ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Blood Viscosity and the Other Laboratory Parameters as Diagnostic Determinants of Pulmonary Embolism

Pulmoner Embolide Tanısal Belirleyici Olarak Tam Kan Viskositesi ve Diğer Laboratuvar Parametreleri

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ABSTRACT

Aim: *Pulmonary embolism (PE) is a significant cardiovascular condition and a leading cause of mortality worldwide. Diagnosing PE remains challenging due to nonspecific symptoms and limited accessible laboratory tests beyond D-dimer. This retrospective study aimed to evaluate the predictive properties of blood parameters, particularly whole blood viscosity (WBV), for early PE diagnosis.*

Material and Methods: *The study included 72 patients with acute PE and 72 age and sex-matched controls. Data regarding past illnesses, blood tests, and basic echocardiography findings of all patients were obtained. Whole blood viscosity was assessed at low shear rate (LSR) and high shear rate (HSR) using established formulas incorporating hematocrit and total plasma protein.*

Results: *Significant differences were observed in various laboratory parameters between the groups. Whole blood viscosity at both LSR and HSR was significantly higher in the PE group than in controls (p <0.005). Receiver operating characteristic (ROC) analysis demonstrated strong diagnostic capability for WBV, with high specificity and positive predictive value. The optimal cut-off values for WBV at LSR and HSR were ≥4.20 and ≥27.22, respectively. Correlation analyses revealed a significant positive relationship between WBV and pulmonary arterial pressure.*

Conclusions: *The findings suggest that WBV, which can be calculated using routine laboratory parameters, holds potential as a diagnostic tool for PE. Integrating WBV assessment could enhance the accuracy and efficiency of PE diagnosis, potentially reducing the need for invasive or radiation-exposing procedures. Further research is necessary to validate these findings in larger populations and establish standardized cut-off values for clinical application.*

Key words: *blood viscosity; pulmonary embolism; venous thromboembolism; hypercoagulability; shear rate*

ÖZET

Amaç: *Pulmoner emboli (PE) önemli bir kardiyovasküler hastalıktır ve dünya çapında önde gelen ölüm nedenlerinden biridir. Pulmoner emboli tanısı, nonspesifik semptomlar ve D-dimer dışında erişilebilir laboratuvar testlerinin sınırlı olması nedeniyle zorlu olmaya devam etmektedir. Bu retrospektif çalışma, erken PE tanısı için kan parametrelerinin, özellikle tam kan viskozitesinin (WBV) öngördürücü özelliklerini değerlendirmeyi amaçlamaktadır.*

Gereç ve Yöntem: *Çalışmaya akut PE tanısı almış olan 72 hasta ve 72 benzer yaş ve cinsiyet özelliklerine sahip gönüllü dâhil edildi. Tüm katılımcıların geçmiş hastalıkları, kan testleri ve temel ekokardiyografi bulgularına ilişkin veriler kaydedildi. WBV, hematokrit ve toplam plazma proteinini içeren yerleşik formüller kullanılarak düşük shear rate (LSR) ve yüksek shear rate (HSR) değerlerinde incelendi.*

Bulgular: *Gruplar arasında çeşitli laboratuvar parametrelerinde önemli farklılıklar gözlendi. Hem LSR hem de HSR'deki WBV, PE grubunda kontrollerle karşılaştırıldığında önemli ölçüde daha yüksekti (p <0,005). Alıcı işletim karakteristiği (ROC) analizi, WBV'in yüksek özgüllük ve pozitif öngörücü değere sahip olduğunu ve güçlü tanısal kapasite gösterdiğini saptadı. Düşük shear rate ve HSR'de WBV için optimum cut-off değerleri sırasıyla ≥4,20 ve ≥27,22 idi. Korelasyon analizleri WBV ile pulmoner arter basıncı arasında önemli bir pozitif ilişki olduğunu ortaya koydu.*

