The association between whole blood viscosity and high thrombus burden in patients with non-ST elevation myocardial infarction

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ABSTRACT

Background: Prior studies showed that patients with elevated whole blood viscosity (WBV) had a higher risk of arterial thrombosis, acute stent thrombosis, and left ventricular apical thrombus presence after acute coronary syndrome. This investigation aimed to determine the association between WBV and high thrombus burden (HTB) in non-ST elevation myocardial infarction (NSTEMI) patients treated with percutaneous coronary intervention (PCI).

Methods: This retrospective cohort investigation included data from consecutive 290 NSTEMI patients who received PCI at a tertiary institution. Patients with grade 1–3 thrombus burden were categorized as having low thrombus burden (LTB) (n = 178), whereas those with grade 4–5 thrombus burden were classified as having HTB (n = 112). WBV at high shear rate (HSR) and low shear rate (LSR) were estimated using hematocrit (HTC) and total protein levels.

Results: Patients with HTB had higher WBV at both LSR and HSR. In HTB patients, the frequency of infarct-related artery (IRA) reference vessel diameter, distal embolization, and no-reflow was also higher. Multivariable logistic regression models indicated that WBV at LSR (odds ratio [OR], 1.028; 95% confidence interval [CI], 1.014–1.043; $P < 0.001$) and HSR (OR, 1.606; 95% CI, 1.334–1.953; $P < 0.001$) were independent predictors of HTB in NSTEMI patients. Notably, the area under the curve value of WBV at both shear rates was greater than that of its components, including total protein and HTC.

Conclusion: This is the first study showing that WBV at both shear rates is a significant predictor of HTB in NSTEMI patients.

Key words: whole blood viscosity, thrombus burden, high, non-ST elevation myocardial infarction

INTRODUCTION

The main underlying cause of acute coronary syndrome (ACS) is atherosclerotic plaque erosion or injury, which leads to thrombus formation due to the exposure of thrombogenic plaque components to cellular constituents of the blood flow [1]. Notably, excessive thrombus development is a strong predictor of poor outcomes in individuals with ACS [2]. High thrombus burden (HTB) is commonly detected in ST-elevation myocardial infarction (STEMI) patients [2]. Besides that, the presence of HTB is also related to worse clinical outcomes, such as an increased risk of myocardial infarction, no-reflow, and stent thrombosis, in patients with non-ST elevation myocardial infarction (NSTEMI) [3]. Thus, predicting HTB in the infarct-related artery (IRA) before the interventional procedure may assist physicians in improving short- and long-term outcomes of NSTEMI patients.

Whole blood viscosity (WBV) is termed as internal resistance of blood flow that is closely associated with endothelial shear stress (ESS) [4]. It had long been noted that both higher ESS and blood viscosity might trigger the thrombus formation [5]. WBV is also a crucial element of Virchow's triad, which is the primary mechanism for thrombi. Since it is believed to be an appropriate indicator of blood flow,

WHAT'S NEW?

Patients with high whole blood viscosity (WBV) were more likely to develop arterial thrombosis or acute stent thrombosis. In this research, WBV at low shear rate (LSR) and high shear rate (HSR) were found to be independent predictors of high thrombus burden (HTB) in non-ST elevation myocardial infarction (NSTEMI) patients. Notably, the area under the curve value of WBV was greater at both shear rates than that of its components, including total protein and hematocrit. This is the first study to indicate that WBV at both shear rates is a significant predictor of HTB in patients with NSTEMI.

WBV has been evaluated in several cohort settings. It has been demonstrated that patients with elevated WBV have a higher risk of arterial thrombosis, acute stent thrombosis, and left ventricular apical thrombus presence after ACS [6–8]. However, to the best of our knowledge, no data suggest that WBV is also associated with HTB in patients with NSTEMI undergoing percutaneous coronary intervention (PCI). As a result, this investigation aimed to determine the association between WBV and HTB in NSTEMI patients treated with PCI.

