European Review for Medical and Pharmacological Sciences 2024; 28: 327-335

Interrelationship between platelets and BUN in postmenopausal patients with coronary heart disease: findings of the NHANES from 2003 to 2016

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Abstract. – OBJECTIVE: During menopause, women are more likely to develop coronary heart disease (CHD) due to the significant changes in body metabolism brought on by the loss of estrogen. The purpose of this study was to investigate the independent association between platelet parameters and blood urea nitrogen (BUN) in postmenopausal patients with coronary artery disease in order to clarify the function performed by platelet parameters and BUN in thrombosis.

PATIENTS AND METHODS: We took information from the NHANES between 2003 and 2016. Platelet count (PC), mean platelet volume (MPV), and PC/MPV were the independent variables, BUN was the dependent variable, and age, ethnicity, marital status, body mass index (BMI), inflammation indicators, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were the covariates.

RESULTS: BUN decreased with increasing PC in postmenopausal heart disease patients after controlling for other factors. When PC/MPV was less than 30.5, there was a strong negative correlation with BUN. In addition, there was a strong positive correlation with BUN when MPV was less than 9.3 fL.

CONCLUSIONS: The findings of this study will contribute to a better understanding of the mechanisms underlying thrombosis in postmenopausal women with CHD and offer fresh perspectives on how to create novel antithrombotic medications for an aging population.

Key Words:
Coronary heart disease, Platelet count, Mean platelet volume, PC/MPV, Postmenopausal women.

Abbreviations

CHD: coronary heart disease; BMI: body mass index; WBC: white blood cell count; PC: platelet count; MPV: mean platelet volume; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen.

Introduction

The most common cause of death in the world is coronary heart disease (CHD)[1]. Postmenopausal women have a higher incidence of CHD compared to premenopausal women and men at the same age[2,3]. Women go through considerable metabolic changes during menopause as a result of decreased estrogen production[4]. Platelets are essential in the inflammatory phase of CHD because they bind to leukocytes and help them find their way to endothelial cells[5]. Antiplatelet medications have been proven in prior research[6,7] to be beneficial in delaying the onset of CHD and enhancing its prognosis.

The two most accessible platelet metrics are mean platelet volume (MPV) and platelet count (PC)[8]. It has been demonstrated that PC and MPV represent platelet activity and can offer crucial details regarding the progression and prognosis of various clinical situations, including ischemic stroke, sepsis, and a variety of other illnesses[9,10]. Particularly, earlier research in CHD[11,12] has demonstrated that PC and MPV play a significant role in the progression of disease. A common measure of renal function is blood urea nitrogen (BUN); however, in recent years, BUN has also been used to forecast cardiac arrest and acute coronary syndromes[13,14]. Therefore, it is crucial to investigate how platelet parameters and BUN affect the development of CHD illness.

This study looked at the link between platelet parameters and BUN in postmenopausal individuals with coronary artery disease in an effort to better understand the role of platelets and BUN in the development of CHD. Additionally, this study will advance knowledge of the connection between platelet parameters, BUN, and the onset

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and progression of postmenopausal CHD, offering fresh perspectives for the creation of novel antithrombotic drugs for an aging population.

Patients and Methods

Study Design and Population

All subject data were obtained from the National Health and Nutrition Examination Survey (NHANES), which employed a cross-sectional design to evaluate the health and nutritional status of all US citizens. The NHANES, which is updated every two years, is connected to the Centers for Disease Control and Prevention (USA). The criteria for inclusion were: women who are postmenopausal and have coronary heart disease, as well as participants who have complete PC, MPV, BUN, and general information data. Data from the NHANES 2003-2016 (2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012, 2013-2014, and 2015-2016) were extracted. The following participants were excluded from the study: (i) those with a history of female hormones use; (ii) those with a doctor-diagnosed cancer; (iii) pregnant participants; and (iv) those with a history of using glucocorticoids. Each participant provided their informed consent, and the study was authorized by the ethics review board of the National Center for Health Statistics[15].

Menopausal Status Definitions

Menopausal status was established using the self-reported reproductive health questionnaire. The term "postmenopausal" was used to describe women who answered "no" to the question "Have you had at least one menstrual period in the past 12 months?" and "menopause/change of life" to the follow-up query "What is the reason that you have not had a period in the past 12 months?" You can learn more about the self-reported reproductive health questionnaire on the NHANES website[16].

