NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2023;60:265–270
https://doi.org/10.29399/npa.28394

Blood Viscosity and Inflammation in First-Episode and Acute Exacerbations of Schizophrenia: A Case-Control Study with Healthy Controls

Yasin Hasan BALCIOĞLU[1], Hasan GÖKÇAY[2], Ümit Haluk YEŞİLKAYA[1,3], Mustafa Nuray NAMLI[4,5]

[1]Department of Psychiatry, Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, Istanbul, Turkey
[2]Department of Psychiatry, Bagcilar Training and Research Hospital, Istanbul, Turkey
[3]Regenerative and Restorative Medicine Research Center (REMER), Institute for Health Sciences and Technologies (SABITA), Istanbul Medipol University, Istanbul, Turkey
[4]Department of Psychiatry, Hamidiye Faculty of Medicine, University of Health Sciences, Istanbul, Turkey
[5]Department of Psychiatry, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey

ABSTRACT

Introduction: Elevated proinflammatory status and alterations in blood flow, both of which are associated with the pathophysiology of schizophrenia, may be linked with an increased risk of cardiovascular diseases. However, such a relationship at different acute stages of schizophrenia has not been evaluated. We aimed to examine whether blood viscosity and systemic inflammatory status varied between first-episode schizophrenia (FES) and acute exacerbations of schizophrenia.

Methods: Fifty-two patients with FES, 69 schizophrenia patients with acute exacerbation (S-AE) and 56 healthy controls (HC) were included in the study. Whole blood viscosity (WBV) was calculated according to de Simone's formula at low and high shear rates (LSR and HSR). Systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) were calculated from hemogram screening data at admission.

Results: When adjusted for age, WBV at both LSR and HSR were significantly decreased in both FES and S-AE groups compared to HCs. Systemic inflammatory response index was significantly higher in FES patients than in the S-AE and HC groups. Total cholesterol (TC) and WBV at HSR were correlated in patients. Total cholesterol predicted WBV at LSR in patients with FES whereas other independent variables including age and SIRI did not.

Conclusion: Both first and subsequent episodes of schizophrenia are associated with reduced blood viscosity. Increased inflammatory status may not fully explain such a relationship. Extrapolation of hemorheological characteristics in schizophrenia may help to stratify cardiovascular risk and reflect the pathophysiological process in the early and later stages of schizophrenia.

Keywords: Blood viscosity, cardiovascular risk, first-episode schizophrenia, inflammation, schizophrenia

Cite this article as: Balcıoğlu YH, Gökçay H, Yeşilkaya ÜH, Namlı MN. Blood Viscosity and Inflammation in First-Episode and Acute Exacerbations of Schizophrenia: A Case-Control Study with Healthy Controls. Arch Neuropsychiatry 2023;60:265–270.

INTRODUCTION

Schizophrenia is a complex disorder with a highly heterogeneous combination of symptoms that affects nearly 1% of the population and contributes substantially to the global burden of disease. The disorder is associated with an increased risk of cardiovascular diseases, which may decrease life expectancy by up to 20 years compared to the general population (1).

The mechanisms by which schizophrenia patients are susceptible to cardiovascular diseases are complex and include lifestyle factors such as excessive smoking, unhealthy dietary choices, alcohol/substance use, sedentary behavior and lack of physical activity, along with side effects of antipsychotic drugs and genetic factors (2). In addition to these well-known risk factors for cardiovascular diseases, one common physiological process that may be involved in the pathogenesis of both schizophrenia and cardiometabolic-vascular diseases is chronic inflammation (3). Furthermore, it has been already reported that chronic inflammation affects blood viscosity, another variable associated with an increased risk of cardiovascular diseases. Indeed, there is accumulating evidence that increased proinflammatory status and blood viscosity are associated with an increased risk of cardiovascular diseases (4).

