

A New Insight Into the Treatment-Naive HIV Infected Patients: Whole Blood Viscosity

Hakan Evren¹, Emine Ünal Evren¹, Elif Çekirdekçi², Kaya Süer³, Figen Sarıgül Yıldırım⁴, Ali Asan⁵, Barış Buğan²

¹Department of Clinical Microbiology and Infectious Diseases, University of Kyrenia, Kyrenia, Cyprus

²Department of Cardiology, University of Kyrenia, Kyrenia, Cyprus

³Department of Clinical Microbiology and Infectious Diseases, Near East University, Nicosia, Cyprus

⁴Department of Clinical Microbiology and Infectious Diseases, Antalya Training and Research Hospital, Antalya, Turkey

⁵Department of Clinical Microbiology and Infectious Diseases, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

Abstract

BACKGROUND/AIMS: The thickness and stickiness of an individual's blood are measured by blood viscosity depending on frictional interactions between all major blood constituents such as red blood cells and plasma proteins. Blood viscosity, when it is elevated, is essential in the pathophysiology of vascular diseases. The present study employed an approach to determine if there is a correlation between blood viscosity and vascular comorbidities in human immunodeficiency virus (HIV)-positive subjects.

MATERIALS AND METHODS: Two hundred and seventeen people were selected to participate in this study. The HIV group included 110 treatment naive patients, and the control group had 107 people of similar age and sex. Whole blood viscosity (WBV) was measured by a formula from the protein concentration of plasma and haematocrit at a high shear rate (208 s⁻¹) and a low shear rate (0.5 s⁻¹).

RESULTS: In contrast to the control group, WBV for LSR (53.5 25 vs. 39.1 25; p=0.001) and high shear rate (HSR) (16.8 1.2 vs. 15.9 1.4; p=0.001) was substantially higher in HIV infected patients. There was a substantial inverse correlation between the CD4 count and WBV in correlation analysis for LSR (r=-0.467; p<0.001) and HSR (r=-0.461; p<0.001) in patients with HIV. A significant correlation was detected for the WBV and high-sensitivity C-reactive protein (hsCRP) for LSR (r=0.506; p<0.001) and HSR (r=0.488; p<0.001) in the HIV group.

CONCLUSION: Our result shows a remarkable correlation between WBV and inflammation in treatment-naive HIV-positive individuals. The higher blood viscosity levels observed in those subjects with lower CD4 counts may also point to a link between viscosity and the severity of the immune deficiency.

Keywords: HIV, C-reactive protein, blood viscosity, CD4 cell count

Introduction

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) poses a significant public health challenge, with a currently estimated 40 million individuals living with the virus

globally.¹ HIV-infected patients' lifespans have dramatically increased since antiretroviral therapy, and as a result, HIV treatment has evolved to include long-term comorbidities.² Patients with HIV infection have been shown to have a variety of cardiovascular, renal, metabolic, and endocrine disorders.³

To cite this article: Evren H, Ünal Evren E, Çekirdekçi E, Süer K, Sarıgül Yıldırım F, Asan A, Buğan B. A New Insight Into the Treatment-Naive HIV Infected Patients: Whole Blood Viscosity. Cyprus J Med Sci 2022;7(2):186-190

ORCID iDs of the authors: H.E. 0000-0001-8247-8144; E.Ü.E. 0000-0001-9455-0473; E.Ç. 0000-0002-3675-423X; K.S. 0000-0002-2565-3425; F.S.Y. 0000-0001-8646-2203; A.A. 0000-0002-8856-7356; B.B. 0000-0002-7210-9537.