METHODS

Data collection

The NSTEMI was accepted as persistent angina pectoris for more than 20 minutes with a rise in cardiac troponin I level beyond the upper normal limit in the context of non-ST segment elevation on a surface electrocardiogram [9]. The current study was related to the data from consecutive NSTEMI patients who had PCI at a tertiary hospital. Initially, the medical records of consecutive NSTEMI cases who were treated with PCI were screened retrospectively. Patients who had an acute infection, end-stage chronic liver disease, autoimmune illness, and those who underwent hemodialysis or peritoneal dialysis were not included. Additionally, patients with moderate to severe cardiac valvular disease and cardiac valve surgery were excluded. Lastly, to calculate WBV, hematocrit (HTC) levels should be between 32% and 53%, and plasma protein levels should be between 54 g/l and 95 g/l; thus, those who were not in the range of specified limits were excluded from the study (Figure 1). All patients' baseline characteristics, comorbidities, and previous medications were obtained from the hospital database. Our study design was evaluated and approved by the Local Ethics Commission (no. 2021/21).

Laboratory examination

Following admission to our center, all blood samples were obtained from the antecubital vein. All hematologic parameters, including white blood cell count, HTC, and hemoglobin, were determined using a hematology analyzer (Beckman Coulter, FL, US). All biochemical parameters,

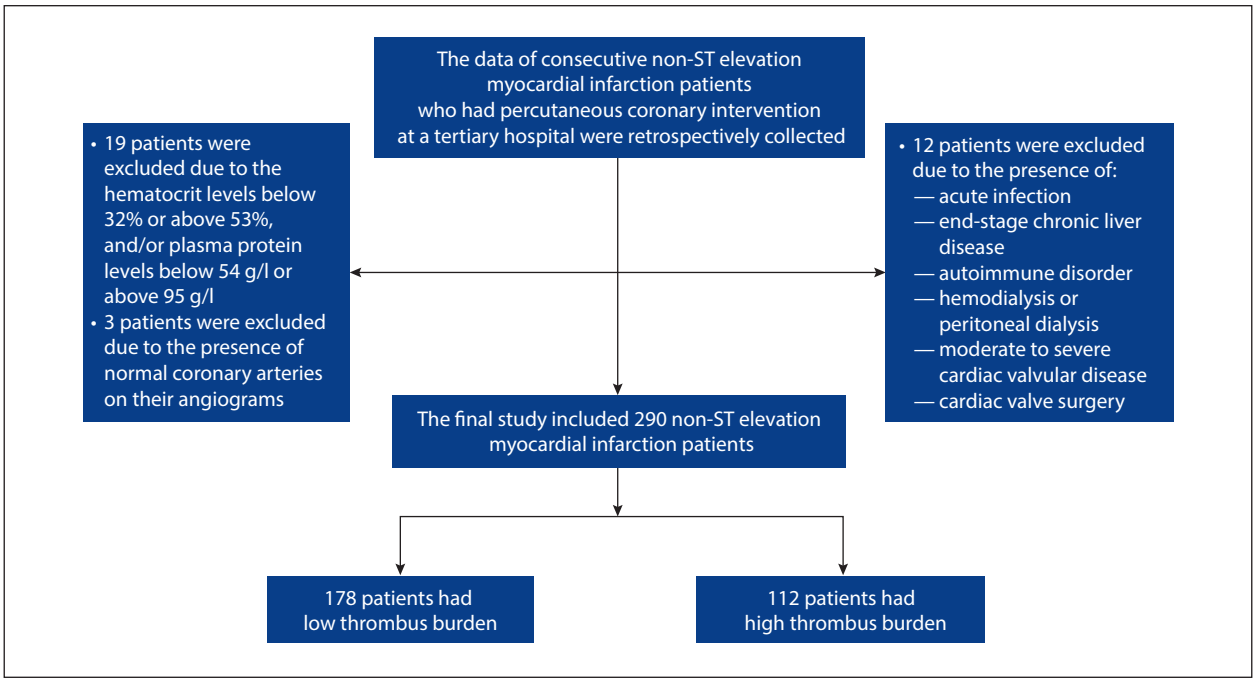

Figure 1. Flow chart of the study participants

including total protein levels, were determined using the conventional methods.

