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ORIGINAL ARTICLE

Increased platelet volume in a general population with prehypertension: a cross-sectional study of 80 545 participants from China

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Mean platelet volume (MPV), an indicator of platelet activation, has been shown to be elevated in patients with hypertension. However, data available on the association between MPV level and prehypertension are limited. Prehypertension is also associated with an increase in cardiovascular morbidity and mortality. A cross-sectional study was performed among 80 545 standardized medical checkup participants ⩾18 years in age without hypertension or diabetes in China between April 2009 and May 2010. Blood pressure was categorized as prehypertensive (systolic blood pressure, 120–140 mm Hg and/or diastolic blood pressure, 80 to 90 mm Hg, $n=36\,586$) and normotensive (systolic blood pressure, <120 mm Hg and diastolic blood pressure, <80 mm Hg, $n=43\,959$). Mean systolic blood pressure and the prevalence of prehypertension increased significantly with increasing MPV. After adjusting for demographics, body mass index, smoking and serum cholesterol, the odds ratio for prehypertension, when comparing the highest category of MPV (>12.0 fl) with the lowest category (<10.1 fl), was 1.08 (95% confidence interval, 1.02–1.13; *P* for trend = 0.014). This association persisted in separate analysis among men but not among women. In nonparametric models, the positive association between MPV and prehypertension appeared to be present across the full range of MPV, without any threshold effect. Increased MPV is associated with prehypertension in a large sample of Chinese adults that are free of cardiovascular disease and hypertension.
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Keywords: cardiovascular disease; mean platelet volume; prehypertension

INTRODUCTION

Platelets secrete and express a large number of substances that are crucial mediators of coagulation, inflammation, thrombosis and atherosclerosis.[1] Platelets have a central role in the pathophysiology of cardiovascular diseases.[2] It has been well demonstrated that patients with hypertension have evidence of platelet activation.[3]

Within an individual, platelets are heterogeneous in size and density. Mean platelet volume (MPV), an indicator of platelet activation,[4] is one of the platelet function indices that reflects the rate of platelet production and stimulation.[5] It has been shown that MPV is helpful in the differentiation of idiopathic thrombocytopenic purpura from other thrombocytopenias.[6] MPV is an important biological variable that is drawing increased interest as an independent risk factor for myocardial infarction.[7] The literature on the association between MPV and stroke is inconsistent[8,9] and may also relate to the use of different methods to assess MPV and the variable time points used for MPV measurement after stroke onset.[10] Moreover, emerging evidence has shown that known cardiovascular risk factors, such as smoking,[11] diabetes mellitus,[12] obesity[13] and hypertension,[14,15] are associated with MPV.

Prehypertension, as defined by the Seventh Joint National Committee,[16] includes those with systolic blood pressure ranging 120–139 mm Hg or diastolic blood pressure ranging 80–89 mm Hg, is identified as a predictor for developing hypertension[17] and a stage where the primary prevention of hypertension is possible.[18] Prehypertension is a risk factor for overt hypertension, and several small-scale studies have demonstrated the association of prehypertension with increased CVD morbidity.[19] However, there are few data available on the association between MPV levels and prehypertension.

Our primary hypothesis is that MPV increases in prehypertensive individuals. Therefore, in this study, we examined whether an elevated MPV level was associated with blood pressure among non-diabetic and non-hypertensive subjects without a history of cardiovascular disease who attended a standardized medical checkup in 2009–2010, after adjusting for several important confounders. We also employed nonparametric analytical tools to graphically examine the dose-response nature of the association between MPV levels and prehypertension. These findings might help identify prehypertensive

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individuals who are at increased risk for cardiovascular events and who might benefit from long-term treatment with antiplatelet agents.