Coronary Heart Disease Status Definition

A standardized medical condition questionnaire for coronary heart disease was administered during the personal interview. The participants were asked if they had ever been told they had coronary heart disease by a doctor or other healthcare provider. Participants were labeled as having coronary heart disease if they responded "yes" to any of the earlier questions[17].

PC, MPV, PC/MPV and BUN

The NHANES website provides the laboratory procedures for the standard biochemistry profile and complete blood count test[18]. The ratio of PC to MPV is computed as PC/MPV.

Variables

This study's analysis additionally included covariates to account for the possibility of other factors having an impact on BUN. The NHANES database's covariate selection was based on findings from earlier research[4,5]. Finally, potential confounders for this investigation included age, ethnicity, marital status, body mass index, inflammation indicators, alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

Statistical Analysis

First, as all analyses depended on participants having the necessary data, individuals who lacked the necessary covariate data were not included in the calculation. Second, the baseline characteristics were revealed by the weighted mean and standard error (SE) (continuous variables) and weighted percentage (categorical variables). The weights that would be used for the analysis were chosen after consulting the NHANES database's instructions[19]. Due to the fact that several of the variables utilized in the current investigation were collected at the MEC, we used the exam weight from the MEC (WTMEC2YR) for analysis. Due to the integration of seven NHANES survey cycles, the sample weights utilized in the final analysis were likewise equivalent to one-seventh of the "WTMEC2YR". Third, connections between PC, MPV, and PC/MPV were investigated using multivariate weighted linear regression models with smoothed curve fitting and generalized weighted models to capture the non-linear correlations between PC, MPV, PC/MPV, and BUN. The mean and standard deviation (SD), which are used to describe variables with a normal distribution, can be used to express continuous variables in two different ways. Categorical variables are expressed as frequencies or percentages. We used the two-test (categorical variables) and one-way ANOVA (normal distribution) to compare group differences (quartiles). Data analysis was done in two steps. Step 1 involved the creation of three models using univariate and multivariate linear regression analysis: Model I (without adjusting for covariates), Model II (adjusting simply for socio-demographics), and Model III (adjusting for variables in Model II and Table I). The R

Table I. Baseline characteristics of the study population.

	Mean ± SD
Age (years, mean ± SD)	67.31 ± 12.93
Ethnicity, n (%)	
Mexican American	33 (9.65%)
Other Hispanic	68 (19.88%)
Non-Hispanic White	175 (51.17%)
Non-Hispanic Black	47 (13.74%)
Other ethnicities	19 (5.56%)
Marital Status, n (%)	
Married	113 (33.04%)
Widowed	125 (36.55%)
Divorced	74 (21.64%)
Separated	14 (4.09%)
Never married	13 (3.80%)
Living with partner	3 (0.88%)
BMI (kg/m^2, mean ± SD)	31.43 ± 7.64
WBC (1,000 cells/uL, mean ± SD)	8.76 ± 7.31
Lymphocyte number (1,000 cells/uL, mean ± SD)	2.88 ± 2.21
Segmented neutrophils number (1,000 cells/uL, mean ± SD)	4.00 ± 2.26
Lymphocyte percent (%, mean ± SD)	0.28 ± 0.10
Segmented neutrophils percent (%, mean ± SD)	0.58 ± 0.15
PC (1,000 cells/uL, mean ± SD)	246.67 ± 74.00
MPV (fL, mean ± SD)	8.21 ± 0.92
PC/MPV (mean ± SD)	30.79 ± 11.16
ALT (U/L, mean ± SD)	21.06 ± 10.97
AST (U/L, mean ± SD)	26.12 ± 10.03
BUN (mg/dL, mean ± SD)	18.04 ± 9.44

CHD: coronary heart disease; BMI: body mass index; WBC: white blood cell count; PC: platelet count; MPV: mean platelet volume; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen.

statistical software (http://www.R-project.org R Foundation) was used for all studies. The *p*-value cut-off for statistical significance (bilateral) was chosen at 0.05.

