] Begum Uygur[1] and Ender Ozal[2]

Background: Although it has been shown that high mean platelet volume (MPV) is associated with target organ damage in hypertensive patients, the relationship between MPV and the development of long-term major adverse cardiovascular events (MACE) has not been thoroughly investigated. In this study, we investigated the relationship between MPV and long-term MACE in hypertensive patients.

Methods: From September 2011 to July 2017, 1507 patients with hypertension were included in this study. Ambulatory blood pressure monitoring was performed in all patients. Patients with chronic renal failure, cardiovascular disease, chronic systemic disease and white coat hypertension were excluded from the study. MACE were defined as myocardial infarction, stroke and cardiovascular mortality. Patients were followed-up until january 2020.

Results: The mean follow-up duration was 87 (83.3 ± 24.4) months, and 876 patients completed the study. MACE developed in 79 patients, while 797 patients were event-free. In univariate Cox regression analysis, age, diabetes mellitus (DM), MPV, creatinine, 24-hour systolic blood pressure, and non-dipper hypertension were found to be associated with the development of MACE. In multivariate Cox regression analysis, creatinine and 24-hour systolic blood pressure lost significance, and age, DM, non-dipper hypertension and MPV were found to be independent predictors for MACE development ($p < 0.001$, $p < 0.001$, $p = 0.044$, and $p = 0.049$, respectively).

Conclusions: MPV, age, DM, and non-dipper hypertension were independent predictors of long-term MACE in hypertensive patients.

Key Words: Cardiovascular event • Hypertension • Long-term • Mean platelet volume

INTRODUCTION

Mean platelet volume (MPV) is an indirect finding of platelet activation and is affected by many conditions such as diabetes mellitus (DM) and atherosclerosis.[1] A high MPV value may reflect the presence of active large platelets which contain more dense granules that are metabolically and enzymatically more active than small ones, leading to high thrombus burden lesions that result in fatal or non-fatal cardiovascular events.[2] Platelet activity is increased in essential hypertension.[3] The development of target organ damage in hypertensive patients is a predictor of cardiovascular events, and previous studies have shown that increased MPV values are associated with target organ damage.[4]

In a large study, MPV values were found to be higher in unstable angina patients compared to patients with stable angina.[5] In another study conducted with coronary artery disease (CAD) patients, it was shown that a high MPV was an independent predictor of myocardial infarction (MI) and mortality.[6] Contrary to these studies, some studies have not shown a difference between healthy subjects and MI patients in terms of MPV, and MPV was not found to be an independent predictor of mortality in long-term follow-up after MI.[7,8]

Although many studies in the literature have investi-

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[1]Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center, Training and Research Hospital; [2]Department of Cardiology, Bagcılar Training and Research Hospital, Istanbul, Turkey.
Corresponding author: Dr. Ender Ozal, Talatpaşa C. No: 27/1/7 Bahçelievler, Istanbul, Turkey, 34180. Tel: 90-536-342 62 88; Fax: 90-212-471 9494; E-mail: drender38@hotmail.com

gated the relationship between MPV and target organ damage, non-dipper hypertension, malignant and resistant hypertension in hypertensive patients, few studies have investigated its relationship with the development of long-term major adverse cardiovascular events (MACE). The aim of this study was to investigate whether there was a relationship between MVP and long-term MACE development in hypertensive patients.

METHODS

Patient selection

This study was a single center prospective cohort study. Starting from September 2011 to July 2017, a total of 1539 patients with a previous diagnosis of hypertension and under antihypertensive treatment with an office blood pressure (OBP) ≥ 140/90 in at least two measurements in the outpatient clinic were included in this study. Blood pressure (BP) was measured by a physician using auscultatory or oscillometric semiautomatic or automatic sphygmomanometers, after the patients had relaxed in a seated position for at least 5 minutes. BP was measured three times and recorded as the average of the last two readings. The patients were followed-up until january 2020. Echocardiography and ambulatory blood pressure monitoring (ABPM) were performed in all patients. Medical history, physical examination findings and anthropometric measurements of the patients were recorded by an experienced cardiologist. The local ethics committee approved the study protocol and informed consent was obtained from all patients.