METHODS

Participants

We reviewed the medical records of 1 18 842 participants ($\geqslant$18 years, 66 551 men and 52 291 women) who voluntarily underwent medical examinations at the Health Management Center of the Third Xiangya Hospital in Hunan Province, China. The standardized medical checkup services included the administration of a medical questionnaire, physical examination and laboratory tests for a variety of adult diseases, such as hypertension, diabetes, hypercholesterolemia, liver disease, kidney disease and malignancy. The questionnaire and examinations were conducted by medical staff according to a standard protocol. Demographic, anthropometric and laboratory data were gathered for each subject within the same day. This study followed the recommendations of the Declaration of Helsinki. All the participants provided informed consent before entering the study, and approval was obtained from the Human Subjects Committee at the Third Xiangya Hospital, Central South University.

Data on systolic and diastolic blood pressure were available for 1 16 465 participants (98%). Ultimately, 21 587 participants with prevalent hypertension, 5816 participants with diabetes (subjects with fasting blood glucose $>7.1\,\mathrm{mmol\,l^{-1}}$, self-reported diabetes and/or treatment with insulin or oral antidiabetic medication were considered diabetics), 1458 participants with missing covariable data and subjects meeting any of the following criteria were excluded ($n=7059$) to exclude the possibility of an inflammatory disorder, bone marrow suppressive disorder, renal and hepatic dysfunction, lipid-lowering therapy or treatment with platelet function-modifying medications. The following subjects were also excluded from the study: those with a history of cardiovascular disease, stroke, malignancy and chronic liver disease; those with white blood cell counts of <3.0 or $>10.0\times10^9$ cells$\,\mathrm{l^{-1}}$; those with platelet counts of <150 or $>400\times10^9$ cells$\,\mathrm{l^{-1}}$; those with hemoglobin levels of $<12.0\,\mathrm{g\,dl^{-1}}$ for females or $13.0\,\mathrm{g\,dl^{-1}}$ for males; and those currently taking antiplatelet medication. After these exclusions, 80 545 participants (47 710 men and 32 835 women, aged 18–79 years) were included in the final analysis.

Measurement of blood pressure

Seated blood pressures were measured by skilled, trained physicians after subjects had rested for 15 min using a mercury sphygmomanometer according to the American Heart Association's recommendations.[20] The average of three readings was recorded. The participants were considered hypertensive if they reported current blood pressure-reducing medication use and/or had systolic blood pressures $\geqslant$140 mm Hg and/or diastolic blood pressures $\geqslant$90 mm Hg.[16] Prehypertension was defined as systolic blood pressure measurements between 120 and139 mm Hg and/or diastolic blood pressures between 80 and 89 mm Hg.[16] Control subjects who had systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg were diagnosed as normotensive controls.

Measurement of other variables

The assessment of medical history, smoking status and medication was based on the standardized questionnaire in the medical record. Body mass index (BMI) was computed as weight in kilograms divided by the square of height in meters. Blood samples were drawn from the antecubital vein by careful venipuncture using a 21-G sterile syringe without stasis at 0800–1000 hours after a fasting period of 12 h. Lipid profiles were determined using the standard methods. MPV was measured in a blood sample collected in dipotassium EDTA tubes. An automatic blood counter (Sysmex XT 2000i analyzer, Sysmex Corporation, Kobe, Japan) was used for whole-blood counts. MPV was measured within 90 min after sampling to prevent EDTA-induced platelet swelling. The expected values for MPV in our laboratory ranged from 7.6 to 13.2 fl.

