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Implications of mean platelet volume in health and disease: A large population study on data from National Health and Nutrition Examination Survey

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ABSTRACT

Introduction: Mean platelet volume (MPV) is a measure of platelet size and activity. We conducted a population study with National Health and Nutrition Examination Survey (NHANES) data to understand the relationship of MPV with health and diseases.

Materials and methods: The NHANES is a cross-sectional survey of non-institutionalized adult population, administered every 2 years by the Centers for Disease Control and Prevention. Participants answer a questionnaire, receive a physical examination, and undergo laboratory tests. Values of MPV were collected over 6 years (2011–2016). Logistic regression was used to predict likelihood of being in categories with MPV < 10th percentile or > 90th percentile. Statistical analysis was performed using Stata/SE 15.1.

Results: In our study with 17,969 individuals, the mean MPV was 8.40 [SD = 0.92] femtoliter. Individuals with male sex, age 45–64 years, and recent hospital-stay were more likely to have MPV < 10th percentile. Obese, Blacks and Mexican Americans had higher odds of having MPV > 90th percentile. Individuals with emphysema had significantly higher adjusted Odds [OR 1.92, 95% CI: 1.11–3.31, $p = 0.021$] of MPV < 10th percentile. Individuals with cancer were less likely to have MPV > 90th percentile [OR 0.74, 95% CI: 0.55–0.99, $p = 0.042$]. A diagnosis of coronary artery disease, asthma, and chronic obstructive pulmonary disease did not have significant associations with MPV.

Conclusions: Obese individuals are more likely to have higher MPV. Individuals with emphysema had higher odds of having MPV < 10th percentile and those with cancer were less likely to have MPV > 90th percentile.

1. Introduction

Platelets are important mediators of coagulation, inflammation, and atherosclerosis [1]. In circulation, platelets vary in size and activity. The mean platelet volume (MPV) is a measure of the average size of platelets and is thought to be an indicator of platelet activation. In general, the value of MPV should increase when more giant platelets enter the circulation [2]. To date, MPV has remained more of a research tool than a clinical decision-making tool. The range of MPV varies depending on the type of anticoagulant (e.g., ethylene diamine tetra acetic acid or EDTA) and duration of exposure to it and on the technology used in the analyzer [3]. Studies to determine the normal range of MPV in healthy individuals have produced variable results [4,5]. The normal range tends to vary across different age groups, with the mean value increasing significantly with age in individuals but not differing between males and females [6]. Obesity has been associated with higher platelet reactivity, with some studies showing higher MPV values with increases in body mass index (BMI) [7,8]. A higher MPV has been associated with various disease conditions. For example, in patients with acute coronary syndrome (ACS), studies have shown that MPV can be an independent predictor of clinical outcome, thus triggering new research on possible implication of platelet volume in pathophysiology and therapeutics in these patients [9]. In a recently published large prospective cohort study, a large MPV was associated with low overall mortality in subjects without cardiovascular disease (CVD), but in those with a history of CVD, it predicted mortality risk [10].

Mean platelet volume (MPV) is an easily available routine laboratory test reported as part of a complete blood count in patients both in outpatient and inpatient healthcare settings. Although there are some varying reports regarding the true normal range of MPV in healthy individuals, standardization of method for estimation of MPV and understanding its association with different disease conditions should help

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us use it as a potential clinical tool in our practice. Hence, we conducted a large population study involving the National Health and Nutrition Examination Survey (NHANES) data to identify and characterize the relationship of MPV with health and disease in human subjects.

2. Materials and methods

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative cross-sectional survey of the non-institutionalized U.S. adult population, administered every two years by the Centers for Disease Control and Prevention. Participants answer a demographic and health questionnaire, receive a physical examination, and undergo laboratory tests [11]. Mean Platelet Volume (MPV) and Total Platelet Count (TPC) are measured as a part of complete blood count (CBC) with the UniCel DxH 800 Analyzer (Coulter) using the EDTA-mixed blood sample from the participants [12]. NHANES data were aggregated for a 6-year period (2011–2016). Statistical analysis was performed using the Stata/SE 15.1 (StataCorp LP, College Station, TX, USA) software.