Calculation of WBV

As suggested by De Simone et al. [10], WBV at a high shear rate (HSR) (208 sec^{-1}) and a low shear rate (LSR) (0.5 sec^{-1}) were determined using HTC (percent) and total protein (g/l) levels; WBV at HSR (208 sec^{-1}) = (0.12 × HTC) + (0.17 × [total protein-2.07]) and WBV at LSR (0.5 sec^{-1}) = (1.89 × HTC) + (3.76 × [total protein-78.42]).

Coronary angiography and PCI

Conventional coronary angiography (CAG) was performed by an experienced operator utilizing either a trans-radial or a trans-femoral approach. In very high-risk NSTEMI patients, an urgent CAG (within 2 hours) was performed to accomplish revascularization [9]. CAG was performed within 24 hours of hospital admission in high-risk NSTEMI patients [9]. Before the CAG procedure, all patients were treated with 300 mg of acetylsalicylic acid and a loading dose of P_2Y_{12} inhibitors. The choice to use a glycoprotein IIb/IIIa receptor inhibitor was left to the discretion of the attending cardiologist as per hospital protocol. The PCI technique was carried out in accordance with the current European Society of Cardiology NSTEMI guidelines [9]. Two experienced operators who were blinded to the clinical data meticulously evaluated the angiographic scans of all patients. In this investigation, angiographic thrombus burden was graded as the followings: grade 0: no thrombus, grade 1: possible thrombus (reduced contrast density, haziness, irregular lesion contour), grade 2: the greatest dimension of thrombus was less than 1/2 vessel diameter, grade 3: the greatest dimension of thrombus was more than 1/2 but less than <2 vessel diameter, grade 4: the greatest dimension of thrombus was more than 2 vessel diameter, and grade 5: total vessel occlusion by a thrombus [11]. Grade 5 angiographic thrombus burden was reclassified after restoring antegrade flow through guidewire or small balloon dilatation. Based on the final thrombus burden, the patients who had grade 1–3 thrombus burden were classified as low thrombus burden (LTB) and those who had grade 4–5 thrombus burden were classified as HTB, as suggested in prior studies [11, 12]. The thrombolysis in myocardial infarction (TIMI) flow grade classification was used to determine the TIMI flow after PCI [13]. Patients were divided into four categories according to the final TIMI myocardial blush grade (TMBG) as follows: grade 0: no myocardial blush, grade 1: minimum myocardial blush, grade 2: moderate myocardial blush, and grade 3: normal myocardial blush. The TIMI flows 0, I, and II were regarded as no-reflow [14].

Statistical analysis

All statistical analyses were performed using R-software v. 3.6.3 (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria). The Kolmogorov-Smirnov test was used to determine normality. Continuous variables with a normal distribution were presented as the arithmetical mean (SD), whereas those without a normal distribution were given as the median (interquartile range [IQR]). Categorical variables were presented as numbers and percentages. The independent Student's t-test and Mann-Whitney U tests were used to compare continuous variables between the groups. The χ^2 test or Fisher's exact test was performed to compare categorical variables, as appropriate. The Kruskal-Wallis test was employed to compare WBV at both shear rates based on the thrombus burden grade. For *post-hoc* comparisons between the subgroups, the Dunn's procedure with Bonferroni correction was used. Univariable logistic regression analysis was used to detect the association of variables with HTB. A multivariable logistic regression analysis was performed with clinically relevant variables that had a *P*-value <0.1 in univariable logistic regression analysis. To avoid multicollinearity, WBV at LSR and HSR were entered into two different multivariable models separately with the same cofounders. Since multicollinearity was detected between HTC, total protein, and WBV (variance inflation factor >3, tolerance <0.1), we did not enter HTC and total protein in the multivariable models. Receiver operating characteristic (ROC) curve analysis was used to calculate the best cutoff values of WBV at HSR and LSR for detecting patients with HTB. ROC curve comparisons were calculated using the DeLong test between variables to compare the discrimination ability for HTB. A 2-sided *P* <0.05 was considered significant.