Statistical analysis

Mean values and proportions were compared using analysis of variance and χ^2 tests, respectively. We examined MPV levels as quintiles: <10.1, 10.1–10.7, 10.7–11.3, 11.3–12.0 and >12.0 fl. The relationship between MPV and blood pressure values was analyzed using multiple linear regression. Because of the skewed distribution of platelet parameters and to prevent the undue influence of observations with extreme values, these variables were log-transformed (natural log (x)). The odds ratio (95% confidence interval) of prehypertension was calculated for each MPV level, with the lowest quartile as the reference, using multivariable logistic regression models. We used age (years) and sex-adjusted multivariable models that were additionally adjusted for smoking (never, former and current), alcohol intake (g per day), BMI ($\mathrm{kg\,m^{-2}}$), and serum cholesterol ($\mathrm{mmol\,l^{-1}}$). Trends in the odds ratio of prehypertension across increasing MPV categories were determined, modeling MPV categories as an ordinal variable. To examine the consistency of the observed association between MPV levels and prehypertension, we performed subgroup analyses by gender, age (<50 and $\geqslant50$ years), current smoking (absent and present) and BMI (<24 and $\geqslant24\,\mathrm{kg\,m^{-2}}$). All the analyses were conducted using SAS statistical software (SAS Institute, Cary, NC, USA). All the statistical tests were two-sided and significance was determined at a P-value <0.05.

RESULTS

Among the 80 545 adults without hypertension, diabetes and cardiovascular disease included in the current analysis, mean age was 40.11 years (range from 18 to 79 years), 32 835 (40.77%) were women and 36 586 (45.42%) individuals had prehypertension. Descriptive characteristics of the study population are presented in Table 1 and Table 2, for both the overall population and by MPV categories. Compared with those with lower MPV values, participants with higher levels of MPV (>11.3 fl) included a larger proportion of women, persons aged $\geqslant50$ years, former smokers, those with education at the high school level or below, those with a higher waist circumference and those who were obese (Table 1). As expected, MPV was strongly associated with platelet count as well as platelet distribution width. Interestingly, increasing quintiles of MPV were also associated with slightly lower levels of total cholesterol and low-density lipoprotein cholesterol and increasing levels of high-density lipoprotein cholesterol. Systolic blood pressure and the prevalence of prehypertension increased with increasing MPV categories (Table 2).

Table 3 shows the standardized regression coefficients obtained from the multiple linear regression models for systolic blood pressure. Excluding female participants, MPV was linearly associated with systolic blood pressure after the adjustment for demographics and BMI.

Table 4 presents the odds ratios of prehypertension by increasing MPV quintiles. Increasing MPV quintiles were positively associated with prehypertension; models evaluating the trend in this association were also statistically significant. When MPV was analyzed as a continuous variable, the positive association with prehypertension persisted. In Table 5, we present the gender-specific analysis for the association between increasing MPV levels and prehypertension. A clear positive association between MPV and prehypertension was present among men, but among women, the results were indicative of a negative association.

In Table 6, we examined the odds ratio of prehypertension associated with increasing levels of log-transformed MPV within subgroups for education, age, current smoking and BMI. The associations between MPV and hypertension were present in all subgroups. The associations between MPV and prehypertension among women were markedly weakened in the fully adjusted model (including BMI, age and serum cholesterol). Similarly, the association between MPV and prehypertension seemed stronger among those who were younger than 50 years. The opposite was observed in both relative weight and smoking-status categories in this population but seemed to be stronger in the present smoking and high-body-weight groups.

Table 1 Characteristics of the study population by categories of mean platelet volume[a]

		Mean platelet volume categories					
Characteristics	*Overall* (n = *80 545*)	*< 10.1 fl* (n = *16 931*)	*10.1–10.7 fl* (n = *17 970*)	*10.7–11.3 fl* (n = *13 763*)	*11.3–12.0 fl* (n = *16 115*)	*> 12.0 fl* (n = *15 766*)	P-*value*
Age ⩾50 years, %	18.8	17.6	18.1	18.0	19.2	20.9	<0.001
Men, %	59.2	61.8	60.0	59.9	58.8	55.5	<0.001
Education categories, %							
Below high school	33.1	31.2	32.2	35.1	34.6	33.2	<0.001
High school	24.4	22.1	23.5	24.6	25.7	26.2	
Above high school	42.5	46.7	44.3	40.3	39.7	40.6	
Smoking, %							
Never	44.0	48.3	44.0	42.8	43.7	40.6	<0.001
Past	38.9	32.2	34.6	38.5	43.1	46.8	
Current	17.1	19.5	21.4	18.7	13.2	12.6	
Body weight, %[b]							
Normal	58.3	58.9	58.3	58.2	57.6	58.5	0.20
Overweight	33.3	33.3	33.2	33.1	33.9	33.0	0.47
Obese	8.4	7.8	8.5	8.7	8.5	8.5	0.04
BMI,kg m^{-2},mean	23.34	23.30	23.33	23.36	23.38	23.33	0.43
WC, cm, mean	79.64	79.72	79.73	79.65	79.72	79.38	<0.01