Address for Correspondence: Hakan Evren

E-mail: hakan.evren@med.kyrenia.edu.tr

ORCID ID: orcid.org/0000-0001-8247-8144

Received: 21.04.2021

Accepted: 13.07.2021



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The viscosity of blood is its intrinsic resistance to flow, depending on frictional interactions between all major blood constituents such as red blood cells and plasma proteins.⁴

Under normal physiological conditions, regulatory mechanisms keep the blood viscosity at a relatively stable level. However, inflammation-related disorders in these regulatory mechanisms increase blood viscosity, usually correlated with endothelial cell dysfunction. As a factor affecting tissue perfusion, blood viscosity has a potential role in cardiac disease, cerebral ischemia, renal disease, and metabolic disorders.^{4,6} Understanding this hemorheological change may provide insight into the pathogenesis of HIV-related vascular diseases and their clinical sequela. The current research aims to understand the correlation between the severity of the infection and blood viscosity in newly identified, treatment-naive HIV-positive individuals.

MATERIALS AND METHODS

In this multicenter study, we retrospectively reviewed HIV-infected subjects between January 1, 2013 and December 31, 2019. Age, sex, clinical findings, laboratory, electrocardiographic, and echocardiographic imaging were studied from the patients' medical records.

The study's power analyses and sample size were computed using G*Power Version 3.1.9.2. (Aichach, Germany) The sample size was calculated using a 1:1 allocation ratio to estimate the number of people that could be enrolled in a reasonable period. According to the calculations, the minimal sample size for all groups was 210 subjects to detect differences in results with a statistical power (1-value) of 95% and a type 1 (α) error of 0.05. The HIV-infected group needed to be 105 people, and the control group needed to be 105. In the current study, a total of 217 participants were recruited. The HIV group included 110 newly diagnosed individuals (68 males, 41.3±9.1 years), while the control group consisted of 107 people (71 males, 40.8±12.0 years).

This study did not include patients with documented cardiac and cerebrovascular disease, renal failure, chronic lung disease, pregnancy, or metabolic disorders. Those patients taking antiretroviral drugs that potentially impact the blood's basic viscosity measures were also excluded from this trial. The CD4 cell counts were obtained from the patients' medical records. The participants in the control group gave their informed consent. The Ethics Committee of the University of Kyrenia approved the report (reference no: 2019/01-2015, date: 07.05.2019).

Blood samples were taken via antecubital veins and collected in serum separation gel tubes (yellow) for biochemical tests and Becton Dickinson Vacutainer for haematological tests. Glucose, hsCRP, creatinine, and lipids were delivered by conventional methods.⁷ A blood counter (Cell-Dyn Ruby; Abbott Laboratories™ 08H6701) was used for whole blood counts.

Htc (%) and plasma protein concentration (TP; g/L) at a high shear rate (HSR; 208 s⁻¹) and a low shear rate (LSR; 0.5 s⁻¹)⁸ were used for WBV calculation using a validated method of de Simone et al.⁹ and Nwose and Richards⁹ recommendations:

$$\text{HSR: WBV (208 s}^{-1}\text{)} = (0.12 \times \text{HCT}) + 0.17 \times (\text{TP} - 2.07) \quad (1)$$

$$\text{LSR: WBV (0.5 s}^{-1}\text{)} = (1.89 \times \text{HCT}) + 3.76 \times (\text{TP} - 78.42) \quad (2)$$

Statistical Analysis

For statistical analysis (SPSS Inc. Chicago, IL, USA), SPSS version 22 was employed. Visuals (histograms, probability plots) were used to examine all numerical variables. Analytic techniques (Kolmogorov–Smirnov/Shapiro–Wilk's test) were used to verify if they were normally distributed. Continuous variables were described as the mean ± standard deviation, or medians (with interquartile ranges). Categorical variables were defined as the number of patients and percentages. The participants in the trial were divided into two groups: control and HIV. Statistical comparisons of categorical data were made using the Pearson's χ^2 test and Fisher's exact test. The student's t-test was used for normally distributed parameters, and the Mann–Whitney U test was used for non-normally distributed values. The correlation coefficients and significance of the correlations between non-normally distributed hsCRP, CD4 counts, and WBV scores were determined using the Spearman correlation test. ROC curve analysis was used to examine the potential of WBV and its ability to predict WBV for both LSR and HSR in the context of HIV. When a significant cut-off value was found, the specificity, sensitivity, and positive and negative predictive values were presented. A p-value below 0.05 was considered to indicate a statistically significant difference.