The laboratory manual provides the reference ranges on CBC parameters (including MPV) in the form of lower (2.5th percentile) and upper (97.5th percentile) limits, based on the age and gender of the survey respondents [12]. Population weights are used to account for complex survey design of NHANES. Weighted 10th and 90th percentiles were calculated to create binary variables indicating each of these thresholds. Logistic regression models predict likelihood of being in one of the above categories, below the 10th percentile or above the 90th percentile for either measure. These thresholds are used primarily for descriptive purposes, to detail the groups more likely to fall at the outer edges of the distribution, and they do not necessarily have clinical significance. Comorbidities in NHANES are identified via self-reported doctor diagnosis (SRDD), where respondents are asked whether their doctor ever told them that they had a particular diagnosis. This study explores a number of common comorbidities, including asthma, emphysema, chronic obstructive pulmonary disease (COPD), congestive heart failure, coronary heart disease, and cancer. Additional covariates explored include race/ethnicity, age, gender, insurance status, body mass index (BMI) category, marker of systemic inflammation (like C-reactive protein), and hospitalization for a night in the past 12 months.

3. Results

Our study included 17,969 individuals. The overall mean value of mean platelet volume (MPV) in the population was 8.40 femtoliter (fL) (SD = 0.92, 95% CI: 8.36–8.44), with the 10th percentile in the population being 7.3 fL and the 90th percentile 9.6 fL. The mean values of MPV for the respective survey years during our study period (6 years) were the following: 8.40 fL (SD = 0.92) for the year 2011–2012, 8.45 fL (SD = 0.93) in 2013–2014, and 8.34 fL (SD = 0.92) for 2015–2016. The 10th percentile value for total platelet count (TPC) in the population was 170,000/μL, whereas the 90th percentile was 311,000/μL, with the mean TPC being 236,670/μL (SD = 59,100) Mean MPV in males was 8.36 fL and 8.44 fL in female participants. The distribution of MPV in study population with respect to several baseline characteristics is summarized in Table 1. On logistic regression analysis for baseline characteristics, Black race and obesity were associated with lower odds of a MPV < 10th percentile, relative to their reference groups. Males, individuals with age 45–64 years, and participants who spent a night in hospital in last 12 months were more likely to have a MPV value of < 10th percentile. Odds Ratios (OR) for MPV value < 10th percentile with reference to various baseline characteristics are summarized in Table 2. When the same analysis was repeated for prediction of MPV > 90th percentile, it was noted that obese individuals, Blacks, and Mexican Americans had higher odds of having MPV > 90th percentile, and males were less likely for the same. Table 3 describes the ORs for MPV value > 90th percentile with reference to baseline characteristics of the study population. On the regression analysis for total platelet counts (TPC), obesity was associated with a significantly higher odds of TPC > 90th percentile. With increasing age > 45 years and in individuals in a state of good health, the odds of having high TPC was lower compared to respective reference groups. We searched for the data on levels of C-reactive protein (CRP) as a marker of systemic

Table 1
Distribution of mean platelet volume in different percentiles in study population with respect to baseline characteristics.

Baseline characteristics	MPV value (fL)			MPV percentile				
	Mean	SD	95% CI	10	25	50	75	90
Overall (n = 17, 969)	8.40	0.92	(8.36, 8.44)	7.3	7.8	8.3	8.9	9.6
Survey years								
2011–12	8.40	0.92	(8.33, 8.48)	7.3	7.8	8.3	8.9	9.6
2013–14	8.45	0.93	(8.39, 8.51)	7.4	7.8	8.4	9.0	9.6
2015–16	8.34	0.92	(8.28, 8.41)	7.3	7.7	8.3	8.9	9.6
Gender								
Male	8.36	0.90	(8.32, 8.40)	7.3	7.7	8.3	8.9	9.6
Female	8.44	0.94	(8.40, 8.48)	7.3	7.8	8.4	9	9.6
Age								
18–44	8.43	0.91	(8.39, 8.48)	7.3	7.8	8.3	9	9.6
45–64	8.37	0.87	(8.32, 8.41)	7.3	7.7	8.3	8.9	9.6
65 plus	8.38	1.04	(8.32, 8.44)	7.3	7.7	8.3	8.9	9.6
Race/ethnicity								
NH White	8.37	0.69	(8.33, 8.42)	7.3	7.7	8.3	8.9	9.6
NH Black	8.51	1.33	(8.46, 8.56)	7.4	7.9	8.4	9.1	9.8
Mexican American	8.53	1.20	(8.46, 8.61)	7.4	7.9	8.4	9.1	9.8
Other Hispanic	8.50	1.20	(8.41, 8.60)	7.4	7.9	8.4	9.1	9.7
Others	8.25	1.23	(8.18, 8.33)	7.2	7.6	8.1	8.8	9.5
Education								
< 9 years	8.51	1.32	(8.43, 8.60)	7.4	7.9	8.4	9.1	9.8
9–11 years	8.45	1.08	(8.38, 8.53)	7.4	7.8	8.4	9	9.8
HS diploma	8.42	0.94	(8.36, 8.48)	7.3	7.8	8.3	9	9.6
Some college	8.40	0.90	(8.35, 8.45)	7.3	7.7	8.3	9	9.6
College or more	8.34	0.80	(8.30, 8.39)	7.3	7.7	8.2	8.9	9.5

