Relation between mean platelet volume and C-reactive protein

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ABSTRACT

Mean platelet volume (MPV) is a measure of platelet activation, and C-reactive protein (CRP) is an established marker of inflammation. Studies on the correlation between MPV and CRP have produced ambiguous results. We undertook a population study with the National Health and Nutrition Examination Survey (NHANES) data (2005–2010) to investigate the relationship between CRP and MPV. CRP was analyzed both as a continuous variable and as a categorical variable (low, intermediate, or high). Multivariate ordinary least squares regression analysis was used to predict the association. Statistical analyses were performed with Stata MP 15.1. In 16,329 participants, mean MPV was 7.9 fL (standard deviation 0.87). Overall mean CRP in the population was 0.4 mg/dL (standard deviation 0.78). In adjusted regression models with CRP as a continuous measure, individuals with high CRP had significantly lower MPV ($b = -0.04$; standard error 0.01; 95% confidence interval -0.06 to -0.01 ; $P = 0.002$). In adjusted regression models using CRP categories, participants with high CRP (>3 mg/dL) had significantly lower MPV compared with the low CRP group ($b = -0.20$; standard error 0.09; 95% confidence interval -0.38 to -0.01 ; $P = 0.035$). Our study revealed a significant inverse correlation between MPV and CRP in NHANES participants.

KEYWORDS C-reactive protein; inflammation; mean platelet volume; NHANES; platelet activation

Platelets have an important role as mediators of inflammation and hemostasis. They potentiate inflammation and immunity against infective agents through active phagocytosis, degranulation, and recruitment of leukocytes to sites of infection.¹ Mean platelet volume (MPV) is a measure of platelet size and activation and has been implicated in various diseases in recent studies.^{2,3} An increase in MPV has been associated with increased mortality in sepsis, which is a severe acute inflammatory state.⁴ C-reactive protein (CRP), an acute-phase reactant produced by the liver, is an established marker of inflammation.⁵ Inflammatory cytokines and chemokines increase the formation and activation of platelets and lead to the dissociation of proinflammatory monomeric CRP from its native pentameric form.⁶ Clinical studies investigating the potential correlation between CRP and MPV values in patients with inflammatory states have produced variable results.^{7–9} Information on possible dynamic aspects of this relationship across physiological and pathological conditions is not available. We hypothesized that a positive

correlation between MPV and CRP might indicate that MPV could be used as an inflammatory marker, and thus a simple complete blood count (including MPV) could be useful in the assessment of the degree of inflammation in patients. Alternatively, MPV depends on multiple factors and thus lacks a simple correlation with CRP. Hence, we undertook a large population study with data from the National Health and Nutrition Examination Survey (NHANES) to determine the relationship between values of MPV and CRP and to explore the potential role of MPV in the assessment of the severity of inflammation.

METHODS

NHANES is a nationally representative survey of the noninstitutionalized adult population of the United States, conducted biennially by the Centers for Disease Control and Prevention. Participants complete a questionnaire, including questions on demographic and health characteristics, have a physical examination, and undergo some basic

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laboratory tests, including complete blood count and CRP. Testing for CRP has been omitted since the 2010 survey due to cost.¹⁰ The NHANES laboratory manual provides the reference ranges on laboratory parameters in the form of lower and upper limits, based on the age and gender of the survey respondents. MPV was measured as a part of a complete blood count with the Coulter HMX Hematology Analyzer using the ethylenediaminetetraacetic acid-mixed blood sample from the participants. The latex enhanced nephelometry method was used to quantify CRP in NHANES.¹¹

We pooled the data (with MPV and CRP values) for a period of 6 years (2005–2010) to obtain a large national sample of individuals. MPV was analyzed as a continuous variable. CRP was analyzed separately as a continuous variable and as coded into three categories, low (<1 mg/dL), intermediate (1–3 mg/dL), and high (>3 mg/dL). Percentile distributions of MPV were examined by CRP categories and other clinical variables, including age, gender, race/ethnicity, body mass index categories, and self-reported doctor diagnosis of hypertension, high cholesterol, and diabetes. Multivariate ordinary least squares regression analysis on the continuous variable for MPV predicts a possible association with CRP, adjusting for demographics, body mass index, and comorbidities. Regression coefficients were calculated in the form of a 'b' value, with respective standard errors and 95% confidence intervals. Sampling weights were used to account for the complex survey design of NHANES using the "svy" command in Stata. Statistical significance was set at a *P* value < 0.05. Statistical analysis was performed using Stata MP 15.1 (Stata Corp. LLC 2017, Stata Statistical Software Release 15, College Station, TX).