RESULTS

The final study comprised 290 NSTEMI cases. In all, 231 patients (73.4%) were male with a mean age (SD) of 63.4 (12.4) years. Patients were divided into two groups based on the thrombus burden; those with HTB (n = 112 cases) and those with LTB (n = 178 cases). The total in-hospital mortality rate was 5.5% (n = 16 cases).

Table 1 displays baseline properties, previous medications, and laboratory results of all patients. There was only one significant difference between the groups with respect to family history of coronary artery disease (CAD) and Killip class >2 on admission. Other baseline characteristics were comparable between groups. The previous medications between the groups were not different. In terms of laboratory results, patients with HTB exhibited greater HTC, triglyceride, baseline cardiac troponin I, total protein, WBV at LSR and HSR. Furthermore, the lymphocyte and high-density lipoprotein (HDL) cholesterol levels in these individuals were lower. Other laboratory results did not differ between the groups.

When we compared WBV at HSR and LSR according to the grades of thrombus burden, there were statistically significant differences in WBV at both shear rates from grade 1 thrombus burden through grade 5 thrombus burden (*P* <0.001, for all comparisons) (Table 2). In *post-hoc* comparisons, patients with grade 4 and 5 thrombus burden

Table 1. Baseline features and laboratory results of all patients according to high and low thrombus burden

	High thrombus burden (n = 112)	Low thrombus burden (n = 178)	*P*-value
Age, years	63.2 (12.6)	65.2 (16.8)	0.28
Male sex, n (%)	86 (76.8)	127 (71.3)	0.38
Body mass index, kg/m^2	25.6 (2.2)	25.4 (2.6)	0.63
Risk factors, n (%)			
Diabetes mellitus	15 (13.4)	29 (16.3)	0.62
Hypertension	66 (58.9)	115 (64.6)	0.40
Hyperlipidemia	31 (27.7)	68 (38.2)	0.09
Smoking	70 (62.5)	106 (59.6)	0.71
Previous history of CAD	43 (38.4)	79 (44.4)	0.38
Family history of CAD	30 (26.8)	28 (15.7)	0.03
Congestive heart failure	27 (24.1)	50 (28.1)	0.54
Cerebrovascular event	5 (4.5)	5 (2.8)	0.52
LV ejection fraction, %	48.6 (7.2)	47.6 (6.9)	0.19
Killip class >2	22 (19.6)	17 (9.6)	0.02
Previous medications, n (%)			
Acetylsalicylic acid	42 (37.5)	72 (40.4)	0.71
P_2Y_{12} inhibitors	21 (18.8)	38 (21.3)	0.70
Beta-blockers	42 (37.5)	74 (41.6)	0.57
ACE inh/ARBs	62 (55.4)	94 (52.8)	0.76
Statin	17 (15.2)	45 (25.3)	0.06
Laboratory data			
White blood cell count, 10^3/µl	9.6 (8.1–11.7)	9.7 (7.2–11.6)	0.32
Hemoglobin, g/dl	13.6 (1.9)	13.8 (2.4)	0.65
Hematocrit, %	44.5 (4.3)	39.7 (6.3)	<0.001
Neutrophil, 10^3/µl	7.1 (4.9–9.3)	6.3 (5–8.8)	0.47
Lymphocyte, 10^3/µl	1.7 (1.2–2.1)	2 (1.4–2.5)	0.01
Platelet, 10^3/µl	246 (93)	242 (76)	0.62
Serum creatinine, mg/dl	0.9 (0.8–1)	0.9 (0.8–1.1)	0.13
LDL cholesterol, mg/dl	104 (38)	110 (44)	0.16
HDL cholesterol, mg/dl	35 (31–42)	39 (35–46)	<0.001
Triglycerides, mg/dl	119 (75–179)	104 (77–123)	0.03
Baseline troponin I, ng/ml	8 (2.4–14)	5 (2.3–6.5)	0.01
Total protein, g/l	72 (6)	69 (8)	0.01
Albumin, mg/dl	4.4 (4.1–4.6)	4.2 (3.8–4.5)	0.01
WBV at LSR	62 (46–75)	45 (38–61)	<0.001
WBV at HSR	17.2 (1.2)	16.3 (1.5)	<0.001
In-hospital mortality, n (%)	11 (9.8)	5 (2.8)	0.02