[CI - confidence interval, SD - standard deviation, MPV - mean platelet volume, fL - femtoliter, NH - non-Hispanic, HS - high school]

Table 2
Odds ratios for MPV value < 10th percentile with reference to baseline characteristics.

Logistic regression odds ratios predicting MPV < 10th percentile			
Baseline characteristics	OR	95% CI	p Value
Race (ref = NH White)			
NH Black	**0.77**	**(0.66, 0.90)**	**0.001**
Mexican American	0.79	(0.62, 1.00)	0.053
Other Hispanic	0.75	(0.55, 1.02)	0.068
Others	**1.45**	**(1.25, 1.69)**	**< 0.001**
Age group (ref = 18–44)-years			
45–64	**1.18**	**(1.02, 1.35)**	**0.024**
65 plus	1.09	(0.90, 1.33)	0.383
Male	**1.21**	**(1.04, 1.40)**	**0.014**
Self-reported health (ref = poor/fair)			
Good Health	0.87	(0.70, 1.08)	0.201
Very good or Excellent health	1.03	(0.83, 1.29)	0.758
BMI (ref = normal weight)			
Underweight	1.15	(0.64, 2.06)	0.634
Overweight	0.90	(0.77, 1.04)	0.151
Obese	**0.79**	**(0.68, 0.92)**	**0.003**
Insured	1.15	(0.93, 1.44)	0.198
Night in hospital past 12 months	**1.42**	**(1.13, 1.79)**	**0.004**
Constant	0.10	(0.07, 0.15)	< 0.001

[OR - odds ratio, CI - confidence interval, MPV - mean platelet volume, ref - reference, BMI - body mass index]. Values in bold font are statistically significant (p < 0.05).

Table 3
Odds ratios for MPV value > 90th percentile with reference to baseline characteristics.

Logistic regression odds ratios predicting MPV > 90th percentile			
Baseline characteristics	Odds ratio	95% CI	*p* Value
Race (ref = NH White)			
NH Black	**1.20**	**(1.04, 1.38)**	**0.011**
Mexican American	**1.25**	**(1.04, 1.50)**	**0.018**
Other Hispanic	1.12	(0.83, 1.50)	0.454
Others	0.80	(0.62, 1.04)	0.092
Age group (ref = 18–44)-years			
45–64	0.86	(0.72, 1.02)	0.077
65 plus	0.87	(0.73, 1.03)	0.093
Male	**0.81**	**(0.72, 0.93)**	**0.002**
Self-reported health (ref = poor/fair)			
Good health	1.19	(0.99, 1.42)	0.060
Very good or excellent health	1.07	(0.87, 1.30)	0.524
BMI (ref = normal weight)			
Underweight	0.54	(0.28, 1.06)	0.072
Overweight	1.08	(0.89, 1.31)	0.453
Obese	**1.24**	**(1.05, 1.45)**	**0.010**
Insured	0.87	(0.75, 1.02)	0.083
Night in hospital past 12 months	1.09	(0.91, 1.31)	0.338
Constant	0.13	(0.10, 0.17)	< 0.001

[OR - odds ratio, CI - confidence interval, MPV - mean platelet volume, ref - reference, BMI - body mass index]. Values in bold font are statistically significant (p < 0.05).

inflammation in survey participants to find out the potential relationship between inflammation and MPV, but NHANES lacked information on this for the selected study period (2011–2016).

We calculated the adjusted odds ratios (OR) for self-reported chronic medical conditions. Individuals who reported a diagnosis of emphysema had significantly greater odds [OR 1.92, 95%CI: 1.11–3.31; $p = 0.021$] of having MPV < 10th percentile, compared to those who did not have the diagnosis, controlling for all variables in the base model (age, race/ethnicity, sex, self-reported health, BMI, insurance status, and recent hospitalization). Individuals reporting a diagnosis of cancer were less likely to have MPV > 90th percentile than those without a cancer diagnosis, controlling for the base model variables [OR 0.74, 95% CI: 0.55–0.99, $p = 0.042$]. A self-reported diagnosis of coronary artery disease did not have any significant association with likelihood (greater or lesser) of MPV value being < 10th or > 90th percentiles. Similarly, individuals with congestive heart failure, asthma, and COPD (asked about in surveys in year 2013–2016 only) were not found to have any significant association with the value of MPV. Odds Ratios for MPV value < 10th percentile and > 90th percentiles across various clinical conditions are summarized in Tables 4 and 5.