Results

Baseline Patient Characteristics

Figure 1 depicts the flowchart for participant selection. From the NHANES (2003-2004: N = 10,122; 2005-2006: N = 10,348; 2007-2008: N = 10,149; 2009-2010: N = 10,537; 2011-2012: N = 9,756; 2013-2014: N = 10,175; 2015-2016: N = 9,971), information on 71,058 participants was retrieved. First, we omitted the 35,122 male participants. Premenopausal women (N = 10,054) who lacked information on their menopausal status were also left out of this study. Additionally, we did not include postmenopausal women (N = 25,004) who did not have coronary heart disease. Then, we removed postmenopausal women (N = 274) without PC, MPV, BUN, or general information. Second, those participants (N = 84) who matched the exclusion criteria were eliminated. Thirdly, participants (N = 178) with missing covariate data were disqualified. The final study comprised 342 postmenopausal women who had developed coronary heart disease. The baseline characteristics of the chosen patients are displayed in Table I. The mean age of all participants was 67.31 ± 12.93 years, and the mean body mass index was 31.43 ± 7.64 kg/m^2. The mean values of white blood count (WBC), lymphocyte number, segmented neutrophils number, lymphocyte percent, segmented neutrophils percent, PC, MPV, PC/MPV, ALT, AST and BUN were 8.76 ± 7.31*1,000 cells/uL, 2.88 ± 2.21*1,000 cells/uL, 4.00 ± 2.26*1,000 cells/uL, 0.28 ± 0.10%, 0.58 ± 0.15%, 0.58 ± 0.15% and 0.58 ± 0.15% respectively, 0.58 ± 0.15%, 246.67 ± 74.00*1,000 cells/uL, 8.21 ± 0.92 fL, 30.79 ± 11.16, 21.06 ± 10.97 U/L, 26.12 ± 10.03 U/L, and 18.04 ± 9.44 mg/dL.

Univariate Analysis of BUN Levels

The results of the univariate analyses are presented in Table II. Body mass index (BMI), ethnicity, marital status, WBC, MPV, alanine aminotransferase (ALT), and azelaic transaminase (AST) were not associated with BUN in the study population. Age (β = 0.25, 95% CI = 0.16, 0.33) was significantly and strongly associated with BUN in all study populations. Secondly, PC (β = -0.02, 95% CI = -0.04, -0.01) and PC/MPV (β = -0.13, 95% CI = -0.23, -0.04) were negatively associated with BUN.

Unadjusted and Adjusted Linear Regression Results

Two models were developed in the present investigation to study the different effects of PC, MPV, and PC/MPV on serum albumin levels (Table III). In the unadjusted model (Model I), PC and PC/MPV were negatively correlated with BUN. After adjustment for all covariates (model III), PC (β = -0.02, 95% CI = -0.04, -0.01), PC/MPV (β = -0.14, 95% CI = -0.24, -0.04) remained negatively associated with BUN.

Correlation Between PC, MPV, PC/MPV and BUN

In this work, we investigated the relationship between BUN, PC, MPV, and PC/MPV (Table IV, Figures 2-4). After considering all factors, the results of the smoothed fitted curves and general-