Abbreviations: BMI, body mass index; WC, waist circumference.
[a]Includes all participants, unadjusted.
[b]Normal weight is defined as having a BMI between 18 and 23.9 kg m^{-2}; overweight,between 24 and 27.9 kg m^{-2}; obese,BMI >28 kg m^{-2}.

Table 2 Prevalence of prehypertension, mean levels of platelet parameters and mean blood pressures, by categories of mean platelet volume, adjusted for age and sex

		Mean platelet volume categories					
Variables	*Overall* (n = *80 545*)	*< 10.1 fl* (n = *16 931*)	*10.1–10.7 fl* (n = *17 970*)	*10.7–11.3 fl* (n = *13 763*)	*11.3–12.0 fl* (n = *16 115*)	*> 12.0 fl* (n = *15 766*)	P-*value for trend*
MPV, fl, mean	10.96	9.50	10.41	11.00	11.58	12.47	<0.001
Platelet count, 10^9 l^{-1}, mean	202.83	232.24	214.03	202.53	190.48	171.36	<0.001
PDW, fl, mean	13.53	11.00	12.42	13.42	14.54	16.54	<0.001
Prehypertension, %	45.4	44.8	45.4	45.0	45.9	46.0	<0.05
SBP, mm Hg, mean	117.02	116.89	116.95	116.97	117.15	117.17	<0.05
DBP, mm Hg, mean	73.39	73.34	73.39	73.39	73.51	73.32	0.15
Total cholesterol, mean, mmol l^{-1}	4.74	4.79	4.75	4.74	4.72	4.70	<0.001
Triglycerides, mean, mmol l^{-1}	1.46	1.47	1.45	1.47	1.46	1.46	0.14
LDL cholesterol, mean, mmol l^{-1}	2.70	2.76	2.72	2.70	2.68	2.64	<0.001
HDL cholesterol, mean,mmol l^{-1}	1.37	1.36	1.37	1.37	1.37	1.39	<0.001

Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MPV, mean platelet volume; PDW, platelet distribution width; SBP, systolic blood pressure.

DISCUSSION

This large cross-sectional study in healthy Chinese adults shows that MPV is associated with prehypertension. After controlling for the main potential confounders (age, sex and BMI), as well as for other potentially relevant variables (smoking and serum cholesterol), high levels of MPV were associated with greater odds of prehypertension in a dose-response fashion (Table 4). The large sample size allowed us to conduct subsequent analysis employing nonparametric models (Table 6). The observed positive association between MPV and prehypertension was present continuously across the full range of

MPV. Another interesting finding was the negative correlation between MPV and plasma lipid levels, which is considered a major cardiovascular risk factor. Although several studies have previously shown the association between MPV and hypertension,[14,15,21,22] its relationship in subjects without hypertension is unknown. The latest studies have shown that prehypertension causes platelet activation, as demonstrated by increased MPV.[23,24] To our knowledge, the present study is by far the largest study of the general population to examine the association of MPV with prehypertension.