RESULTS

In the study population of 16,669 individuals, the overall mean value of MPV was 7.9 fL (standard deviation [SD] 0.87), with the 10th percentile at 6.9 fL and the 90th percentile at 9.0 fL (Table 1). Women had slightly higher mean MPV than men. Elderly individuals (age > 65 years) had a lower MPV (mean 7.87 fL) than participants in younger age groups (18–44 years, mean 7.94 fL). Obese individuals had higher mean MPV (7.94 fL) than overweight, normal weight, and underweight individuals.

In 16,608 individuals with a CRP value reported in the dataset, the overall mean CRP was 0.4 mg/dL (SD 0.78) (Table 2). Women had higher CRP values than men (mean CRP 0.45 vs. 0.34 mg/dL). Individuals >65 years had higher mean CRP levels (0.47 mg/dL) than those in the 18- to 44-year age group (0.36 mg/dL). Approximately 88.8% (*n* = 14,811) of study participants had a low CRP value (<1 mg/dL), and 1.3% (*n* = 226) had a high CRP value (>3 mg/dL). Individuals in the high CRP group had a lower mean MPV (7.71 fL) than those in the intermediate and low CRP groups (7.90 fL). The distribution of MPV values against CRP is depicted in a scatterplot diagram in Figure 1.

The unadjusted ordinary least squares regression models using CRP as a continuous measure did not reveal any significant association between CRP and MPV values (*b* = −0.02, SE 0.01, 95% CI −0.05 to 0.00, *P* = 0.065). However, in the adjusted model controlling for demographic and health factors, MPV and CRP exhibited a statistically significant inverse correlation (*b* = −0.04, SE 0.01, 95% CI −0.06 to −0.01, *P* = 0.002). Table 3 summarizes the unadjusted and adjusted regression coefficients for predicting MPV (with CRP as a continuous measure) in the study population. Table 4 shows unadjusted and adjusted regression coefficients using CRP coded in categories (low, intermediate, and high). These results suggest that much of the association between CRP and MPV is rooted in differences at the higher values of CRP, as participants in the group with high CRP (>3 mg/dL) had significantly lower MPV values (*b* = −0.20, SE 0.09, 95% CI −0.38 to −0.01, *P* = 0.035) compared to those with low CRP (<1 mg/dL). However, an intermediate CRP value (1–3 mg/dL) did not have any significant correlation with the MPV value (*b* = −0.04, SE 0.03, 95% CI −0.11 to 0.03, *P* = 0.221).

DISCUSSION

We found that high CRP levels (both as a continuous measure and in the high category) were associated with a low MPV in study participants, thus showing a significant inverse correlation between these two parameters. The lack of significant correlation in individuals in the intermediate category CRP group compared to the low CRP category suggests that much of the significant association is related to individuals with high CRP levels. Approximately 1.3% of all participants had a CRP level of >3 mg/dL. Elderly individuals (age > 65 years) had relatively higher mean CRP and lower mean MPV levels in our study population. These results do not support our hypothesis that MPV could represent a simple parameter for inflammation.