Continuous variables are presented as median (IQR) or mean (SD), nominal variables presented as frequency (%)

Abbreviations: ACE inh/ARBs, angiotensin converting enzyme/angiotensin receptor blockers; CAD, coronary artery disease; HDL, high-density lipoprotein; HSR, high shear rate; IQR, interquartile range; LV, left ventricle; LDL, low-density lipoprotein; LSR, low shear rate; SD, standard deviation; WBV, whole blood viscosity

Table 2. Whole blood viscosity at both shear rates according to the thrombus burden grade

	Thrombus burden grade					*P*-value
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
WBV at HSR	14.4 (1.2)	15.9 (1.6)	16.5 (1.4)	17.1 (1)	19.3 (0.5)	<0.001
WBV at LSR	41.4 (32.6–42.3)	43 (35.5–54.6)	46.9 (39.3–64)	59.2 (44.5–72.4)	84.1 (79.9–86.8)	<0.001

Continuous variables are presented as median (IQR) or mean (SD)

Abbreviations: see Table 1

had higher WBV at both shear rates than those with grade 3, 2, and 1 thrombus burden (P <0.05, for all comparisons).

Table 3 presents the angiographic data for all patients based on thrombus burden. In HTB patients, the frequency of IRA reference vessel diameter, distal embolization, and no-reflow was greater. These patients also showed lower postprocedural TIMI flow >II and TMBG >II. There was no difference between the groups with respect to the use of glycoprotein IIb/IIIa receptor inhibitors and P_2Y_{12} treatments. Other angiographic results were also comparable between the groups.

Table 4 shows the results of univariable and multivariable logistic regression analyses for independent predictors of HTB. According to univariable logistic regression analysis, HTB was related to family history of CAD, HTC, Killip class >II, HDL cholesterol, triglyceride, baseline troponin I, total

Table 3. Angiographic findings and medications of all patients according to high and low thro`mbus burden

	High thrombus burden (n = 112)	Low thrombus burden (n = 178)	*P*–value
Culprit lesion location, n (%)			
LAD	49 (43.8)	95 (53.4)	
Cx	32 (28.6)	41 (23)	0.45
RCA	30 (26.8)	41 (23)	
LMCA	1 (0.9)	1 (0.6)	
CTO, n (%)	14 (12.5)	14 (7.9)	0.27
Multivessel disease, n (%)	41 (36.6)	46 (25.8)	0.07
IRA reference vessel diameter >4 mm	18 (16.1)	19 (10.7)	0.25
IRA lesion length, mm	32 (24–38)	25 (21–36)	0.01
Procedure, n (%)			
Direct stenting	0 (0)	8 (4.5)	
PTCA+stenting	108 (96.4)	167 (93.8)	0.06
Only PTCA	3 (2.7)	1 (0.6)	
CABG	1 (0.9)	2 (1.1)	
Glycoprotein IIb/IIIa inhibitors, n (%)	95 (85)	139 (78)	0.16
P_2Y_{12} inhibitors, n (%)			
Clopidogrel	94 (84)	143 (80)	
Ticagrelor	15 (13)	33 (19)	0.34
Prasugrel	3 (3)	2 (1)	
Postprocedural TIMI flow >2, n (%)	77 (69.8)	157 (88.2)	<0.001
TMBG >2, n (%)	54 (48.2)	116 (65.2)	0.01
Distal embolization, n (%)	8 (7.1)	3 (1.7)	0.03
No-reflow, n (%)	35 (31.2)	21 (11.8)	<0.001

Continuous variables are presented as median (IQR) or mean (SD), nominal variables are presented as frequency (%).