MPV is the most commonly used measure of platelet size and is a marker of platelet reactivity. Large platelets aggregate *in vitro* more rapidly to agonists, such as ADP, collagen and adrenaline, than small platelets, release more thromboxane A_2, serotonin and ATP, contain more dense granules and express an increased number of P-selectin and GP IIb/IIA receptors.[25]

Several lines of recent evidence suggest that an association between MPV and hypertension is plausible. Nadar *et al.*[26] found that MPV was significantly higher in patients with hypertension than in normotensive control subjects; within the hypertensive group, those with evidence of target organ damage had significantly larger platelets with greater mass than those without target organ damage. Coban *et al.*[15] reported that MPV was significantly higher in essential hypertensives and white-coat hypertensives than in normotensives, and MPV was also higher in essential hypertensives than in white-coat hypertensives. Ordu *et al.*[14] also showed that MPV is higher in non-dipping hypertensive patients than in dipping hypertensive patients.

It is well demonstrated that prehypertension is related to an increased risk of death from cardiovascular disease.[27–29] Despite much evidence for platelet activation in hypertension, data on prehypertensive patients are limited. In agreement with previous findings,[30,31] we observed a strong association of increased MPV with older age, increasing BMI and smoking; however, after adjusting for these factors, the association of MPV with risk of prehypertension persisted, indicating that MPV was associated with a risk of prehypertension independently of these risk factors. The pathophysiological mechanisms leading to increased cardiovascular risk in prehypertension are still not understood.[28] In hypertensive patients, there is a compelling evidence on the role of platelet activation in hypertensive thrombotic complications including stroke[32] and myocardial infarction.[7] Increased platelet activation might be related to increased vascular thrombotic risk in

Table 3 Linear regression analyses of systolic blood pressure on mean platelet volume ($n = 80\,545$)

	Systolic blood pressure, mm Hg, men (n = *47 710*)		*Systolic blood pressure, mm Hg, women* (n = *32 835*)	
Variables	*β (s.e.)*	*P-value*	*β (s.e.)*	*P-value*
Mean platelet volume (log-transformed)				
Age adjusted	5.40 (1.07)	<0.001	−0.21 (1.32)	0.88
Age and BMI-adjusted	3.78 (1.04)	<0.001	0.42 (1.29)	0.74

Abbreviation: BMI, body mass index.

Table 4 Association between mean platelet volume and prehypertension

Mean platelet volume categories	*Number at risk* (n = *80 545*)	*Prehypertension cases* (n = *36 586*)	*Age, sex-adjusted OR (95% CI)*	*Multivariable-adjusted OR (95% CI)*[a]
<10.1 fl	16 931	7585	1 (referent)	1 (referent)
10.1–10.7 fl	17 970	8151	1.04 (0.99–1.09)	1.03 (0.99–1.08)
10.7–11.3 fl	13 763	6191	1.02 (0.98–1.07)	1.01 (0.96–1.06)
11.3–12.0 fl	16 115	7404	1.07 (1.02–1.11)	1.05 (1.00–1.10)
>12.0 fl	15 766	7255	1.09 (1.04–1.14)	1.08 (1.02–1.13)
P-trend			0.01	0.01
Mean platelet volume (log-transformed)	80 545	36 586	1.86 (1.41–2.80)	1.85 (1.31–2.63)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Adjusted for age (years), sex (men and women), smoking (never, former and current), body mass index ($kg\,m^{-2}$), serum uric acid and serum cholesterol ($mmol\,l^{-1}$).

Table 5 Association between increasing mean platelet volume levels and prehypertension by gender

	Men (n = *47 710*)		*Women* (n = *32 835*)	
Mean platelet volume quintiles	*Numbers of prehypertension*	*Multivariable-adjusted OR (95% CI)*	*Numbers of prehypertension*	*Multivariable-adjusted OR (95% CI)*
Quintile 1 (<10.1)	5650	1 (referent)	1935	1 (referent)
Quintile 2 (10.1–10.7)	5978	1.05 (0.99–1.11)	2173	0.99 (0.92–1.07)
Quintile 3 (10.7–11.3)	4527	1.02 (0.96–1.09)	1663	0.97 (0.90–1.06)
Quintile 4 (11.3–12.0)	5374	1.08 (1.02–1.15)	2029	0.97 (0.90–1.06)
Quintile 5 (>12.0)	4963	1.08 (1.01–1.14)	2291	1.05 (0.98–1.14)
P-trend		0.04		0.24
Mean platelet volume (log-transformed)		1.98 (1.28–3.07)		1.36 (0.76–2.46)