C-reactive protein is an established marker of systemic inflammation. Native pentameric CRP (p-CRP) is considered the stable physiological form. Under certain circumstances, it undergoes dissociation to form the monomeric CRP (m-CRP), which has potent proinflammatory properties.⁵ Several genetic polymorphisms have been associated with the baseline level of CRP in individuals. High-fat diets seem to increase the levels of CRP, and physical exercise leads to a decrease in levels.¹² Mean platelet volume, on the other hand, is a measure of size and activity of platelets. In a large population study, cardiovascular risk factors were associated with high MPV in men, whereas the use of oral contraceptives and menstruation were found to be determinants for high MPV in female participants. The same study suggested that several single nucleotide polymorphisms could be related to higher MPV in individuals.¹³ Cytoskeletal genes in megakaryocytes have been linked to platelet size and MPV in

Table 1. Distribution of mean platelet volume: means, standard deviations, and percentiles by demographic and health characteristics

Variable	N	Mean (SD)	MPV percentile				
			10th	25th	50th	75th	90th
Overall	16,669	7.90 (0.87)	6.9	7.3	7.9	8.4	9.0
Male	8098	7.88 (0.87)	6.8	7.3	7.8	8.4	9.0
Female	8571	7.92 (0.87)	6.9	7.3	7.9	8.4	9.0
Age (years)							
18–44	7743	7.94 (0.84)	6.9	7.4	7.9	8.4	9.1
45–64	5101	7.85 (0.80)	6.8	7.3	7.8	8.4	8.9
≥65	3825	7.87 (1.07)	6.8	7.3	7.8	8.4	9.0
Race/ethnicity							
White	7923	7.87 (0.71)	6.8	7.3	7.8	8.4	9.0
Black	3359	8.04 (1.22)	6.9	7.4	8.0	8.6	9.2
Mexican American	3207	8.05 (1.29)	7.0	7.5	8.0	8.6	9.1
Other Hispanic	1409	7.95 (1.17)	6.9	7.4	7.9	8.4	9.1
Other race	771	7.79 (0.75)	6.7	7.2	7.8	8.3	8.8
Body mass index (kg/m ²)							
<18.5	293	7.87 (0.94)	6.6	7.1	7.9	8.5	9.1
18.5 to <25	4745	7.85 (0.83)	6.8	7.3	7.8	8.4	8.9
25 to <30	5523	7.90 (0.86)	6.9	7.3	7.9	8.4	9.0
≥30	5874	7.94 (0.90)	6.9	7.3	7.9	8.4	9.1
Self-reported doctor diagnosis							
Hypertension	5411	7.91 (0.94)	6.8	7.3	7.9	8.4	9.1
High cholesterol	4776	7.88 (0.87)	6.8	7.3	7.8	8.4	9.0
Diabetes mellitus	1814	7.99 (1.05)	6.9	7.4	8.0	8.5	9.1
C-reactive protein (mg/dL)							
<1	14,811	7.90 (0.86)	6.9	7.3	7.9	8.4	9.0
1–3	1521	7.90 (0.94)	6.9	7.3	7.8	8.4	9.0
>3	226	7.71 (0.91)	6.6	7.1	7.6	8.2	8.8

MPV indicates mean platelet volume; SD, standard deviation.

genomic association studies.¹⁴ Lifestyle modification measures lead to a decrease in MPV levels.¹⁵

Platelets have an intricate bidirectional relationship with inflammation. Inflammatory states induce the formation and activation of platelets, which are essential mediators of the inflammatory response.⁶ Thrombopoietin acts as an acute-phase reactant and leads to thrombocytosis. However, recent research indicates the potential roles of several cytokines and chemokines in the modulation of number and activity of platelets in the setting of inflammation.^{6,16} For example, Tunjungputri et al reported a positive association between platelet number and the serum concentration of interleukin 1 beta.¹⁷ Interleukins 6 and 11 have been shown to induce the proliferation of megakaryocytes through autocrine and

paracrine mechanisms.^{18,19} Inflammatory chemokines act on receptors expressed on the surface of platelets and lead to the proliferation of megakaryocytes and activation of platelets resulting in degranulation of mediators.^{20,21} Atherosclerotic plaques contain m-CRP, which colocalizes with CD41-positive platelets. This interaction between platelets and m-CRP is mediated by surface glycoproteins. Activated platelets enhance the dissociation of m-CRP from native p-CRP, thus causing propagation of inflammation.⁶ Platelet age and activation likely depend on the type and severity of inflammation and also on the time frame for the inflammatory condition.