The exclusion criteria of this study were secondary hypertension, heart failure (HF), CAD, stroke, moderate-to-severe valvular disease, chronic renal failure (CRF), chronic systemic diseases and white-coat hypertension. Twenty-five patients with secondary hypertension, 152 with white-coat hypertension, 234 with chronic ischemic heart disease, congestive HF, CRF, moderate to severe valvular heart disease, stroke and chronic systemic diseases were excluded from the study. Another 252 patients were excluded due to missing clinical or laboratory findings or could not be reached during follow-up (Figure 1). Therefore, a total of 876 patients completed this study.

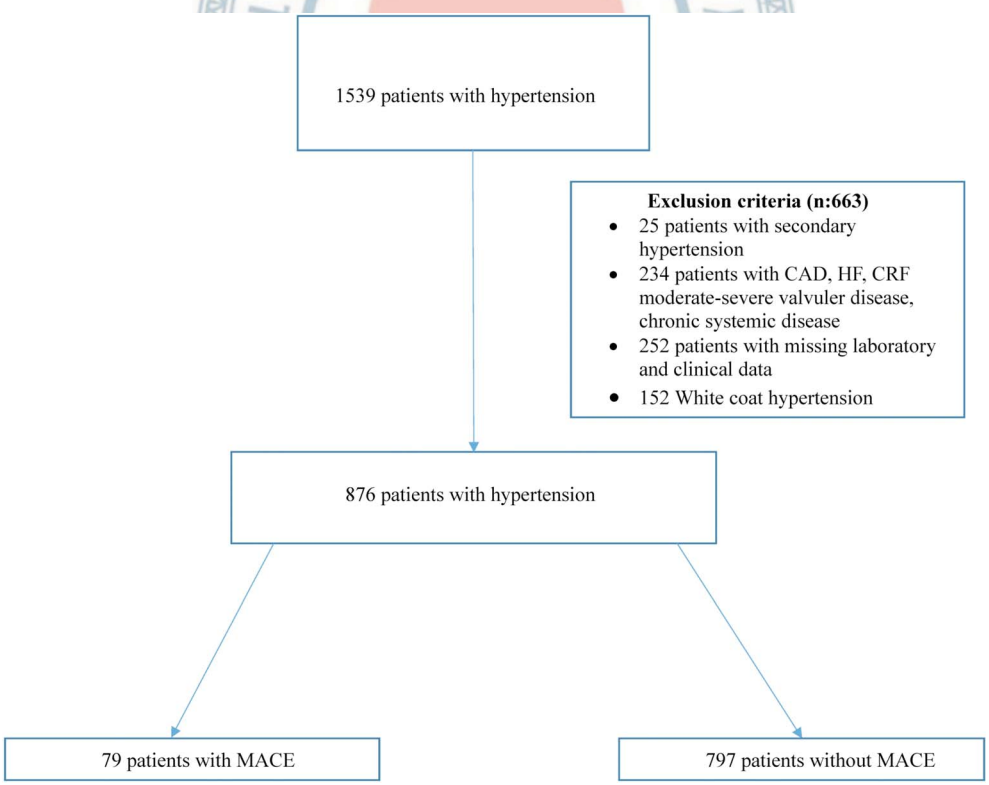

Figure 1. *Selection of study participants. CAD, coronary artery disease; CRF, chronic renal failure; HF, heart failure; MACE, major adverse cardiovascular events.*