Highlights

- **First-episode schizophrenia (FES) is closely linked with decreased blood viscosity (BV).**
- **Initial schizophrenia episode shows higher proinflammatory state than relapses.**
- **Blood viscosity is decreased in first episode and relapses of schizophrenia.**
- **BV and inflammation link to cardiovascular risks in psychoses via distinct pathways.**

Elevated inflammation has been increasingly reported in both chronic schizophrenia and first psychotic episode of schizophrenia cohorts (5).

Correspondence Address: Yasin Hasan Balcıoğlu, Bakırköy Prof. Dr. Mazhar Osman Ruh Sağlığı ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi, Psikiyatri Kliniği, 34147, İstanbul, Turkey • **E-mail:** yhasanbalcioglu@gmail.com
Received: 01.01.2023, **Accepted:** 22.02.2023, **Available Online Date:** 09.08.2023

Allostatic load, which is a useful concept to operationalize biological representations and multisystem alterations related to chronic stress, was reported to be higher in acutely relapsed schizophrenia patients compared to those with first psychotic episode of schizophrenia (6). On the other hand, while first psychotic episode of schizophrenia is closely associated with increased inflammatory status, data on whether inflammation is alleviated during the later stages of the illness, especially under antipsychotic treatment is inconsistent (7).

Parameters such as blood fluidity and blood viscosity, are influenced by inflammation-triggered by environmental changes, metabolic abnormalities, and the psychological state of the patient (8). Previous research has demonstrated that both physical and psychological stress can cause changes in hemorheology measures such as hemoglobin content, hematocrit (Hct), total protein (TP) and blood viscosity (9,10). Viscosity, defined as the thickness and stickiness of the blood, is one of the major determinants of local blood flow. Blood viscosity is relatively high at low shear rates (LSR), such as when the blood is moving at a low velocity during diastole and is relatively lower during systole at high shear rates (HSR) (11). Whole blood viscosity (WBV), a primary determinant of endothelial shear stress, is a physiological parameter that is considered to be a reliable tool for the assessment of blood fluidity in various patient groups (12).

Patients with schizophrenia are known to suffer from cardiovascular morbidity. Therefore, blood viscosity and systemic proinflammatory status have the potential to reflect this relationship. However, to our knowledge there are no clinical studies on WBV in this patient group, leading to a lack of clear and sound postulations on the association between inflammatory indexes, hemorheology and clinical stage of schizophrenia. In light of recent reports suggesting that different clinical stages of schizophrenia vary in terms of allostatic load (6,7), we examined both blood viscosity and inflammatory indexes in the first psychotic episode of schizophrenia and clinically relapsed patients with schizophrenia. In the current study, WBV was calculated according to the de Simone formula. We hypothesized that blood viscosity, which potentially indicates the cardiovascular risk status, would be altered in patients with both first psychotic episode of schizophrenia and acute exacerbation of schizophrenia compared to controls, whereas increased inflammatory status, which is associated with both cardiovascular risk and etiopathogenesis of schizophrenia, would be found in first psychotic episode of schizophrenia more prominently compared to previously diagnosed schizophrenia patients and healthy subjects.