Sonuç: *Bulgular, rutin laboratuvar parametreleri kullanılarak hesaplanabilen WBV'nin PE için değerli bir tanı aracı olarak kullanılabileceğini göstermektedir. Tam kan viskozitesi (WBV) sonuçlarının tanı algoritmasına eklenmesi, PE tanısının doğruluğunu ve verimliliğini artırabilir; böylece invaziv veya radyasyona maruz bırakan prosedürlere olan ihtiyacı azaltabilir. Bu yeni tekniğin klinik kullanıma geçebilmesi için bulguların daha geniş popülasyonlarda doğrulanması ve klinik uygulama için standart cut-off değerlerinin belirlenmesi gereklidir.*

Anahtar kelimeler: *kan viskositesi; pulmoner emboli; venöz tromboemboli; hiperkoagülabilite; shear rate*

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Introduction

Pulmonary Embolism (PE) is a significant cardiovascular condition, ranking as the third most common cause of cardiovascular death worldwide, after stroke and heart attack. The exact prevalence of Venous Thromboembolism (VTE), which includes PE and Deep Vein Thrombosis (DVT), is challenging to determine because of the wide range of nonspecific presenting signs and symptoms. It is shown that for every nonfatal PE, 2.5 PE cases are diagnosed at autopsy[1]. In the United States, the annual incidence of VTE is estimated to be between 300.000 and 600.000. Necroscopic studies indicate that PE accounts for approximately 5%–10% of deaths in hospitalized patients. The mortality rate of untreated PE can reach up to 25%; however, with appropriate treatment, it decreases to 1–5%[2]. The pathophysiology of VTE, as described by Virchow in the 19th century, involves three key factors: stasis, endothelial disruption, and hypercoagulability[3].

Diagnosing PE can be challenging because of nonspecific symptoms. The common presenting symptoms include pleuritic chest pain (39%), dyspnea at rest (50%), hemoptysis (up to 20%), and syncope (in hemodynamically significant PE). A thorough evaluation of the risk factors and clinical presentation is essential for accurate diagnosis. The diagnostic process often involves clinical assessment, laboratory tests, and imaging studies. D-dimer testing is frequently used as an initial screening tool, with elevated levels suggesting the need for further investigation. Computed tomography pulmonary angiography (CTPA) is considered the gold standard for confirming PE, providing detailed images of the pulmonary vasculature and enabling the visualization of emboli. Echocardiography can be valuable in assessing right ventricular function and identifying signs of right heart strain, which may indicate more severe PE. Early recognition and prompt treatment are crucial for improving the outcomes of patients with PE[4,5].

Venous thrombosis is primarily attributed to three key factors: endothelial injury, hemodynamic alterations, and hypercoagulability. This pathological condition arises from modifications in the blood flow dynamics and viscosity, with hyperviscosity playing a particularly significant role[6]. Moreover, elevated shear stress associated with hyperviscosity leads to endothelial damage and subsequent thrombosis. Blood is a non-Newtonian fluid, and its viscosity varies with shear rate. Red blood cells (RBCs) tend to aggregate at low shear rates and significantly increase viscosity[7]. Conversely, at higher shear rates, RBCs disaggregate, deform, and align with the flow direction, reducing viscosity. The primary determinants of blood viscosity include hematocrit, plasma macromolecules, and RBC deformability[8]. This phenomenon of RBC behavior at different shear rates is known as shear thinning, a key characteristic of blood rheology. The interplay between these determinants of blood viscosity can significantly impact blood flow dynamics, especially in the microcirculation. Whole blood viscosity has been found to predict future cardiovascular events in the short and long term. The relationship between blood viscosity and cardiovascular risk underscores the importance of hemorheological factors in vascular health and disease progression[9,10].

Apart from the D-dimer test, the lack of easily accessible, fast-yielding, and low-cost laboratory tests to help diagnose PE makes the diagnosis difficult and sometimes leads to failure to diagnose PE. In this study, we aimed to evaluate the predictive properties of blood parameters, especially whole blood viscosity, which can be calculated through routine laboratory examinations for the early diagnosis of PE.