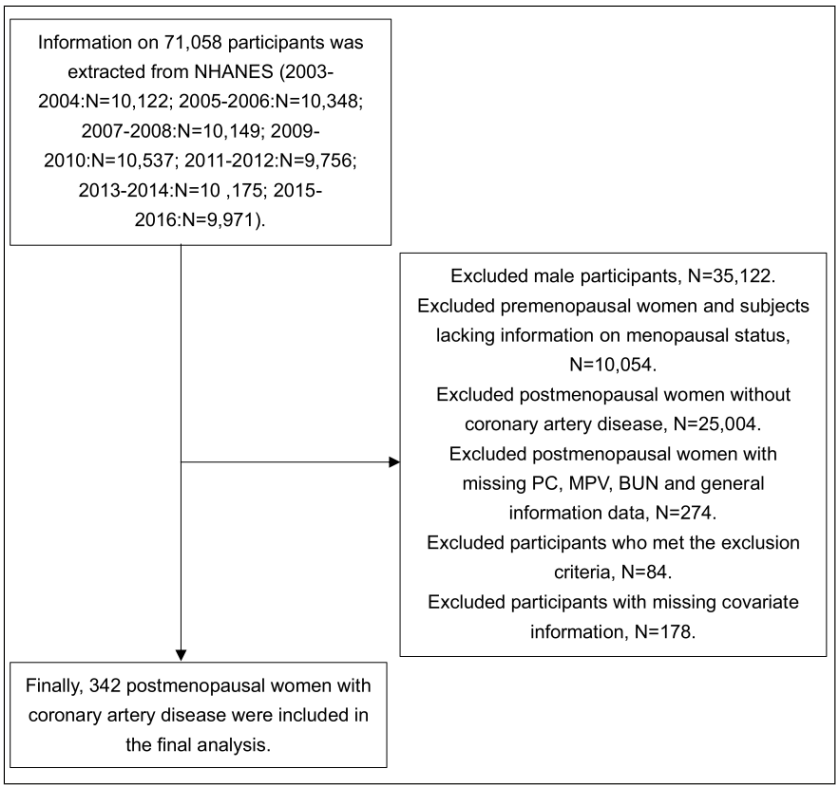

Figure 1. Patient inclusion flowchart.

Table II. Univariate analysis of BUN (mg/dL).

	BUN β (95% CI) *p*-value
Age, years	0.25 (0.16, 0.33) < 0.0001
Ethnicity, n%	
Mexican American	Reference
Other Hispanic	-0.95 (-5.12, 3.21) 0.6547
Non-Hispanic White	3.96 (0.39, 7.52) 0.0304
Non-Hispanic Black	2.66 (-1.61, 6.94) 0.2230
Other ethnicities	3.99 (-1.41, 9.39) 0.1483
Marital Status, n%	
Married	Reference
Widowed	2.21 (-0.26, 4.67) 0.0808
Divorced	-2.29 (-5.23, 0.66) 0.1286
Separated	-1.06 (-6.87, 4.76) 0.7223
Never married	0.72 (-4.87, 6.32) 0.7998
Living with partner	-2.69 (-13.44, 8.05) 0.6237
BMI, kg/m^2	0.09 (-0.05, 0.23) 0.2107
WBC, 1,000 cells/uL	-0.09 (-0.24, 0.06) 0.2526
Lymphocyte number, 1,000 cells/uL	-1.21 (-1.71, -0.71) < 0.0001
Segmented neutrophils number, 1,000 cells/uL	0.92 (0.45, 1.38) 0.0001
Lymphocyte percent, %	-31.26 (-42.45, -20.06) < 0.0001
Segmented neutrophils percent, %	12.94 (5.50, 20.39) 0.0008
PC, 1,000 cells/uL	-0.02 (-0.04, -0.01) 0.0044
MPV, fL	1.00 (-0.15, 2.16) 0.0887
PC/MPV	-0.13 (-0.23, -0.04) 0.0052
ALT, U/L	-0.08 (-0.18, 0.01) 0.0948
AST, U/L	-0.01 (-0.12, 0.09) 0.8077

CHD: coronary heart disease; BMI: body mass index; WBC: white blood cell count; PC: platelet count; MPV: mean platelet volume; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen.

Table III. Relationship between PC, MPV, PC/MPV and BUN (mg/dL) in different models.

Exposure	Model I β (95% CI) *p*-value	Model II β (95% CI) *p*-value
PC	-0.02 (-0.04, -0.01) 0.0044	-0.02 (-0.04, -0.01) 0.0041
MPV	1.00 (-0.15, 2.16) 0.0887	0.69 (-0.47, 1.84) 0.2447
PC/MPV	-0.13 (-0.23, -0.04) 0.0052	-0.14 (-0.24, -0.04) 0.0083

Model I is the unadjusted model. Model II adjusted for age (smooth), ethnicity, marital status, BMI (smooth), WBC (smooth), lymphocyte number (smooth), monocyte number (smooth), segmented neutrophils number (smooth), lymphocyte percent, segmented neutrophils percent, ALT (smooth), AST (smooth). CHD: coronary heart disease; BMI: body mass index; WBC: white blood cell count; PC: platelet count; MPV: mean platelet volume; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen.

ized additive models showed that BUN decreased with increasing PC and PC/MPV. When PC was below 219*1,000 cells/uL, PC was negatively correlated with BUN (β = -0.07, 95% CI = -0.11, -0.02). However, when PC was above 219*1,000 cells/uL, it was not significantly correlated with BUN. When MPV was below 9.3 fL, it was positively correlated with BUN (β = 1.64, 95% CI = 0.19, 3.08). However, when MPV was above 9.3 fL, there was no significant correlation with BUN. When PC/MPV was below 30.5, there was a negative correlation with BUN (β = -0.32, 95% CI = -0.55, -0.10). However, there was no significant correlation when PC/MPV was above 30.5.