Abbreviations: CABG, coronary aorta bypass grafting; CTO, chronic total occlusion; Cx, circumflex artery; IRA, infarct-related artery; LAD, left anterior descending artery; LMCA, left main coronary artery; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction; TMBG, TIMI myocardial blush grade; other — see Table 1

Table 4. Multivariable models for independent predictors of high thrombus burden

	Multivariable model[1]		Multivariable model[2]	
	OR (95 %CI)	*P*-value	OR (95 %CI)	*P*-value
Family history of CAD	2.386 (1.351–4.253)	0.012	2.411 (1.377–4.257)	0.01
Lymphocyte	0.622 (0.472–0.805)	0.003	0.663 (0.508–0.853)	0.01
Triglyceride	1.004 (1.002–1.008)	0.016	1.005 (1.002–1.008)	0.01
Baseline troponin I	1.071 (1.022–1.121)	0.015	1.080 (1.033–1.131)	0.01
WBV at LSR	—	—	1.028 (1.014–1.043)	<0.001
WBV at HSR	1.606 (1.334–1.953)	<0.001	—	—

Model[1]: WBV at HSR was an independent variable with covariates in this model; Model[2]: WBV at LSR was an independent variable with covariates in this model

Abbreviations: OR, odds ratio; CI, confidence interval; other — see Table 1

protein, IRA lesion length, WBV at LSR, and WBV at HSR. We constructed two separate multivariable models to determine whether WBV at LSR and HSR was an independent predictor of HTB. Multivariable logistic regression models indicated that family history of CAD, lymphocyte, triglyceride, baseline troponin I, WBV at LSR (odds ratio [OR], 1.028; 95% confidence interval [CI], 1.014–1.043; *P* <0.001), and WBV at HSR (OR, 1.606; 95% CI, 1.334–1.953; *P* <0.001) were independent predictors of HTB in NSTEMI patients. The use of glycoprotein IIb/IIIa receptor inhibitors and P_2Y_{12} inhibitors were not associated with HTB in the logistic regression analysis (*P*-values = 0.152 and 0.338, respectively).

The area under the curve (AUC) values of WBV at LSR and HSR in a ROC analysis were 0.716 (95% CI, 0.659–0.771) and 0.767 (95% CI, 0.713–0.823), respectively (Figure 2). Notably, the AUC value of WBV at both shear rates was greater than that of its components, including total protein (AUC, 0.605) and HTC (AUC, 0.615). To predict HTB in NSTEMI patients, the optimum value of WBV at LSR was >45.5 with 85% sensitivity and 52% specificity, while the ideal value of WBV at HSR was >16.7 with 82% sensitivity and 64% specificity.

DISCUSSION

This is the first report to suggest that WBV at both shear rates seems to be a significant determinant of HTB in NSTEMI individuals.

HTB is a clinical entity that can adversely affect both short- and long-term outcomes of NSTEMI patients with an increased risk for occurrence of no-reflow phenomenon, stent thrombosis, and intraventricular thrombus formation [7, 15, 16]. Additionally, a final TMBG after PCI was lower in coro-

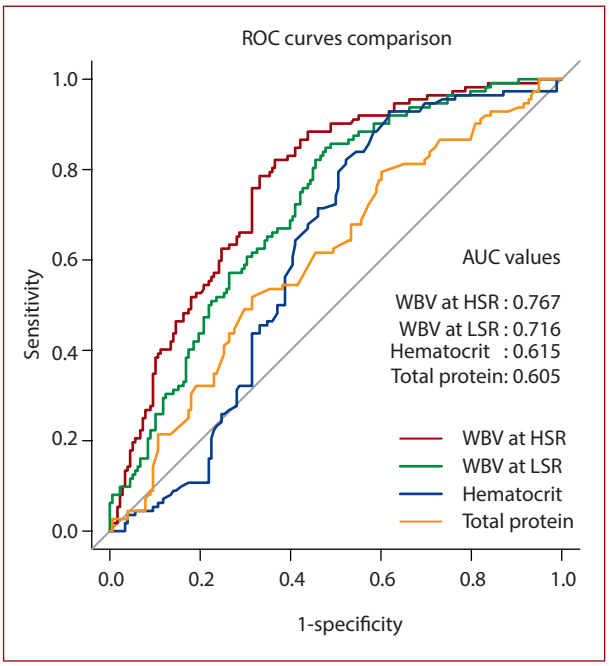

Figure 2. Receiver operating characteristic (ROC) curve analyses of whole blood viscosity (WBV) at high shear rate (HSR) and low shear rate (LSR), hematocrit, and total protein

naries with HTB, leading to the observation that even after successful reperfusion with PCI, residual ischemia may persist in such patients [17]. This was consistent with our findings, as the final TMBG >2 and TIMI flow >2 were lower, and the NR phenomenon was more prevalent in patients with HTB.