Material and Methods

Patients and Study Design

Patients diagnosed with acute pulmonary embolism at Amasya Sabuncuoğlu Şerefeddin Training and Research Hospital between 01.01.2022 and 01.01.2024 were included in our retrospective study. The criterion for definitive diagnosis of acute pulmonary embolism was determined as the detection of embolism in the pulmonary arteries on computed tomographic angiography, which is considered the gold standard for diagnosis. All patients diagnosed with acute pulmonary embolism within the specified criteria between the specified dates were scanned from our hospital's electronic record system, and all patients who met the exclusion and inclusion criteria were included in the study. Exclusion criteria were determined as known malignancy history, previous deep vein thrombosis (DVT) or pulmonary thromboembolism (PTE), known genetic or acquired coagulation disorder, heart failure diagnosis, recent trauma or major surgery history, long-term immobility, and the patient is under 18 or over 75 years of age. A hundred and sixty six patients diagnosed with pulmonary embolism within the specified dates were evaluated, and the remaining 72 patients were included in the study after the exclusion

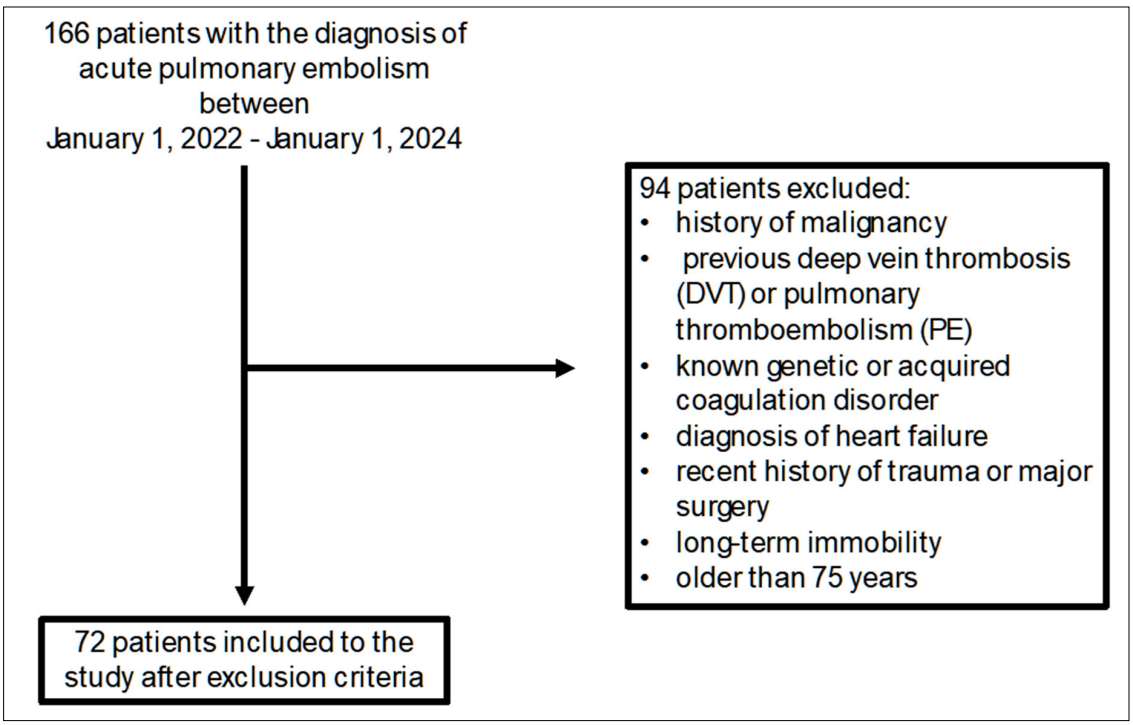


Figure 1. *Flow chart showing the patient selection process.*

criteria were applied (Figure 1). The control group was selected from patients who applied to our outpatient clinic and had age and sex characteristics similar to those of the study group by following the same exclusion criteria. Data regarding past illnesses, blood tests, and basic echocardiography findings of all patients included in the study were obtained from our hospital's electronic record system and compared. The laboratory parameters on the date when the patients were admitted to the emergency department and diagnosed with acute pulmonary thromboembolism were used.