Discussion

This study combined univariate analysis, multiple regression analysis, and saturation threshold analysis to analyze the relationship between PC, MPV, PC/MPV, and BUN. After adjusting for all variables, BUN decreased as PC increased. When PC/MPV was lower than 30.5, PC/MPV and BUN were significantly negatively correlated. However, when MPV was < 9.3 fL, the relationship between MPV and BUN was significantly positive.

The accumulation of atherosclerotic plaque in the blood vessels that supply the heart with oxygen and nutrients is known as coronary artery disease[20]. Early in life, the complicated process of atherosclerosis is assumed to start with coronary endothelial cell failure because these cells are no longer able to control vascular tone through nitric oxide signaling correctly. Additionally, the inflammation caused by cholesterol-loaded macrophages, often known as "foam cells", is spread by the gradual infiltration of lipoprotein particles carrying cholesterol into the artery wall. The proliferation of smooth muscle cells beneath the artery wall causes vascular remodeling and ultimately results in blood vessel narrowing, which reduces blood flow. Blood clots that rupture on

Table IV. Threshold effect analysis of the relationship between PC, MPV, PC/MPV and BUN levels.

Exposure:	PC β (95% CI) *p*-value	MPV β (95% CI) *p*-value	PC/MPV β (95% CI) *p*-value
Model I			
One linear effect	-0.02 (-0.04, -0.01) 0.0041	0.69 (-0.47, 1.84) 0.2447	-0.14 (-0.24, -0.04) 0.0083
Model II			
Break point (k)	219	9.3	30.5
< k segment effect 1	-0.07 (-0.11, -0.02) 0.0044	1.64 (0.19, 3.08) 0.0270	-0.32 (-0.55, -0.10) 0.0043
> k segment effect 2	-0.01 (-0.03, 0.01) 0.3699	-3.46 (-7.44, 0.53) 0.0902	-0.04 (-0.18, 0.11) 0.6074
Effect difference between 2 and 1	0.06 (0.00, 0.11) 0.0484	-5.09 (-9.78, -0.40) 0.0343	0.29 (-0.01, 0.59) 0.0614
Predicted value of equation at break point	18.31 (16.59, 20.04)	20.72 (18.52, 22.91)	17.26 (15.56, 18.96)
LRT test	0.040	0.028	0.051

Model 1: Linear analysis. Model 2: Nonlinear analysis. LRT and logarithmic likelihood ratio tests ($p < 0.05$ means that model II is significantly different from model I, representing a nonlinear relationship). Adjusted variables: age, ethnicity, marital status, BMI, WBC, lymphocyte number, monocyte number, segmented neutrophils number, lymphocyte percent, segmented neutrophils percent, ALT, AST. Statistical significance was set at $p < 0.05$. CHD: coronary heart disease; BMI: body mass index; WBC: white blood cell count; PC: platelet count; MPV: mean platelet volume; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen.

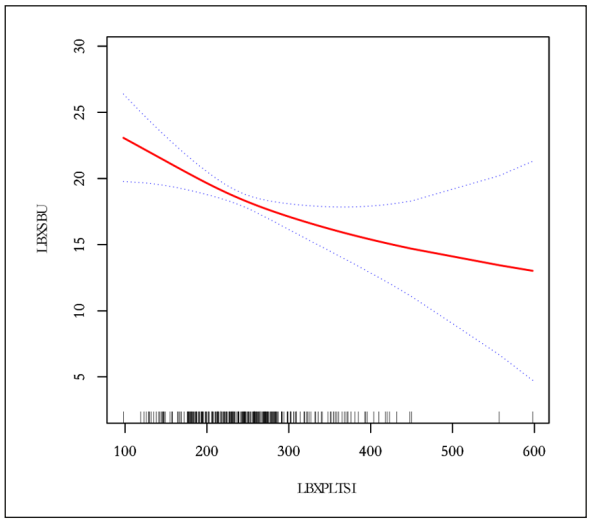

Figure 2. Association between PC and BUN (mg/dL).