METHODS

Study Sample and Procedure

This study was designed in a cross-sectional nature and included patients with first psychotic episode of schizophrenia who were admitted to either the psychiatry outpatient or inpatient units at Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery (İstanbul, Türkiye), between April 2022 and October 2022. After a follow-up period of 4–6 months by a senior psychiatrist, six out of 66 patients with the first psychotic episode were excluded as they were diagnosed with disorders other than schizophrenia. Within the time frame of the study, 128 schizophrenia patients who were admitted to the same institution with acute clinical exacerbation were identified. Two senior psychiatrists independently diagnosed both groups of patients with schizophrenia on the basis of the Structured Clinical Interview for DSM-5 Disorders-Clinician Version (SCID-5-CV). This tool ensured that the diagnostic criteria of psychiatric disorders according to Diagnostic and Statistical Manual of Mental Disorders (DSM-5) were met (13,14), along with an assessment of individual medical records. Only those patients who never used any antipsychotics or had completely ceased the use of their recommended antipsychotics for at least one month prior to the start of the study were included. Exclusion criteria for both patients groups were as follows: the presence of a comorbid psychiatric disorder, the presence of a systemic disease that may influence hemorheology and inflammatory statuses such as previous cardiovascular diseases, diabetes mellitus, hepatic or renal failure, hypertension, acute infection, acute or chronic immuno-inflammatory disease or pregnancy, heavy smoking (>20 cigarettes per day), use of anti-inflammatory or immunosuppressive medication or any psychotropic medication, documented laboratory findings of liver or renal pathology, nutritional deficiency of vitamin B12 or folate and iron-deficiency anemia, and not having a laboratory screening at admission. After applying the exclusion criteria, 52 patients with the first psychotic episode of schizophrenia (31 males, 21 females) and 69 schizophrenia patients with acute exacerbation (40 males, 29 females) were included. A comparison group of healthy controls consisted of 56 individuals (36 males, 20 females) who were selected from hospital employees with no psychiatric disorders, no previous history of cardiovascular diseases, no alcohol and/or substance abuse, no systemic disease that could affect blood viscosity or inflammatory statuses such as diabetes mellitus, hepatic or renal failure, hypertension, acute infection, acute or chronic immuno-inflammatory disease or pregnancy, heavy smoking (>20 cigarettes per day), vitamin B12 or folate nutritional deficiency, and iron deficiency anemia. Control subjects were matched to both patient groups according to smoking status.

All participants were normal on physical examination at admission. Blood samples were collected from an arm vein between 8–9 a. m. . The patients were asked to refrain from eating or drinking for at least eight hours before blood sampling to standardize water-food intake. Routine hemogram and biochemical screenings including hemogram, serum lipids and total protein were carried out for all participants. In addition, sociodemographic and clinical characteristics of the patients such as age, gender, and Positive and Negative Syndrome Scale (PANSS) (15,16) scores at admission were recorded. According to de Simone's formula, WBV was calculated from hematocrit and total plasma protein for LSR as WBV (0.5 sec-1)=(1.89 × Hct) + [3.76 × (TP – 78.42)] and for HSR as (208 sec-1)=(0.12 × Hct) + [0.17 × (TP – 2.07)] (17). In addition, systemic immune-inflammation index (SII) [neutrophils × platelets/lymphocytes], systemic inflammation response index (SIRI) [neutrophils × monocytes/lymphocytes], neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR) and platelet/lymphocyte ratio (PLR) were calculated from the routine blood screening data at first admission.

The study protocol was reviewed and approved by the Scientific Research Ethics Committee of the University of Health Sciences, Hamidiye Faculty of Medicine (Date: 11.03.2022; Number: 22/142) and was conducted according to the principles stated in the Helsinki Declaration. Following a thorough explanation of the study procedure, all participants or their legal representative/guardian (where necessary) provided written informed consent to participate in the study.

Statistical Analysis

The minimum required sample size (n=144) to reach statistical significance in WBV at HSR between groups was calculated with G*Power software V. 3.1.9.2, considering α-error as 0.05, power as 0.90 and effect size as 0.3. The latter is based on a previous study by Kalelioğlu et al. (18). Statistical Package for Social Sciences (SPSS)

software for Mac OS, Version 25.0 (Armonk, NY: IBM Corp.) was used to analyze the study data. The Kolmogorov-Smirnov test was used to determine the normality of the distribution of the numeric data before performing further analyses. Accordingly, chi-square, Kruskal-Wallis, and Mann-Whitney U tests were used for comparisons of categorical and continuous variables between the groups. Analysis of covariance (ANCOVA) was used to adjust levels of biological indexes for age. According to ANCOVA test results, Bonferroni's post-hoc analysis was used for pairwise comparisons. Pearson's correlation coefficient was used to determine the relationship between serum lipids, blood viscosity parameters, SII and SIRI. Multivariate linear regression models using enter method were used to identify potential predictors of WBV at both LSR and HSR in either the first psychotic episode of schizophrenia or schizophrenia-acute exacerbation groups. Potential predictors were determined as independent variables that are thought to have a clinical impact on WBV at both LSR and HSR. A p-value <0.05 was considered to be significant.