The study was approved by the ethics committee of the Amasya University Rectorate Non-Interventional Clinical Research Ethics Committee on 03.10.2024 under the approval number 2024000099–1.

Whole blood viscosity

Whole blood viscosity (WBV) was assessed at both high shear rate (HSR=208/s) and low shear rate (LSR=0.5/s), employing established formulas that integrate hematocrit and total plasma protein concentration measurements.

The formula for WBV at HSR (208/s) is expressed as: (0.12* Hct) + (0.17* [TP-2.07])

And for LSR, WBV (0.5/s) is calculated using: (1.89* Hct) + (3.76* [TP-78.42])

In these equations, Hct represents hematocrit (%), TP denotes total protein concentration (g/L), and WBV is measured in centipoise (cP)[11].

Statistical Analysis

The research data were entered and analyzed using the IBM Statistical Package for Social Sciences (SPSS) for Windows program version 22.0 software (IBM Inc., Chicago, IL). Descriptive statistics were presented as median (Q1-Q3), frequency distributions, and percentages.

The Pearson Chi-Square Test, Fisher's Exact Test, and McNemar Test were employed to evaluate categorical variables. Variable distributions' normality was assessed using visual methods (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov Test/Shapiro-Wilk Test).

For variables that did not conform to a normal distribution, the Mann-Whitney U Test was used to determine statistical significance between two independent groups. The diagnostic ability of WBV at LSR and WBV at HSR to predict pulmonary embolism was evaluated using Receiver Operating Characteristic (ROC) curve analysis. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for significant threshold values.

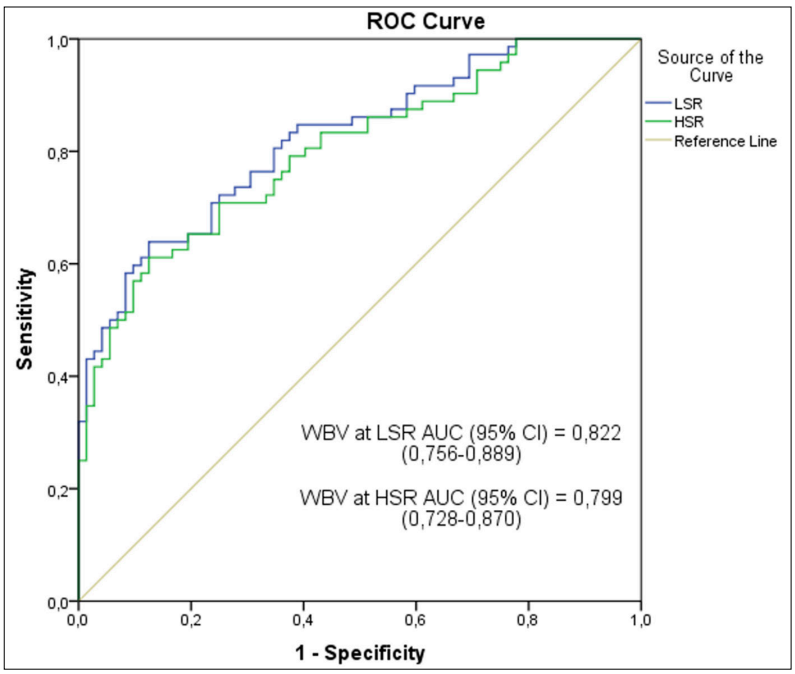


Figure 2. *ROC Analysis Results for Whole Blood Viscosity (WBV) at Low Shear Rate (LSR) and High Shear Rate (HSR).*

The relationships between variables were analyzed using Spearman's Correlation Test. A p-value of <0.05 was considered statistically significant.