Definitions

Hypertension was defined as an OBP of ≥ 140/90 mmHg and 24-h ABPM ≥ 130/90 mmHg, a mean daytime ABPM of ≥ 135/85 mmHg, nighttime mean ABPM of ≥ 120/70 mmHg, or the active use of antihypertensive drugs.[9] White-coat hypertension was defined as an elevated OBP at repeated visits and normal BP on ABPM. Diabetes was defined based on the American Diabetes Association criteria [fasting serum glucose ≥ 126 mg/dL (7 mmol/L), or non-fasting glucose ≥ 200 mg/dL (11.1 mmol/L), or active use of anti-diabetic treatment].[10] Body mass index was calculated as weight in kilograms/(height in meters)^2, and estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology collaboration formula.[11] Urinary albumin was expressed in milligrams per gram (mg/g). Albuminuria was defined as an albumin/creatinine (A/C) ratio of 30 mg/g or higher, and stratified into two groups of microalbuminuria and macroalbuminuria with A/C ratios of 30-299 mg/g and 300 mg/g or higher, respectively. CRF was defined as an eGFR < 60 ml/min/1.73 m^2, which was estimated using the CKD-epidemiology collaboration formula. MI was defined according to the universal definition of MI.[12] Cardiovascular mortality was defined as unexplained sudden death, death due to acute MI, heart failure, or arrhythmia. Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery, and the diagnosis of ischemic or hemorrhagic stroke was confirmed by computed tomography or magnetic resonance imaging. MACE were defined as MI, stroke and cardiovascular mortality (CV mortality). Non-dippers were those with a nocturnal decrease in systolic blood pressure (SBP) of less than 10% of daytime, and dippers were those with a 10% or larger decline in SBP during the nighttime.[13]

Echocardiographic examinations

Echocardiographic examinations were performed by a cardiologist using a Vivid 7 system (General Electric Vivid 7 GE Vingmend Ultrasound AS, Horten, Norway). The left ventricular (LV) mass in grams was calculated from M-mode echocardiograms according to the formula described by Devereux et al.[14] LV mass was indexed to body surface area as LV mass index (LVMI) in g/m^2.

Ambulatory blood pressure monitoring (ABPM)

ABPM was performed for 24 h using an ambulatory blood pressure monitor (Tonoport V, GE Healthcare). The monitor was programmed to measure the blood pressure every 20 min. Daytime and nighttime blood pressure was defined as measurements from 07:00 to 23:00 and from 23:00 to 07:00, respectively.

Blood sampling

Blood samples were taken in the morning after a 12-hour fasting at the first admission to the hospital. MPV was measured from the blood samples collected in ethylenediaminetetraacetic acid (EDTA) tubes, which were analyzed with an automated hematology analysis system (Mindray BC5800). The levels of MPV and other hematologic parameters were measured after 120 min from venipuncture. The expected values for MPV in our laboratory ranged from 6.8 to 10.8 fL. Standard laboratory parameters, including total leukocyte and neutrophil counts, hematocrit, glucose and creatinine levels and lipid profiles were measured.

Study end-points and follow-up

The primary end-point of the study was the development of long-term MACE. Patients were followed up in the outpatient clinics at least once a year. Data of the patients who could not come to the the follow-up visits, were collected by themselves or relatives or family physicians by phone interviews, and other hospital records. Survival data were obtained from the electronic hospital system or National Population Registry.

Statistical analysis

Statistical analysis was performed using SPSS software version 20. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov) to determine whether they were normally distributed. Descriptive analyses were presented using means and standard deviations (SD) for normally distributed variables, medians and maximum-minimum values for non-normally distributed variables, and percentages for categorical variables. Chi-square, Student's t, and Mann-Whitney U tests were used where appropriate. Spearman correlation analysis was performed to determine the association of MPV with the examined variables. Receiver operating characteristic (ROC) curves

were used to determine the MVP cut-off values. The parameters which were statistically different between the two groups and may be related to MACE such as age, gender (male), DM, body mass index (BMI), smoking, hematocrit, platelets, glucose, total cholesterol, triglycerides, urinary albumin to creatinine ratio (UACR), office SBP, office diastolic blood pressure, 24-h SBP, 24-h diastolic blood pressure and non-dipper hypertension were evaluated in univariate analysis, and multivariate analysis was performed for the variables with a p value < 0.05 in univariate analysis. Although they were significant in the univariate analysis, due to the association between glucose and DM, and office SBP and 24-h-SBP, they were not included in the multivariate analysis. Finally, multiple Cox regression analyses were performed to identify the significance of the relationships between MACE and MPV, age, diabetes, creatinine, non-dipper hypertension and 24-h SBP. Event-free survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. An overall 5% type-I error level was used to infer statistical significance.