Several studies have examined the correlation between MPV and CRP in various diseases. In patients with inflammatory bowel disease, active disease was associated with a

Table 2. Distribution of C-reactive protein: means, standard deviations, and percentiles by demographic and health characteristics

Variable	N	Mean (SD)	CRP percentile				
			10th	25th	50th	75th	90th
Overall	16,608	0.40 (0.78)	0.03	0.07	0.17	0.42	0.94
Male	8092	0.34 (0.79)	0.03	0.06	0.14	0.33	0.71
Female	8516	0.45 (0.77)	0.03	0.08	0.21	0.51	1.13
Age (years)							
18–44	7724	0.36 (0.67)	0.02	0.05	0.14	0.38	0.86
45–64	5079	0.42 (0.78)	0.04	0.08	0.20	0.44	0.99
≥65	3805	0.47 (1.07)	0.05	0.09	0.21	0.48	1.07
Race/ethnicity							
White	7898	0.39 (0.64)	0.03	0.07	0.17	0.40	0.91
Black	3327	0.50 (1.15)	0.03	0.08	0.23	0.57	1.23
Mexican American	3203	0.43 (1.20)	0.04	0.08	0.20	0.47	1.06
Other Hispanic	1407	0.40 (1.09)	0.03	0.07	0.18	0.43	0.86
Other race	773	0.28 (0.53)	0.02	0.04	0.12	0.27	0.62
Body mass index (kg/m ²)							
<18.5	289	0.18 (0.49)	0.01	0.02	0.05	0.14	0.42
18.5 to <25	4731	0.24 (0.69)	0.02	0.04	0.08	0.20	0.46
25 to <30	5510	0.33 (0.74)	0.04	0.07	0.15	0.33	0.67
≥30	5849	0.60 (0.83)	0.08	0.17	0.35	0.74	1.39
Self-reported doctor diagnosis							
Hypertension	5383	0.50 (0.87)	0.05	0.10	0.24	0.57	1.18
High cholesterol	4756	0.42 (0.82)	0.04	0.08	0.20	0.45	1.00
Diabetes mellitus	1800	0.55 (0.87)	0.05	0.11	0.28	0.69	1.36
MPV (quartiles)							
<25th percentile	3487	2.55 (1.18)	0.03	0.06	0.17	0.43	0.99
25–49th percentile	4478	2.51 (1.07)	0.03	0.07	0.18	0.41	0.93
50–74th percentile	3692	2.57 (1.12)	0.03	0.07	0.17	0.41	0.93
>75th percentile	4901	2.61 (1.15)	0.03	0.07	0.18	0.42	0.92

MPV indicates mean platelet volume; SD, standard deviation.

significantly decreased MPV, with an observed inverse correlation between MPV and CRP.⁷ However, a significant positive correlation was found between MPV and CRP in clinical studies in patients with cirrhosis of the liver, stroke, and acute infections, such as pneumonia and cellulitis, a range of disease conditions with different pathophysiological mechanisms.^{8,22–25} In a recent study in patients undergoing percutaneous coronary intervention, MPV was positively correlated with high sensitive CRP (hs-CRP), and high levels of both parameters were associated with an increased incidence of major adverse cardiac and cerebrovascular events.²⁶ However, some studies failed to show any significant correlation between MPV and CRP in infective and inflammatory

conditions.^{9,27} Few studies have shown that the value of MPV tends to go down in patients with an active inflammatory state, compared to recovered or stable patients.⁷ Presumably, the stable health condition of participants in NHANES could influence the observed correlation between MPV and CRP in our study. The retrospective nature of our study may have led to recall or misclassification bias. The findings of our study raise some critical questions on the stability of a given value of MPV in an individual. We don't have concrete information on whether MPV has longitudinal, seasonal, or diurnal variation. Knowledge is lacking on the nature of variation in MPV between critically ill hospitalized patients and stable individuals out of the hospital.