Table 4
Odds ratios for MPV value < 10th percentile across various clinical conditions.

Adjusted OR predicting MPV < 10th percentile			
Clinical conditions	OR	95% CI	*p* Value
Emphysema	**1.92**	**(1.11,3.31)**	**0.021**
Congestive heart failure	0.88	(0.60,1.29)	0.496
Coronary heart disease	0.75	(0.51,1.12)	0.160
COPD (2013–16 only)	1.41	(0.95,2.10)	0.085
Asthma	1.16	(0.87,1.53)	0.302
Cancer	1.21	(0.95,1.53)	0.121

[OR - odds ratio, MPV - mean platelet volume, CI - confidence interval, COPD - chronic obstructive pulmonary disease]. Values in bold font are statistically significant (p < 0.05).

Table 5
Odds ratios for MPV value > 90th percentile across various clinical conditions.

Adjusted odds ratios predicting MPV > 90th percentile			
Clinical conditions	OR	95% CI	*p* Value
Emphysema	0.75	(0.38,1.46)	0.386
Congestive heart failure	1.42	(0.96,2.11)	0.078
Coronary heart disease	1.33	(0.89,1.99)	0.153
COPD (2013–16 only)	0.77	(0.43,1.38)	0.371
Asthma	1.05	(0.80,1.39)	0.724
Cancer	**0.74**	**(0.55,0.99)**	**0.042**

[OR - odds ratio, MPV - mean platelet volume, CI - confidence interval, COPD - chronic obstructive pulmonary disease]. Values in bold font are statistically significant (p < 0.05).

4. Discussion

Mean platelet volume is part of the routine labs ordered on patients in the hospital. Hence, research efforts have been directed towards finding out the normal range for MPV and its variation in different common acute and chronic disease conditions, especially cardiovascular and pulmonary pathologies. Several studies have tried to find the potential correlation between platelet size and its activity. Platelet function depends on its metabolic potential, which is determined by the amount of secretory granules, mitochondria and glycoprotein receptors present [9]. Platelet density and volume tend to have a positive correlation with each other, with larger platelets being more likely to be densely packed with granules and mitochondria, and, hence, more active. Since the density of platelet is technically challenging to measure, MPV can be used as a reliable indicator of platelet activity [13]. In a study measuring platelet aggregation velocity in healthy subjects, the aggregation potential correlated best to the number of large platelets, indicating an increase in activity with size. Larger platelets also show an increased potential for degranulation [14,15]. Mean platelet volume is measured from the analysis of platelet size-distribution curve, with the techniques using electrical impedance, optical, or fluorescence methods. The value of MPV in a sample may vary considerably depending on the analyzer and method used [16]. Platelet swelling induced by EDTA may increase the MPV measured by the impedance method, whereas the value may decrease over time when measured by an optical method. Replacing EDTA with citrate as the anticoagulant and minimizing the time interval between sampling and analysis might be helpful in the standardization of estimation of MPV [17]. As per the laboratory procedures manual of NHANES, samples collected in EDTA tube are run in the UniCel DxH 800 Analyzer for the estimation of CBC parameters as soon as possible following preparation [12].

Platelet activity has been linked to both systemic inflammation and thrombogenesis in studies [18]. Soluble p-selectin, a cytokine released following platelet activation, was higher in obese as compared to overweight individuals and those with normal BMI in a cross-sectional study on a healthy population group. In the same study, relatively higher values of MPV in obese participants suggest that MPV may be a predictor of the level of platelet activation in obesity [8]. In another recent study in patients undergoing cardiac surgery investigators noted a higher platelet reactivity in obese or overweight patients compared to matched controls, although the values of MPV did not differ significantly between groups [7]. In our study, obese individuals had a significantly higher odds of having MPV value > 90th percentile. A recently published study examined the potential role of MPV and other platelet indices in the prediction of thrombus burden and the likelihood of no-reflow in the infarct-related artery in patients with ST-elevation myocardial infarction (STEMI). In the subgroup analysis, it was noted that patients with no-reflow after PCI had higher MPV values, as compared to patients with reflow, although there was no significant difference in platelet count between two groups [19]. In our study, we