RESULTS

A total of 876 patients were included in the study, of whom 44.3% were male. The mean follow-up duration was 87 (83.3 ± 24.4) months. At the end of the study, MACE developed in 79 patients. Thirty-four patients had myocardial infarction, 32 patients had stroke, and 18 died due to CV causes (Figure 2). All-cause mortality was recorded in 28 patients. In ROC curve analysis, an MPV value of 9.65 fL was identified as an effective cut-off to predict MACE at 87 months [area under the curve: 0.629, 95% confidence interval (CI) 0.56 to 0.85, p < 0.001] (Figure 3). The patients were divided into a high MPV group (> 9.65 fL; n = 154) and low MPV group (≤ 9.65 fL; n = 722) accordingly (Table 1). Age, DM, glucose, UACR, and office SBP were significantly higher in the high MPV group (Table 1). The usage of antihypertensive agents and statins was higher in the high MPV group (Table 1). Hematocrit and platelet count were lower in the high MPV group (Table 1). Other laboratory values and demographics were similar in the two groups (Table 1). The mean value of MPV was 8.59 ± 1.31 fL, including 8.8 fL in the patients with MI, 9.4 fL in those with stroke, 10.38 fL in those who died from CV causes, and 9.33 fL in the MACE group (Figure 4).

Linear correlations were detected between age, LVMI, UACR, office SBP, office diastolic blood pressure and MPV, while a reverse correlation was found between hematocrit and platelet count (Table 2).

In univariate Cox regression analysis, while age, DM, MPV, creatinine, glucose, 24-h SBP, office SBP, and non-dipper hypertension were found to be associated with MACE development, creatinine and 24-h SBP lost significance. In multivariate logistic regression analysis, only age, DM, non-dipper hypertension and MPV were found to be independent predictors of MACE development (Table 3). The Kaplan-Meier survival plot for MACE at 87

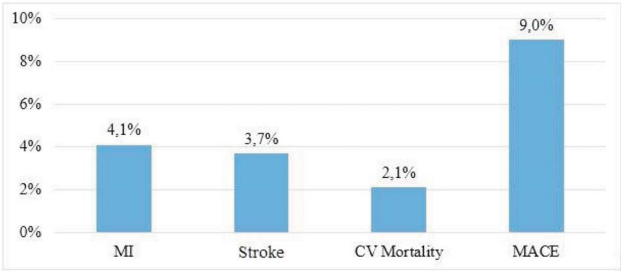

Figure 2. *Major cardiovascular events rate in study. CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.*

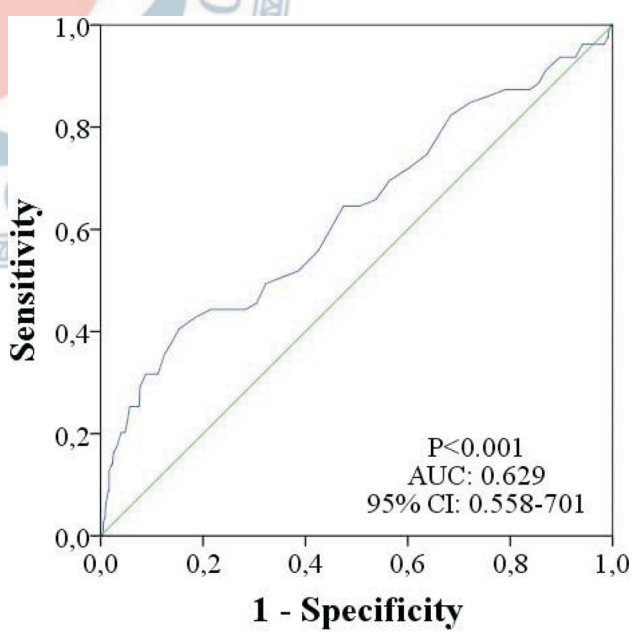

Figure 3. *The receiver operating characteristic (ROC) curve with regard to MACE, at 87 months, for MPV with area under curve of 0.629. AUC, area under curve; CI, confidence interval; MACE, major adverse cardiovascular events; MPV, mean platelet volume.*