Table 3. Weighted regression model predicting mean platelet volume (C-reactive protein as continuous measure)*

Variable	b	SE	95% CI	P value
<i>Unadjusted model</i>				
CRP (continuous)	−0.02	0.01	(−0.05, 0.00)	0.065
<i>Adjusted model</i>				
Age (years) (ref = 18–44)				
45–64	−0.10	0.02	(−0.14, −0.06)	<0.001
≥65	−0.09	0.04	(−0.17, −0.01)	0.021
Male (ref = female)	−0.05	0.02	(−0.08, −0.01)	0.014
Race/ethnicity (ref = white)				
Black	0.15	0.04	(0.07, 0.23)	0.001
Mexican American	0.16	0.04	(0.09, 0.23)	<0.001
Other Hispanic	0.06	0.06	(−0.05, 0.17)	0.287
Other race	−0.09	0.04	(−0.17, 0.00)	0.048
CRP (continuous)	−0.04	0.01	(−0.06, −0.01)	0.002
BMI (ref = 18.5 to <25 kg/m ²)				
<18.5	0.02	0.08	(−0.13, 0.17)	0.788
25 to <30	0.06	0.02	(0.02, 0.10)	0.005
≥30	0.07	0.02	(0.03, 0.12)	0.003
Self-reported doctor diagnosis				
Hypertension	0.04	0.02	(−0.01, 0.08)	0.110
High cholesterol	0.09	0.03	(0.03, 0.15)	0.003
Diabetes mellitus	0.05	0.07	(−0.09, 0.18)	0.506

BMI indicates body mass index, CI, confidence interval; CRP, C-reactive protein; ref, reference; SE, standard error.

*r-squared = 0.013, N = 16,329. Significant P values are presented in bold.

Table 4. Weighted regression model predicting mean platelet volume (C-reactive protein as categorical variable)*

Variable	b	SE	95% CI	P value
<i>Unadjusted model</i>				
CRP (ref = Low, or <1 mg/dL)				
Intermediate (1–3)	0.00	0.04	(−0.07, 0.07)	0.947
High (>3)	−0.18	0.09	(−0.36, 0.01)	0.060
<i>Adjusted model</i>				
Age (years) (ref = 18–44)				
45–64	−0.10	0.02	(−0.14, −0.06)	<0.001
≥65	−0.09	0.04	(−0.17, −0.02)	0.019
Male (ref = female)	−0.04	0.02	(−0.08, −0.01)	0.015
Race/ethnicity (ref = white)				
Black	0.15	0.04	(0.07, 0.23)	0.001
Mexican American	0.16	0.04	(0.09, 0.23)	<0.001
Other Hispanic	0.06	0.06	(−0.05, 0.17)	0.291
Other race	−0.09	0.04	(−0.17, 0.00)	0.050
CRP (ref = low or, <1 mg/dL)				
Intermediate (1–3 mg/dL)	−0.04	0.03	(−0.11, 0.03)	0.221
High (>3 mg/dL)	−0.20	0.09	(−0.38, −0.01)	0.035
BMI (ref = 18.5 to <25 kg/m ²)				
<18.5	0.02	0.08	(−0.13, 0.17)	0.773
25 to <30	0.06	0.02	(0.02, 0.10)	0.007
≥30	0.07	0.02	(0.02, 0.11)	0.007
Self-reported doctor diagnosis				
Hypertension	0.04	0.02	(−0.01, 0.08)	0.120
High cholesterol	−0.01	0.02	(−0.06, 0.04)	0.743
Diabetes mellitus	0.09	0.03	(0.03, 0.15)	0.003

BMI indicates body mass index, CI, confidence interval; CRP, C-reactive protein; ref, reference; SE, standard error.

*r-squared = 0.0127, N = 16,329. Significant P values are presented in bold.

Figure 1. Scatterplot diagram showing the distribution of values of mean platelet volume versus C-reactive protein.

Whether MPV varies significantly between infections and noninfectious inflammatory states is not known as well.

In summary, our study showed a significant inverse correlation between MPV and CRP in the NHANES population, and future studies should explore this seemingly complex dynamic relationship between MPV and inflammation.

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