Results

The study included 72 patients in the pulmonary embolism (PE) group and 72 in the control group. Baseline demographic characteristics and laboratory findings are summarized in Table 1. No significant differences were observed between the groups regarding age, gender distribution, or comorbidities such as diabetes mellitus, hypertension, chronic kidney disease, and coronary artery disease (all p >0.05).

Significant differences were noted in laboratory parameters. White blood cell (WBC) counts were markedly higher in the PE group compared to controls (11.2 [8–13.1] × 10^3/μL vs. 6.6 [5.3–7.9] × 10^3/μL, p <0.005). Additionally, hematocrit, blood glucose, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, and C-reactive protein (CRP) levels were significantly elevated in the PE group. In contrast, serum albumin levels were lower (all p <0.005).

Whole blood viscosity (WBV) was assessed at both low shear rate (LSR) and high shear rate (HSR), revealing significantly higher values in the PE group (4.4 [3.9–4.7] vs. 3.8 [3.6–4.0] for WBV at LSR and 30.6 [22.4–35.3] vs. 20.5 [17.7–23.7] for WBV at HSR, p <0.005 for both). The echocardiographic evaluation showed that the PE group's pulmonary arterial pressure (sPAB) and right ventricular (RV) diameter were significantly greater. In contrast, left ventricular ejection fraction (LVEF) was slightly reduced (all p <0.005).

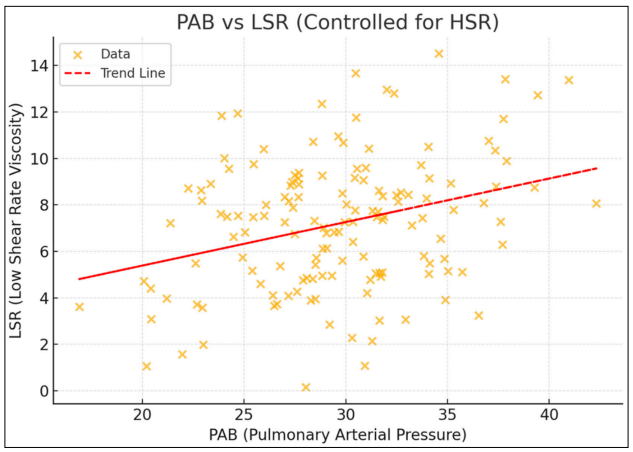
Table 2 presents the diagnostic performance metrics of WBV at LSR and HSR for detecting PE. The ROC analysis demonstrated strong diagnostic capability for both WBV parameters (Figure 2).

For WBV at LSR, the area under the curve (AUC) was 0.822 (95% CI: 0.756–0.889), indicating excellent diagnostic discrimination. A cut-off value of ≥4.20 was identified, achieving a sensitivity of 63.89% (95% CI: 51.71–74.88) and a specificity of 87.5% (95% CI: 77.59–94.12). The positive predictive value (PPV) was 83.64% (95% CI:

Table 2. *Results of whole blood viscosity at low shear rate (LSR) and high shear rate (HSR) in patients with pulmonary thromboembolism*

	WBV at LSR	WBV at HSR
Cut-off value	≥27.22	≥4.20
AUC (95% CI)	0.822 (0.756–0.889)	0.799 (0.728–0.870)
Sensitivity	63.89 (51.71–74.88)	61.11 (48.89–72.38)
Specificity	87.5 (77.59–94.12)	87.5 (77.59–94.12)
Positive predictive value	83.64 (73.03–90.61)	83.02 (72.08–90.25)
Negative predictive value	70.79 (63.78–76.93)	69.23 (62.45–75.28)
Accuracy	75.69 (67.85–82.45)	74.31 (66.36–81.22)

AUC: area under curve, CI: confidence interval.