Table 1. Baseline characteristics, laboratory findings of the study population

N = 876	MPV ≤ 9.65 fL (N = 722)	MPV > 9.65 fL (N = 154)	p
Age (years)	52.7 ± 10.8	55.6 ± 13.0	0.004
Sex (male)	329 (45.9%)	60 (39.7%)	0.167
BMI (kg/m²)	30.6 ± 5.0	31.2 ± 5.5	0.257
Smoking	88 (20.8%)	29 (25.9%)	0.242
Diabetes mellitus	114 (16.2%)	51 (33.6%)	< 0.001
Heart rate	75.2 ± 12.7	75.0 ± 14.9	0.936
LVMI (g/m²)	98.3 ± 24.8	103.0 ± 31.6	0.114
Hematocrit,%	41.7 ± 4.6	40.4 ± 5.1	0.003
Platelets, × 10^3/μl	273.4 ± 72.3	235.1 ± 72.2	< 0.001
Leukocytes, × 10^3/μl	7.66 ± 1.91	7.72 ± 2.07	0.733
Neutrophils, × 10^3/μl	4.57 ± 1.41	4.68 ± 1.71	0.385
Creatinine (mg/dl)	0.80 (0.70-0.90)	0.80 (0.70-0.99)	0.138
Glucose (mg/dl)	99 (91-111)	118 (97-164)	< 0.001
Total – cholesterol (mg/dl)	204.3 ± 40.9	201.3 ± 40.3	0.432
HDL – cholesterol (mg/dl)	47.1 ± 12.7	48.9 ± 15.5	0.144
LDL – cholesterol (mg/dl)	129.7 ± 34.9	124.9 ± 40.8	0.146
Triglycerides (mg/dl)	141 (101-207)	145 (102-209)	0.843
Uric acid	5.44 ± 1.42	5.63 ± 1.59	0.216
UACR (mg/g)	0.020 (0.005-0.099)	0.133 (0.014-0.822)	< 0.001
ACE-ARB	301 (68.7%)	92 (78.0%)	0.050
CCB	187 (42.8%)	65 (55.1%)	0.017
BB	152 (34.9%)	52 (44.1%)	0.066
Diuretic	225 (51.5%)	84 (71.2%)	< 0.001
Other antihypertensives	52 (11.9%)	29 (24.6%)	0.001
ASA	81 (18.7%)	37 (31.9%)	0.002
Statin	42 (9.7%)	24 (21.2%)	0.001
Office SBP (mmHg)	159.9 ± 30.1	167.2 ± 24.6	0.046
Office DBP (mmHg)	90.5 ± 11.7	92.8 ± 11.3	0.109
24-h-SBP (mmHg)	144.3 ± 18.2	143.4 ± 16.3	0.572
24-h-DBP (mmHg)	89.6 ± 12.5	87.8 ± 13.0	0.137
Non-dipper hypertension	409 (61.5%)	87 (64.4%)	0.521

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; ASA, acetylsalicylic acid; BB, beta-blockers; BMI, bady mass index; CCB, calcium channel blockers; DBP, diastolic blood pressure; HDL; high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; LVMI, left ventricular mass index; MPV, mean platelet volume; SBP, systolic blood pressure; UACR, urinary albumin to creatinine ratio.

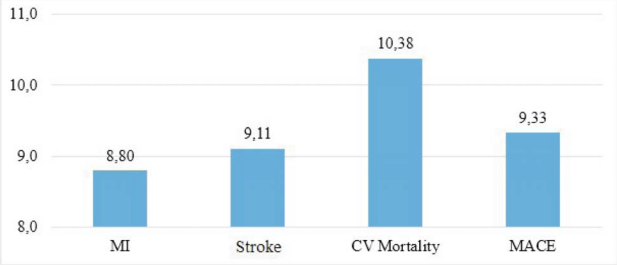

Figure 4. *Mean platelet volume levels in major cardiovascular events. CV, cardiovascular; MACE, major adverse cardiovascular event including myocardial infarction, stroke, cardiovascular mortality; MI, myocardial infarction.*

months is presented in Figure 5.