RESULTS

The participants in this study were divided into groups based on age, gender, smoking status, and body mass index (BMI). The baseline clinical and laboratory values of the research groups are given in Table 1. The HIV group consisted of 110 individuals (68 males, 41.3±9.1 years), and the control group consisted of 107 subjects (71 males, 40.8±12.0 years).

Hematological parameters including hemoglobin, red blood cell distribution (RDW), mean platelet volume (MPV), and biochemical tests such as urea, serum creatinine, glucose, serum albumin, globulin, lipid profile, potassium, and sodium levels were not statistically significant among the groups. However, hsCRP, hematocrit, and total protein levels in the HIV group were considerably higher than those in the control group ($p=0.00$). White blood cell and platelet counts were considerably lower in the HIV group than in the control group (all $p=0.02$) (Table 1).

When compared to the control group, HIV patients had significantly higher WBV for LSR (53.5±25 vs. 39.1±25; $p<0.001$) and HSR (16.8±1.2 vs. 15.9±1.4; $p<0.001$) (Table 2). There was a significantly inverse correlation between CD4 count and WBV for LSR ($r=-0.467$; $p<0.001$) and HSR ($r=-0.461$; $p<0.001$) in the HIV group (Figures 1 and 2) in correlation analysis. Additionally, there was significant correlation between the hsCRP and WBV for LSR ($r=0.506$; $p<0.001$) and HSR ($r=0.488$; $p<0.001$) in the HIV group (Figures 3 and 4).

A WBV for LSR cut-off value of ≥ 44 with a sensitivity of 74% and specificity of 72% [area under the curve (AUC)=0.809, $p<0.001$] and a HSR cut-off value of ≥ 16 with a sensitivity of 80% and specificity of 74% (AUC=0.837, $\pi<0.001$) for the prediction of HIV (Figure 5) were determined in the receiver operating characteristic curve analysis.

DISCUSSION

There is no direct study investigating the effect of WBV for both LSR and HSR in the treatment of naive HIV-positive patients. Our research showed that HIV-infected participants have considerably higher blood viscosity levels than their age, and sex-matched controls. WBV is

responsible for the blood's intrinsic resistance to flow in vessels and it has a remarkable association with vascular diseases.¹⁰⁻¹² Our findings confirm that HIV-infected subjects have increased blood viscosity. A few case reports about hyper-viscosity in HIV-infected patients leading to severe vascular diseases have been described recently. Additionally, these reports claim that the risk of vascular diseases is mostly linked to the use of antiretroviral agents.¹³⁻¹⁵

The current consensus is that WBV is directly proportional to endothelial shear stress.¹⁶ Due to frictional shear force, the blood flowing through the artery wall unit creates endothelial shear stress. In normal conditions, the shear stress is substantially higher than the yield stress, allowing for optimal microvascular circulation perfusion. In particular,

pathophysiologic low shear stresses were found to relate to increased inflammatory parameters.^{17,18} This study suggests that hyper-viscosity may be a sign of inflammation, which is linked to the pathophysiology of HIV-related vascular diseases.

It is known that blood properties are altered in situations such as inflammation, and this variance prevents adequate blood flow leading to the occurrence of cardiovascular diseases, cerebral ischemia, renal failure, and other diseases.^{19,20} This alteration may be associated with relatively higher C-reactive protein (CRP) and immunoglobulins in HIV-infected patients who have been exposed to viral antigens regularly.^{13,15} Several studies have shown that inflammatory parameters such as CRP increases in HIV patients.²¹⁻²³ Our research is also in accordance with previous studies. Given the significance of inflammation, it is reasonable to conclude that WBV and hs-CRP have strong positive associations for HSR and LSR in our research.