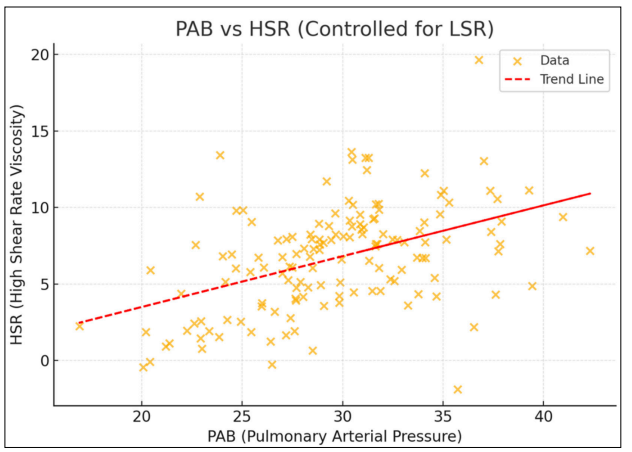


Figure 3. a–b. *Scatter plot illustrating the positive relationship between sPAB (Pulmonary Arterial Pressure) and LSR (Low Shear Rate Viscosity) after controlling for HSR (High Shear Rate Viscosity). The red dashed line represents the trend line (r=0.233, p=0.005)* **(a).** *Scatter plot showing the positive relationship between sPAB (Pulmonary Arterial Pressure) and HSR (High Shear Rate Viscosity) after controlling for LSR (Low Shear Rate Viscosity). The red dashed line highlights the trend (r=0.220, p=0.008)* **(b)**.

Table 1. *Baseline demographic characteristics and the laboratory parameters of the patients*

	Pulmonary Embolism Group (n=72)	Control Group (n=72)	p value
Female, n (%)	41 (56.9%)	43 (59.7%)	0.735
Age	65 (54–69)	59 (51–69.8)	0.195
DM, n (%)	25 (34.7%)	24 (33.3%)	0.860
HT, n (%)	29 (40.2%)	27 (37.5%)	0.732
Chronic kidney disease, n (%)	1 (1.38%)	2 (2.77%)	0.500
Coronary artery disease, n (%)	12 (16.6%)	11 (15.2%)	1.000
WBC (10^3/uL)	11.2 (8–13,1)	6.6 (5,3–7,9)	<0.005
Hemoglobin (g/dl)	13.6 (12.7–14.6)	13.5 (12.7–14.1)	0.363
Hematocrit (%)	43.4 (39.4–45.7)	39.4 (38.1–41.6)	**<0.005**
Platelet count (10^3/uL)	241 (195–297)	216 (193–262)	0.076
Blood glucose (mg/dl)	136.5 (103–194.8)	100 (95–111)	**<0.005**
Creatinine (mg/dl)	0.9 (0.8–1)	0.7 (0.6–0.9)	<0.005
AST (U/l)	27 (19–41)	20 (17–24)	**<0.005**
ALT (U/l)	20 (14–34)	16.5 (13.3–23)	**<0.005**
Total protein (g/dl)	7.1 (6.8–7.6)	6.5 (6.2–6.7)	**<0.005**
Albumin (g/dl)	3.9 (3.7–4.3)	4.2 (4–4.3)	**0.004**
CRP (mg/dl)	37.8 (21–67,1)	2.8 (1,2–4,4)	**<0.005**
Troponin positive at admission, n (%)	28 (38.8%)	N/A	
WBV at LSR	4.4 (3.9–4.7)	3.8 (3.6–4)	**<0.005**
WBV at HSR	30.6 (22.4–35.3)	20.5 (17.7–23.7)	**<0.005**
Echocardiographic parameters			
LVEF (%)	60 (55–60)	60 (60–65)	**<0.005**
sPAB (mmHg)	30 (25–45)	20 (15–20)	**<0.005**
RV diameter (mm)	32 (29–36.8)	30 (28–30)	**<0.005**

Non-categorical data are presented as Median (Q1-Q3). DM: diabetes mellitus, HT: hypertension, WBC: white blood cell count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, WBV at LSR: whole blood viscosity at low shear rate, WBV at HSR: whole blood viscosity at high shear rate, LVEF: left ventricular ejection fraction, sPAB: pulmonary arterial pressure, RV: right ventricle.