DISCUSSION

Mean platelet volume is an important platelet production index that may be indirectly related to platelet function. Furthermore, previous studies have reported that MPV was significantly higher in hypertensive patients than in normotensive subjects.[15] Shear forces, renin-angiotensin system, endothelial dysfunction, elevated

Table 2. Correlation between selected covariates and MVP

	r	p
Age (years)	0.086	0.014
BMI (kg/m²)	0.012	0.787
Heart rate	0.025	0.708
LVMI (g/m²)	0.098	0.030
Hematocrit, %	-0.085	0.014
Platelets, × 10^3/μl	-0.261	< 0.001
Leukocytes, × 10^3/μl	-0.022	0.536
Neutrophils, × 10^3/μl	-0.001	0.988
Creatinine (mg/dl)	0.033	0.355
Glucose (mg/dl)	0.033	0.352
Total – cholesterol (mg/dl)	-0.031	0.405
HDL – cholesterol (mg/dl)	0.034	0.340
LDL – cholesterol (mg/dl)	-0.028	0.434
Triglyceride (mg/dl)	-0.028	0.436
Uric acid	0.058	0.165
UACR (mg/g)	0.254	< 0.001
Office SBP (mmHg)	0.155	0.039
Office DBP (mmHg)	0.128	0.021
24-h-SBP (mmHg)	0.002	0.963
24-h-DBP (mmHg)	-0.013	0.708

BMI, bady mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; LVMI, left ventricular mass index; MPV, mean platelet volume; SBP, systolic blood pressure; UACR, urinary albumin to creatinine ratio.

catecholamines levels and presence of co-morbid conditions promote increased activation of platelets in hypertensive settings.[15]

LVMI and albuminuria are markers of target organ damage in hypertensive patients and are associated with the development of CV events.[16] Many studies have investigated the relationship of MPV with LVMI and albuminuria, some of which have found relationships be-

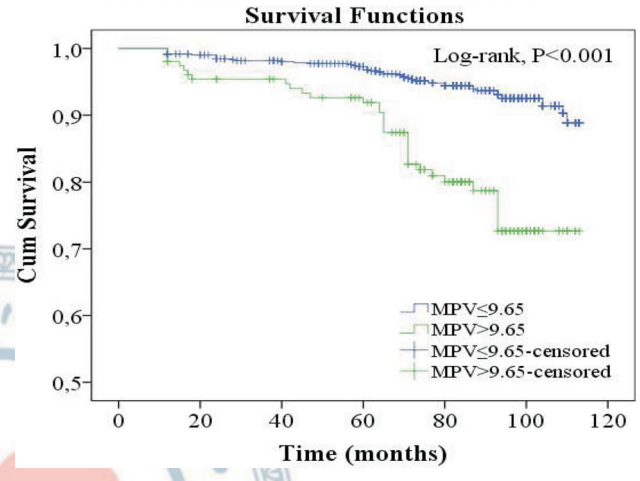

Figure 5. *MACE rations of subgroups in 87 months follow-up. MACE, major adverse cardiovascular events; MPV, mean platelet volume.*

Table 3. Univariate and multivariate Cox regression analysis of MACE

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)	1.067 (1.046-1.089)	< 0.001	1.052 (1.026-1.079)	< 0.001
Sex (male)	1.028 (0.656-1.610)	0.905		
Diabetes mellitus	6.078 (3.877-9.527)	< 0.001	5.219 (3.008-9.055)	< 0.001
BMI (kg/m^2)	1.035 (0.985-1.089)	0.176		
Smoking	1.167 (0.624-2.181)	0.629		
Hematocrit, %	0.981 (0.956-1.037)	0.238		
Platelets, × 10^3/μl	1.000 (0.997-1.003)	0.932		
MPV	1.512 (1.300-1.758)	< 0.001	1.183 (1.001-1.401)	0.049
Creatinine (mg/dl)	1.437 (1.030-2.007)	0.033	0.793 (0.425-1.480)	0.467
Glucose (mg/dl)	1.010 (1.007-1.013)	< 0.001		
Total – cholesterol (mg/dl)	0.998 (0.992-1.004)	0.481		
Triglycerides (mg/dl)	1.002 (1.000-1.003)	0.077		
UACR (mg/g)	1.071 (0.944-1.216)	0.286		
Office SBP (mmHg)	1.012 (1.003-1.021)	0.011		
Office DBP (mmHg)	1.016 (0.994-1.039)	0.152		
24-h-SBP (mmHg)	1.018 (1.006-1.031)	0.004	1.012 (0.995-1.029)	0.166
24-h-DBP (mmHg)	0.995 (0.976-1.014)	0.604		
Non-dipper hypertension	2.851 (1.527-5.324)	0.001	2.202 (1.020-4.755)	0.044

BMI, bady mass index; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; HT, hypertension; MACE, major adverse cardiovascular events; MPV, mean platelet volume; SBP, systolic blood pressure; UACR, urinary albumin to creatinine ratio.

tween MPV and LVMI and UACR, while others have not.[17,18] We found that MPV was associated with albuminuria and weakly correlated with LVMI.