Abbreviations: CI, confidence interval; OR, odds ratio.
Adjusted for age (years), sex (men and women), smoking (never, former and current), body mass index ($kg\,m^{-2}$) and serum cholesterol ($mg\,dl^{-1}$).

Table 6 Association between mean platelet volume level and prehypertension within selected subgroups

Stratified subgroups	*Number of individuals*	*Number of prehypertension*	*Multivariable-adjusted OR (95% CI) of prehypertension associated with log-transformed MPV, fl, within each subgroup*
Age, years			
<50 years	64 441	34 060	2.06 (1.39–3.05)[a]
⩾50 years	15 104	2526	1.75 (0.81–3.79)
Current smoking			
Absent	66 852	30 424	1.03 (1.01–1.05)[a]
Present	13 693	6162	1.52 (1.50–1.55)[a]
Body mass index			
$<24\,kg\,m^{-2}$	47 846	31 695	1.55 (1.22–1.96)[a]
$\geqslant 24\,kg\,m^{-2}$	32 699	4891	2.36 (1.49–3.74)[a]

Abbreviations: CI, confidence interval; OR, odds ratio.
Adjusted for age (years), sex (men and women), smoking (never, former and current), body mass index ($kg\,m^{-2}$) and serum cholesterol ($mg\,dl^{-1}$).
[a]$P<0.05$.

prehypertension. However, in our study, increased MPV was negatively correlated with plasma total cholesterol, and low-density lipoprotein cholesterol was negatively correlated with minimal changes in absolute numbers. Additionally, adjustment for these factors did not change the risk estimates for the association between MPV and prehypertension. Altogether, these results suggest that the risk of prehypertension associated with MPV cannot be explained by atherosclerosis alone and that high MPV may be associated with the risk for prehypertension independently of lipid levels.

This study has several limitations that are worth mentioning. First, because of the observational and cross-sectional nature of the study, these results should be interpreted with caution. The hypothesis of a causal association between platelet activation and prehypertension is supported by the evidence from intervention trials, suggesting a significant increase in MPV in prehypertensive subjects; these trials also showed a decrease in MPV after lifestyle modification for 20 weeks in a small sample of patients.[33] Further, prospective studies on the longitudinal association between MPV in relation to changes in blood pressure and prehypertension will help elucidate the true nature and magnitude of the association. Second, our study took place in a single center from a large urban teaching hospital, and the study population was a relatively homogeneous population in which a number of risk factors had been excluded. Therefore, the results of the current study may not be extrapolated to the entire prehypertensive cohort. Third, the exclusion of participants because of cardiovascular disease relied solely on the patients' history rather on than objective evidence. Another limitation was our use of EDTA as an anticoagulant; EDTA can cause time-dependent swelling in platelets.[34] Platelet counts and MPV were determined using an automatic blood counter within 1.5 h of blood sampling to prevent EDTA-induced platelet swelling.

CONCLUSIONS

In conclusion, our results suggest a positive association between higher MPV levels and prehypertension, as shown by the magnitude of this association. The results also suggest that the prehypertensive status was independent from traditional factors, such as smoking, BMI and age, a dose-response trend in nonparametric models and the consistency of this association in subgroup analyses by gender and several other factors. Although we are unable to determine whether higher MPV levels have a causative effect, these findings suggest that increased MPV levels in a prehypertensive group should be considered as a risk factor for cardiovascular disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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