Table 1. The baseline characteristics and laboratory findings of the study groups (n=217)

Variables	Control group (n=107)	HIV (n=110)	p-value
Clinical parameters			
Age, years	41.3±9.1	40.8±12.0	0.73
Male, n (%)	68 (63%)	71 (65%)	0.87
Current smoker, n (%)	62 (58%)	74 (67%)	0.15
BMI, (kg/m ²), n (%)	24.8±3.3	25.2±2.5	0.31
Laboratory parameters			
Hemoglobin, g/dL	13.6±2.1	13.9±1.9	0.27
Haematocrit, %	40.1±0.4	41.7±0.6	<0.001
WBC, ×10 ³ /μL	8.5± 2.1	7.6±3.5	0.02
MPV, ×10 ³ /μL	9.1±1.1	8.9±0.6	0.09
RDW, ×10 ³ /μL	14.5±3.1	14.2±2.8	0.45
Platelets, ×10 ³ /μL	245±76	223±69	0.02
Glucose, mg/dL	93±15	92±21	0.68
Urea, mg/dL	19 (13–25)	13 (10–16)	0.33
Serum creatinine, mg/dL	0.8 (0.7–1)	0.9 (0.8–1)	0.69
Total protein, g/L	67.2±8.1	73±6.2	<0.001
Total cholesterol, mg/dL	179±41	183±49	0.51
LDL cholesterol, mg/dL	110±35	114±38	0.42
HDL cholesterol, mg/dL	45±16	42±13	0.13
Triglycerides, mg/dL	148±75	148±101	0.92
Sodium, mEq/L	140±2.8	141±3.6	0.41
Potassium, mEq/L	4.4±0.4	4.3±0.5	0.16
hsCRP, mg/dL	0.2 (0.1–0.2)	4 (1–6)	<0.001
CD4 count	-	360 (233–647)	-

HIV: human immunodeficiency virus, BMI: Body Mass Index, hsCRP: high-sensitivity C-reactive protein, HDL: high-density lipoprotein, LDL: low-density lipoprotein, RDW: red cell distribution width, WBC: white blood cell count, MPV: mean platelet volume, n: number.

Table 2. Comparison of the study groups' WBV parameters

Variables	Control group	HIV group	p-value
WBV at HSR, 208 s ⁻¹	15.9±1.4	16.8±1.2	<0.001
WBV at LSR, 0.5 s ⁻¹	39.1±25	53.5±25	<0.001

HIV: human immunodeficiency virus, WBV: whole blood viscosity, HSR: high shear rate, LSR: low shear rate.

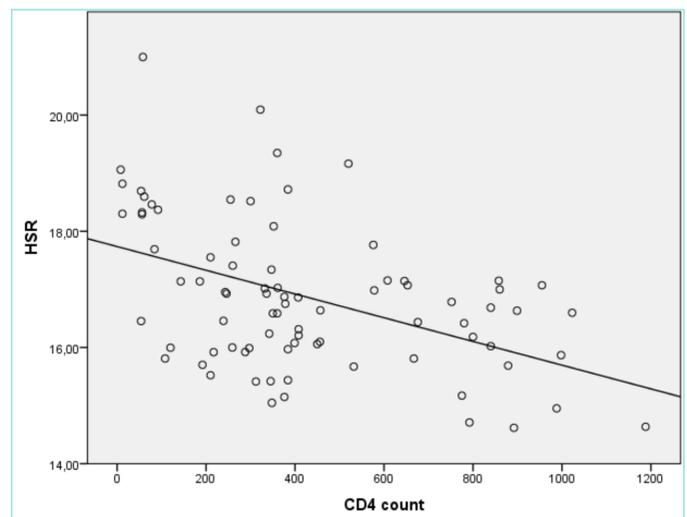


Figure 1. CD4 count and HSR correlation in the HIV group. HSR: high shear rate, HIV: human immunodeficiency virus