In the study conducted by Ismail et al., MPV was not found to be associated with 1-year CV mortality in patients with STEMI, while in contrast, Martin et al. reported that a high MPV was associated with mortality and MI development in patients with MI.[7,19] Martin suggested that MPV is an independent risk factor for the development of recurrent MI, and that MPV is not correlated with traditional coronary artery disease risk factors such as white cell count, blood lipids, and blood pressure. In a meta-analysis conducted by Zhongxiu et al., increased MPV was found to be associated with the development of long-term CV events in patients who underwent percutaneous coronary interventions.[20] Additionally, in studies investigating stroke patients, MPV was found to be higher in the stroke patients than in the control group, and MPV was also associated with stroke severity and 1-year mortality.[21,22] Although many studies have investigated MPV in hypertensive patients, few studies have investigated the effect of MPV on the development of long-term CV events. Different from previous studies on hypertensive patients, the effect of MPV on the development of long-term CV events was investigated in the present study, and we found that MPV was an independent risk factor for the development of CV events. Age and DM, which are traditional CV risk factors, were also found to be independent predictors of CV event development in this study.

Shear stress in hypertension causes endothelial damage resulting in thrombus formation. As a result, in hypertensive patients, due to the consumption of small platelets, the number of thrombocytes decreases and MPV increases.[23] In a few studies, a reverse relationship has been found between MPV and platelet count.[8] In the present study, a reverse correlation was found between MPV and platelet count.

Hypertension is the most common cause of chronic renal failure after diabetes. High creatinine values are also associated with the development of CV events, especially if the eGFR is below 60 ml/min/1.73 m^2. The greater the reduction in renal function, the greater the likelihood of CV event development.[24] In this study, we did not find an independent relationship between creatinine levels and CV event development, since we did not include patients with an eGFR below 60 ml/min/1.73 m^2.

Twenty-four-hour ambulatory blood pressure has been shown to be a better predictor of target organ damage, coronary morbidity, mortality, and stroke than OBP.[25] Previous studies have indicated that SBP has a greater association with mortality than diastolic blood pressure.[26] In this study, office SBP and 24-h SBP values were found to be associated with the development of MACE.

In most previous studies, non-dipper hypertension has been associated with the development of CV events in hypertensive patients.[27,28] Furthermore, non-dipper hypertension was found to be an independent predictor of the development of MACE in this study.

Limitations

Since this study is a single center study, bias is possible in the evaluation of the results. In addition, this study enrolled patients who were previously diagnosed with hypertension and received antihypertensive treatment, and patients who were seen in the outpatient clinic for the first time and had high blood pressures in both office and ABPM. Therefore, patients with white coat hypertension and masked hypertension may not be sufficiently represented in this study. Also, we excluded patients with clinically overt CV diseases (such as coronary artery disease, cerebrovascular disease, and renal failure). Therefore, our results cannot be extrapolated to all hypertensive subjects. Moreover, we did not evaluate leukocyte activation markers, high-sensitivity C-reactive protein and other proinflammatory cytokines. Finally, MPV values was recorded on the first day the patients participated in the study, and we did not investigate changes in MPV values over time or the relationship between the changes and event development.

CONCLUSIONS

In conclusion, although MPV was not as strong a predictor as traditional CV risk factors such as age and DM, it was independently associated with the development of CV events. MPV is a cheap and easily available test that is routinely used in hypertension treatment practice. Therefore, it could be used for risk stratification, follow-up and treatment of hypertensive patients.

CONFLICT OF INTERESTS

All the authors declare that they have no conflict of interest. And this research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

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