could analyze the data on patients with a reported diagnosis of coronary artery disease (CAD) and congestive heart failure (CHF), and the MPV value was not significantly different in these population groups. In patients with acute ischemic stroke receiving intravenous thrombolytic therapy, MPV value has been found to be significantly associated with improvement in National Institutes of Health (NIH) Stroke Scale and the modified Rankin Scale (MRS) scores for physical disability [20]. In patients with acute pulmonary embolism (PE), an index named computed tomography pulmonary arterial obstruction index ratio (CTPAOIR) is used to determine the severity of PE. Mean platelet volume in these patients is positively correlated with this score and, hence, the severity of obstruction in pulmonary vascular bed [21]. Studies have also shown that MPV is associated with the development of right ventricular dysfunction in patients with acute PE, and it is an independent predictor of mortality in them [22]. Patients with pulmonary arterial hypertension (PAH) tend to have a higher MPV than their healthy counterparts, implicating a role for platelet activation in the pathogenesis of this disease [23]. Mean platelet volume was found to be predictive of prognosis in critically ill patients with sepsis and acute kidney injury [24,25]. Our analysis does not include data on these acute conditions.

Several studies have tried to investigate the possible relationship between platelet activity and chronic lung disease. In patients with chronic airflow obstruction, greater MPV was associated with relative hypoxemia [26]. In a study evaluating MPV and platelet distribution width in patients with severe COPD, MPV value was significantly higher in COPD patients as compared to smoker controls who did not have any airflow limitation [27]. A recent study has proposed that MPV may potentially be used to identify the COPD patients who are at risk of exacerbations [28]. In our study, individuals with a self-reported diagnosis of emphysema (a subtype of COPD) had higher odds of having MPV $<$ 10th percentile, which does not support the results of some of the earlier reports. In individuals with COPD and asthma, the odds of having MPV value $<$ 10th percentile or $>$ 90th percentile were not significantly different than other groups in our logistic regression analysis. The use of MPV in the prognostication of cancer patients is an area of active research in the field of clinical oncology. Studies have produced conflicting results on how MPV can predict the complications and overall survival in patients with cancer. In a recently published study on metastatic pancreatic cancer patients, an MPV value of $>$ 8.7 fL was significantly associated with shorter overall survival in patients [29]. Another study done on esophageal cancer patients suggested that MPV may be an independent predictor of survival [30]. A prospective cohort study on patients with a newly diagnosed cancer or a progressive cancer after remission showed that the patients with higher MPV ($>$ 75th percentile) had a significantly decreased risk of venous thromboembolism, compared to their counterparts with a lower MPV. Overall mortality was also significantly lower in individuals with a higher value of MPV [31]. In colorectal cancer (CRC) patients, MPV was significantly higher compared to patients with adenoma and otherwise healthy individuals. The same study also showed that higher MPV level was associated with vascular invasion, thus indicating the potential role of platelet activation in the dissemination of CRC [32]. In our project, we collected data on individuals reporting a diagnosis of cancer in the NHANES survey and found that the individuals with a cancer diagnosis were less likely to have MPV value $>$ 90th percentile than those without cancer.

Overall, our study was directed at improving our understanding of MPV in health and disease. This population study provides some important and interesting findings. The biggest strength of our study is probably the large sample size of 17,969 individuals. Limitations of our study will include its overall retrospective nature and the lack of patient-level data. The fact that the diagnosis of a particular disease in this survey data is self-reported might lead to selection or misclassification bias. Since participants filling out the survey questionnaire need to depend on their memory to answer the questions, recall bias is also a possibility. Finally, the method of measurement, type of analyzer, and the anticoagulant used among other factors might have a bearing on the values of MPV noted in the study.

5. Conclusion

Our study showed that obese individuals are more likely to have higher MPV values. A self-reported diagnosis of emphysema was associated with higher odds of having MPV $<$ 10th percentile. Individuals with a cancer diagnosis were significantly less likely to have an MPV value $>$ 90th percentile. Mean platelet volumes in individual participant groups with a diagnosis of coronary artery disease, congestive heart failure, asthma, and COPD were not significantly different from their counterparts. We believe that this large population study adds to our existing knowledge about MPV. Future research should be directed towards the standardization of methods for estimation of MPV and the determination of its utility and reliability in diagnosis and prognosis of common clinical conditions.

Conflict of interest

None.

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None.

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