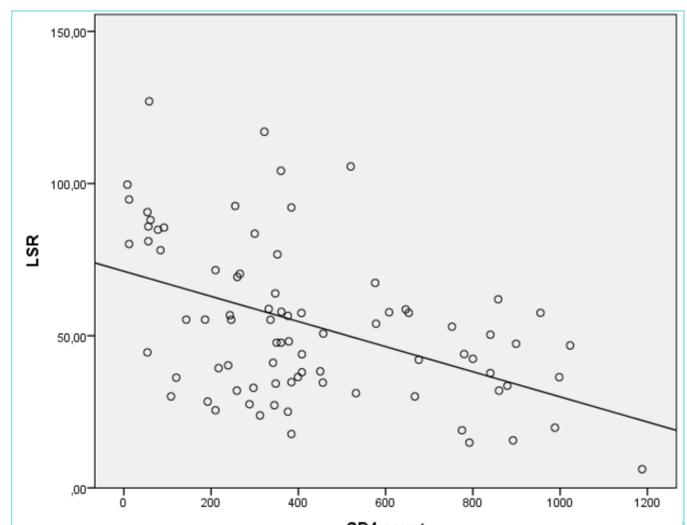


Figure 2. CD4 count and LSR correlation in the HIV group. LSR: low shear rate, HIV: human immunodeficiency virus

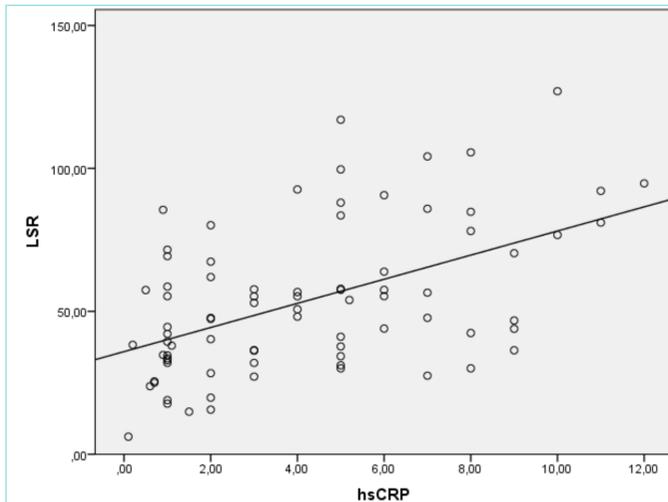


Figure 3. Hs-CRP and LSR correlation in the HIV group.
LSR: low shear rate, HIV: human immunodeficiency virus

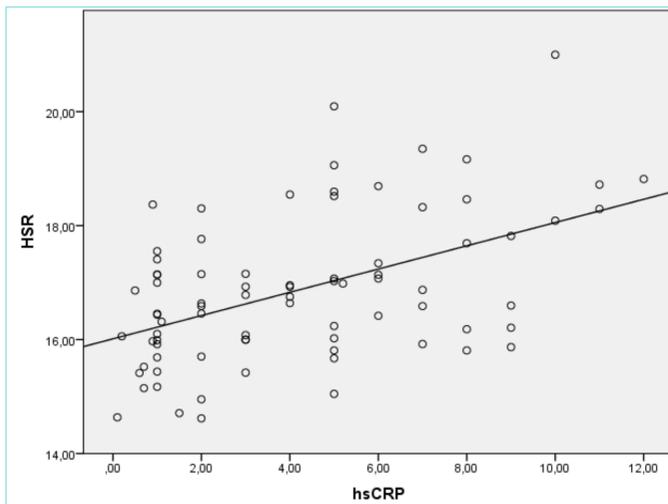


Figure 4. Hs-CRP and HSR correlation in the HIV group.
HSR: high shear rate, HIV: human immunodeficiency virus

CD4 cell count as a significant predictor of the disease severity has a vital role in the decision making and comprehension of the progression in HIV-infected patients.²⁴ In our study, a significant negative association was observed between CD4 and WBV.