73.03–90.61), while the negative predictive value (NPV) was 70.79% (95% CI: 63.78–76.93). The overall diagnostic accuracy for WBV at LSR was 75.69% (95% CI: 67.85–82.45).

Similarly, WBV at HSR demonstrated an AUC of 0.799 (95% CI: 0.728–0.870), reflecting a robust ability to differentiate PE patients from controls. The optimal cut-off value was ≥27.22, with a sensitivity of 61.11% (95% CI: 48.89–72.38) and a specificity of 87.5% (95% CI: 77.59–94.12). The PPV for WBV at HSR was 83.02% (95% CI: 72.08–90.25), and the NPV was 69.23% (95% CI: 62.45–75.28). The diagnostic accuracy was calculated at 74.31% (95% CI: 66.36–81.22).

Correlation analyses (Table 3, Figures 3A and 3B) revealed a significant positive relationship between WBV and sPAB. Spearman correlation coefficients indicated moderate correlations for both WBV at LSR (r=0.319, p <0.005) and WBV at HSR (r=0.294, p <0.005). After controlling for covariates, partial correlation analysis confirmed the persistence of this relationship for WBV at LSR (r=0.233, p=0.005) and WBV at HSR (r=0.220, p=0.008).

Table 3. *Investigation of the relationship between pulmonary artery pressure (PAB) and whole blood viscosity at low shear rate (LSR) and high shear rate (HSR)*

	sPAB			
	r_1	p	r_2	p
WBV at LSR	0.319	<0.005	0.233	**0.005**
WBV at HSR	0.294	<0.005	0.220	**0.008**

r_1:Spearman Correlation, r_2:partial correlation, p: p-value.

These findings highlight that WBV at both LSR and HSR are reliable indicators for diagnosing PE, with high specificity in distinguishing PE patients from controls. While the sensitivity values indicate moderate capability, the high PPV suggests that elevated WBV measurements strongly correlate with the presence of PE, making it a valuable diagnostic tool in clinical practice.

Discussion

The findings of our investigation demonstrate a significant increase in whole blood viscosity (WBV) under high and low shear stress, as measured using standard laboratory parameters, among patients with acute pulmonary embolism. The ROC analysis revealed a strong diagnostic capability with a high positive predictive value of these parameters to detect PE. There was also a strong positive correlation between WBV and sPAB values. Our research aimed to demonstrate that WBV measurement could serve as a valuable diagnostic tool for this condition, which often presents with a broad spectrum of nonspecific symptoms and signs and remains challenging to diagnose without specific laboratory tests beyond D-dimer. This study is among the first to systematically evaluate WBV changes in PE patients, highlighting a novel diagnostic avenue.

Pulmonary embolism diagnostic approaches have evolved significantly, reducing the need for invasive procedures. Modern algorithms use a sequential strategy combining pre-test probability assessment, D-dimer measurement, and chest imaging as necessary, optimizing the process while minimizing unnecessary tests and radiation exposure[12]. Using validated tools like the Wells and Geneva scores, clinical probability assessment is crucial in categorizing patients into low, intermediate, or high-risk groups based on clinical factors such as patient history and physical examination. D-dimer testing, which measures fibrin degradation products indicative of blood clots, is highly sensitive but not specific, requiring further investigation if positive[13,14]. When imaging is required, computed tomography pulmonary angiography is the primary diagnostic tool due to its high sensitivity and specificity for detecting pulmonary emboli. However, it involves radiation exposure and potential contrast-induced nephropathy[15]. Future advancements should focus on refining risk stratification tools, exploring new biomarkers to complement or replace D-dimer testing, and optimizing imaging techniques to reduce radiation exposure and enhance diagnostic accuracy, ultimately improving patient outcomes and healthcare efficiency[16].