the surface of the plaque are often what cause heart attacks because they deny the blood clots downstream of the myocardium enough blood flow, which results in cell death[21-24]. Age, being a man, being obese, leading a sedentary lifestyle, and living a bad lifestyle all raise the risk of myocardial infarction, according to epidemiological studies of coronary heart disease[25,26]. These risk variables can be integrated into clinical practice to offer fresh ideas for the creation of novel antithrombotic medications for the aging population. A woman's risk of developing coronary heart disease rises gradually after menopause, taking into account the significant changes in body metabolism brought on by the loss of estrogen[4].

During the process of producing platelets, non-nucleated, disc-shaped fragments of megakaryocyte cytoplasm are produced. Additionally demonstrated to induce platelet precursor cells in inflammatory settings are IL-6 and IL-1[27]. Increased Tpo synthesis in the liver and a direct impact on megakaryocytes *via* the membrane receptor IL-6R are two effects of IL-6 activity[8]. This suggests that inflammatory circumstances may result in noticeably higher platelet numbers. During standard blood morphology testing, a hematology analyzer calculates MPV, a reliable indicator of platelet size, based on volume distribution. Recent research[28,29] has demonstrated that PC, MPV, and PC/MPV are valuable in diagnosing patients' overall health and have prognostic significance in several illnesses. BUN is a protein

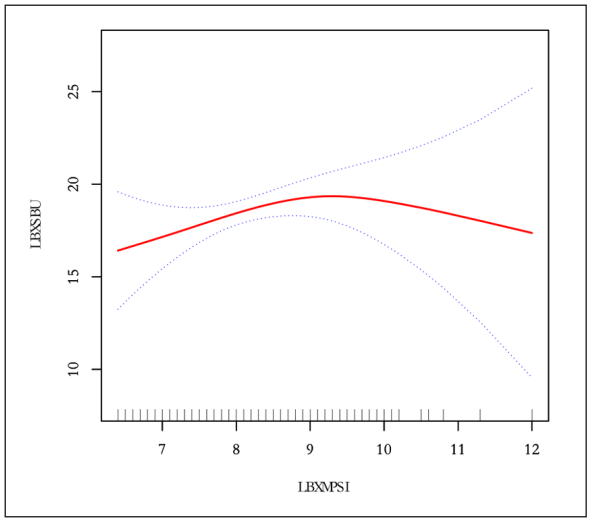

Figure 3. Association between MPV and BUN (mg/dL). Figure 3 shows the smooth fitting curve of mean platelet volume (MPV) and blood urea nitrogen (BUN). The solid red line represents the smooth curve fit between the variables. Blue bands represent the 95% confidence interval of the fit. The model was adjusted for age, ethnicity, marital status, body mass index (BMI), white blood count (WBC), lymphocyte number, monocyte number, segmented neutrophils number, lymphocyte percent, segmented neutrophils percent, alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

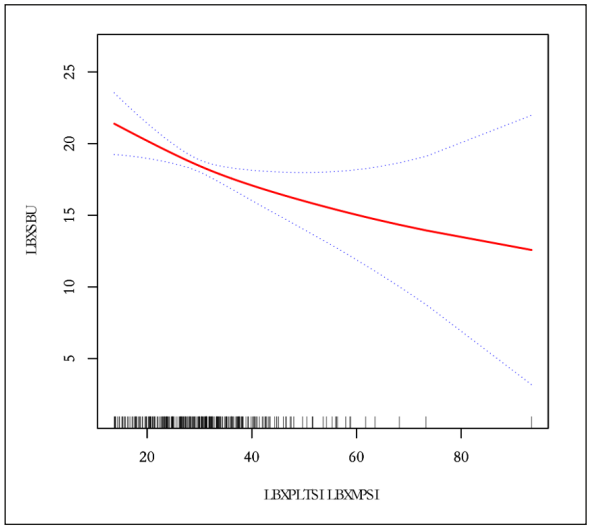

Figure 4. Association between PC/MPV and BUN (mg/dL). Figure 4 shows the smooth fitting curve of Platelet count (PC)/MPV and BUN. The solid red line represents the smooth curve fit between the variables. Blue bands represent the 95% confidence interval of the fit. The model was adjusted for age, ethnicity, marital status, body mass index (BMI), white blood count (WBC), lymphocyte number, monocyte number, segmented neutrophils number, lymphocyte percent, segmented neutrophils percent, alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