As blood viscosity is linked to microvascular diseases, more studies are needed to determine this situation more accurately.

Limitations of the Study

Our study must be interpreted in light of certain limitations. The low sample size of our study is suboptimal for further statistical analysis. Furthermore, WBV was not validated using a viscometer to calculate viscosity reliably.

CONCLUSION

The cause of increased blood viscosity in HIV-infected individuals is probably multifactorial. Our result indicates the endothelium's

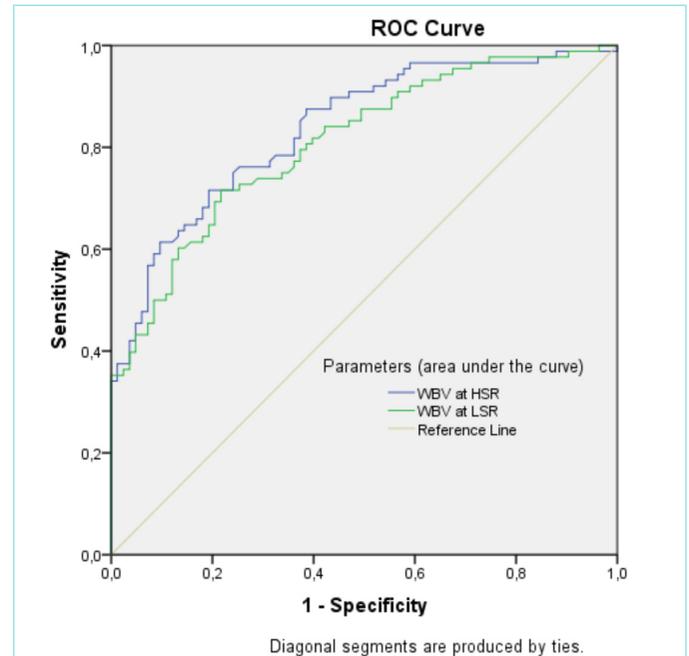


Figure 5. Receiver operating characteristic curve (ROC) analysis of WBV at the HSR and LSR for HIV prediction and 95% confidence intervals curve.

HSR: high shear rate, LSR: low shear rate, WBV: whole blood viscosity, HIV: human immunodeficiency virus

inflammatory injury, pointing to endothelial dysfunction of treatment-naïve HIV-positive participants. The higher blood viscosity levels observed in those patients with lower CD4 counts may also point to a link between viscosity and the severity of the immune deficiency. Despite convincing evidence that blood viscosity regulation is beneficial for disease control, we believe that the bio-effectiveness of this feature is neglected in clinics. We recommend future studies to investigate all determinants of hemorheological alterations in HIV-infected subjects, which may provide insight into the pathogenesis of HIV-related comorbidities.

MAIN POINTS

- Treatment naïve HIV-positive individuals had elevated blood viscosity levels when compared to the control group.
- The higher levels of blood viscosity observed in those patients with lower CD4 counts may also point to a link between viscosity and the severity of immune deficiency.
- In HIV-positive individuals, increased blood viscosity can lead to vascular comorbidities.
- Blood viscosity regulation is helpful in disease control, and future studies may focus on all determinants of hemorheological alterations in HIV-infected patients.

ETHICS

Ethics Committee Approval: The Ethics Committee of the University of Kyrenia approved the study (reference no: 2019/01-015, date: 07.05.2019).

Informed Consent: The participants in the control group gave their informed consents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.E., B.B., Design: E.Ü.E., K.S., B.B., Supervision: E.Ç., K.S., Data Collection and/or Processing: F.S.Y., A.A., Analysis and/or Interpretation: E.Ç., Literature Search: H.E., E.Ç., F.S.Y., A.A., Writing: H.E., E.Ü.E., F.S.Y., A.A., Critical Review: K.S., B.B.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study had received no financial support.

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