ACS is typically characterized by rupture of atherosclerotic plaque, and the aggregation of blood components on top of the rupture site, impeding flow to the segments distal to the occlusion. NSTEMI differs little in this context from STEMI, as it arises from incomplete obstruction of the coronary artery. The rupture of the atherosclerotic plaque is aggravated by localized elevation of shear stress and could be further demonstrated by the fact that nearly all plaque ruptures occur on the proximal "hill" of the plaque, where wall shear stress (WSS) is highest [18]. The WSS is calculated as shear rate multiplied by WBV, and shear rate is calculated as flow velocity divided by lumen diameter [19]. As shear rate, by definition, is a fixed value, WSS can only be increased by an increase in WBV. Due to the non-Newtonian nature of blood as a fluid, which is because it contains blood cells, its viscosity depends on shear stress. In our study, we found that elevated WBV in both shear stress settings was associated with an increased risk of HTB. This could be due to the tendency of red blood cells to aggregate in LSR areas, such as ruptured plaques, and persist in HSR areas distal to the lesion, causing slowing down blood flow and increasing thrombus burden [20].

Ideally, WBV can be measured using a "viscometer", which is expensive and proprietary laboratory equipment. However, most laboratory settings do not have access to these resources. Thus, de Simone and colleagues reported an equation for calculating WBV in an adequate accuracy relative to direct viscometer measurements, utilizing HTC and total protein levels [21]. This formula has been also investigated and validated in a variety of cohort settings [10, 22]. Specifically, changes in HTC and plasma protein levels were in most close relation to actual changes in mechanically measured WBV.

The importance of WBV had been investigated in prior studies. For example, it was demonstrated that high WBV at both shear rates was associated with worse outcomes for ACS patients undergoing PCI with an elevated risk for the no-reflow phenomenon, stent thrombosis, and the presence of apical thrombus [7, 23, 24]. It could also adversely affect the prognosis of acute pulmonary embolism and stroke patients [25, 26]. However, the association between WBV and HTB presence in NSTEMI patients has been unknown. In the present study, we showed that high WBV at HSR and LSR was independently associated with HTB in NSTEMI patients undergoing PCI. In our analysis of the data, we also clearly showed that the AUC of WBV was greater than HTC and total protein alone for predicting HTB, which could further demonstrate the value of WBV as a derived parameter.

The prediction of HTB is crucial in NSTEMI patients to increase procedure success rate and related clinical outcomes. Based on our results, patients with high WBV can be considered to have a high risk for HTB. Thus, some preventive measures, such as using glycoprotein IIb/IIIa inhibitors before PCI, can be applied to decrease the potential thrombus burden [27]. Furthermore, early stent implantation in a highly thrombotic environment may result in a greater risk of complications, such as distal embolization and peri-procedural MI. WBV may thus be estimated before invasive treatment of NSTEMI patients, and it may help us to determine the ideal time of the invasive procedure in such patients.

Limitations

There are a few limitations to our study. First, since only NSTEMI patients were included, the results might not be expanded to all ACS patients. Second, our study was conducted at a single tertiary care center. Therefore, the results might not be expanded universally. Third, although the extrapolation method we used in this study had been validated in previous investigations, a direct comparison of estimated and measured WBV in this specific patient group may strengthen our findings. Fourth, there might be some residual confounding factors even after multivariable analysis. Finally, prospective studies with a larger population are needed to confirm our findings.

CONCLUSION

The present study showed that WBV at both shear rates was an independent predictor of HTB in NSTEMI patients planned to undergo invasive treatment.

Article information

Conflict of interest: None declared.

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