metabolite that is sensitive to outside influences and is a highly sensitive indication of changes in renal perfusion and hemodynamics. BUN is substantially correlated with mortality in individuals with heart failure, according to studies[30,31].

The following can be used to understand the underlying mechanisms of this phenomenon: vascular tone is impacted by coronary endothelial cell failure, cholesterol-carrying lipoprotein particles gradually infiltrating the artery wall trigger an inflammatory response, and platelets form plaques by attracting leukocytes to the endothelium[21,23]. In the end, this causes vascular narrowing and slow blood flow, which then serves as the foundation for the onset of CHD. Our findings show that BUN reduces with increasing PC, PC/MPV in postmenopausal CHD patients after adjusting for other variables. Dynamic monitoring of platelet levels and BUN can guide postmenopausal CHD therapy.

The strenght of this study is that it uses an observational design to analyze non-linearity. It also underwent significant statistical correction to remove impacting factors. The main conclusions of the study may provide valuable suggestions for clinical treatment and future research. Additionally, the study's utilization of a large amount of data considerably reduced population selection bias.

Limitations

The study has some limitations. In this cross-sectional study, a causal relationship between platelet characteristics and BUN could not be established. Furthermore, the sample size was quite small. A prospective study with a bigger sample size is therefore required. Thirdly, some data on variables was gathered through self-reported questionnaires, which could add recollection bias and may not accurately reflect the situation. Due to the lack of contrast angiography, only approximate answers can be derived for cases of coronary artery disease.

Conclusions

To our knowledge, this is the first study analyzing the relationship between platelet parameters and hemodynamics in postmenopausal CHD patients. In postmenopausal individuals with CHD, this study demonstrates a substantial negative association between PC, PC/MPV, and BUN lipids. It also demonstrates that MPV is also connected with CHD, which may be related to the etiology of the disease. The findings of this study will contribute to a better understanding of the mechanisms underlying thrombosis in postmenopausal women with CHD and offer fresh perspectives on how to create novel antithrombotic medications for an aging population.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgements

The authors would like to thank all the medical and nursing staff at the Department of Gynecology, Qingdao University Hospital.

Ethics Approval

The study involving human participants was reviewed and approved by the Ethical Review Board of the National Centre for Health Statistics. The NCHS Research Ethics Review Board (ERB) approved the NHANES study protocol and participants provided written informed consent at enrolment. The approval numbers were Protocol #98-12 (NHANES 1999-2004), Protocol #2005-06 (NHANES 2005-2006), Continuation of Protocol #2005-06 (NHANES 2007-2008), the Continuation of Protocol #2005-06 (NHANES 2009-2010), Protocol #2011-17 (NHANES 2011-2012), Continuation of Protocol #2011-17 (NHANES 2013-2014). Continuation of Protocol #2011-17 (NHANES 2015-2016).

Informed Consent

The patients/participants provided their written informed consent to participate in this study.

Availability of Data and Materials

This study analyzed publicly available datasets. The data can be found here: https://www.cdc.gov/nchs/nhanes/.

Funding

This work was supported by the Shandong Province Medical and Health Science and Technology Development Programme (Grant numbers [2014WS0174]) and the 2021 Clinical Medicine +X Research Project of Affiliated Hospital of Qingdao University (Grant numbers [QDFY+X202101046]).

Authors' Contribution

AC interpreted the patient data on CHD. YD collated the data and was the main contributor to writing the manuscript. ZD analyzed the patient data on CHD. ZC conducted the survey and wrote the manuscript. WS performed the validation. WZ performed the software manipulation. All authors read and approved the final manuscript.

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