The composition of blood determines its viscosity (BV), which demonstrates non-Newtonian fluid properties and changes with shear rate. Blood viscosity is influenced by various rheological factors, with blood cells and plasma components being key contributors. When BV increases, it results in decreased blood flow and subsequent stagnation. The complex effects of elevated BV accelerate atherothrombotic processes and the progression of cardiovascular disease, possibly impacting disease outcomes[17,18].

Technical requirements and a lack of standardized protocols limit the routine clinical measurement of whole blood viscosity using viscometers. De Simone et al. introduced a method to estimate WBV from hematocrit and total plasma protein at specific shear rates[11]. This formula uses different shear rates to represent various hemodynamic conditions: low shear rate (LSR) signifies end-diastolic low-velocity blood flow. In contrast, high shear rate (HSR) represents systolic peak high-velocity flow. The accuracy of this formula has been confirmed in large patient cohorts and through viscometer-based studies, and it has been utilized in various patient populations[19,20].

In a study that included 33 PE patients and 36 healthy controls, blood viscosity was measured with a special type of viscometer. The findings revealed significantly elevated mean plasma viscosity levels in PE patients. Additionally, significant differences were observed in fibrinogen, triglyceride, and hematocrit levels between PE patients and controls[21]. Also, in another study, Carlisi et al. found that elevated blood viscosity was associated with an increased risk of venous thromboembolism in their study of newly diagnosed Multiple Myeloma patients[22].

Pulmonary embolism, an acute inflammatory process, is associated with an expected increase in inflammation-related markers. Indeed, studies have corroborated this hypothesis[23,24]. For instance, in a study conducted by Köse et al. to evaluate neutrophil-lymphocyte (NLR), platelet-lymphocyte (PLR), and lymphocyte-monocyte (LMR) ratios in pulmonary embolism patients, markers such as WBC, platelet, and CRP were also found to be elevated, suggesting that these markers may be valuable in the diagnostic evaluation of PE[25]. In a cohort study conducted by Salinger-Martinovic et

al., hemodynamic deterioration resulting from acute pulmonary embolism was evaluated for its potential to induce multi-organ dysfunction. The investigation also revealed that progressive decline in renal function tests was associated with high mortality (26). Consistent with prior investigations, our findings revealed that individuals diagnosed with pulmonary embolism displayed markedly elevated levels of creatinine, WBC, CRP, AST, and ALT compared to the control group.

Limitations

The primary limitation arises from its retrospective methodology, which considerably restricted the scope of analyzable parameters. Although the dataset's completeness was satisfactory, incorporating additional variables could influence the final estimation models. Moreover, the study's restricted sample size presents an additional challenge. Another limitation of our study is that it is a single-center study. An expanded participant pool would enhance the statistical power of the analyses, particularly about regression techniques.

Conclusion

This study demonstrates that whole blood viscosity (WBV) at both low and high shear rates is significantly elevated in acute pulmonary embolism (PE) patients compared to controls. Receiver operating characteristic (ROC) analysis shows WBV has excellent discrimination ability, with high specificity and positive predictive value for PE detection. The correlation between WBV and pulmonary arterial pressure supports its potential as a valuable diagnostic tool.

The findings suggest that WBV measurement, calculable using routine laboratory parameters, may be a useful adjunct in diagnosing PE and addressing challenges due to its nonspecific presentation and current diagnostic limitations. While D-dimer and imaging remain crucial, integrating WBV assessment could enhance PE diagnosis accuracy and efficiency. The simplicity and accessibility of WBV calculation make it a practical option, potentially reducing the need for invasive or radiation-exposing procedures.

Further research is necessary to validate these findings in larger, diverse populations and establish standardized cut-off values. Prospective studies should also evaluate WBV's role in risk stratification and its potential to guide treatment decisions in PE management.

This study highlights WBV as a promising biomarker in PE diagnosis, suggesting new avenues for improving diagnostic approaches to this critical cardiovascular condition.

Disclosures

The principles of the Declaration of Helsinki conducted this study.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of Conflicting Interests

The author declares no conflicts of interest.

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