RESULTS

Descriptive characteristics and comparison of laboratory parameters between the study groups are presented in Table 1. The mean age of the schizophrenia-acute exacerbation group (35.04±8.43 years) was significantly higher than first psychotic episode of schizophrenia patients (29.73±8.68 years) and healthy controls (31.71±9.15 years) (F=12.554, p=0.02). The study groups did not show a significant difference in gender (χ^2=0.537, p=0.764), or body-mass index (χ^2=1.519, p=0.468). Among the PANSS subscales, a significant difference was observed solely in the Negative subscale score, which was significantly higher in the schizophrenia-acute exacerbation group compared to the first psychotic episode of schizophrenia group (Z=-2.203, p=0.028). The serum lipid levels were not significantly different between the three groups (p>0.05).

When adjusted for age, statistically significant differences were observed in WBV at both LSR and HSR (F=4.693, p=0.010 and F=8.054, p<0.001, respectively) between the groups. Whole blood viscosity values at LSR were 46.48±3.01, 47.51±2.62, and 57.63±2.86 for the first psychotic episode of schizophrenia, schizophrenia-acute exacerbation, and healthy control groups, respectively (pairwise comparisons; first psychotic episode of schizophrenia vs. schizophrenia-acute exacerbation [p=1.000], first psychotic episode of schizophrenia vs. healthy controls [p=0.023], schizophrenia-acute exacerbation vs. healthy controls [p=0.031]). Whole blood viscosity values at HSR were 16.56±0.15, 16.53±0.13, and 17.22±0.14 for the first psychotic episode of schizophrenia, schizophrenia-acute exacerbation, and healthy control groups, respectively (pairwise comparisons; first psychotic episode of schizophrenia vs. schizophrenia-acute exacerbation [p=1.000], first psychotic episode of schizophrenia vs. healthy controls [p=0.004], schizophrenia-acute exacerbation vs. healthy controls [p=0.001]). When adjusted for age, significant differences were identified between the three groups for SII (F=3.831, p=0.024), SIRI (F=5.765, p=0.004), NLR (F=3.924, p=0.022),

Table 1. Descriptive variables and comparison of blood viscosity and proinflammatory markers and indexes between study groups

	First psychotic episode of schizophrenia (n=52)	Schizophrenia acute exacerbation (n=69)	Healthy controls (n=56)		
	Mean ± SD / n (%)			Test statistic	p
Gender (Male/Female)[a]	31/21	40/29	36/20	0.537	0.764
Age[b]	29.73±8.68	35.04±8.43	31.71±9.15	12.554	**0.002**
BMI (kg/m^2)[b]	26.76±3.08	27.04±2.69	26.02±2.85	1.519	0.468
Duration of illness (years)	-	8.46±7.65	-		
PANSS Positive[c]	26.71±8.27	25.32±6.56	-	-0.879	0.379
PANSS Negative[c]	16.90±7.36	17.97±5.39	-	-2.203	**0.028**
PANSS General[c]	43.87±8.02	42.51±7.96	-	-0.987	0.232
PANSS Total[c]	93.14±15.02	91.03±14.28	-	-1.372	0.157
Hct (%)[d]	42.13±0.77	41.28±0.67	43.13±0.73	1.742	0.178
Hemoglobin (g/dL)[d]	14.02±0.27	13.68±0.23	14.36±0.26	1.914	0.151
Total protein (g/L)[d]	69.59±0.74	70.32±0.65	71.42±0.71	1.635	0.198
Total cholesterol (mg/dl)[d]	175.11±5.72	179.36±4.98	190.57±5.44	2.126	0.122
LDL (mg/dl)[d]	125.42±16.77	127.96±14.61	111.52±15.96	0.321	0.726
HDL (mg/dl)[d]	48.13±1.90	45.26±1.65	49.61±1.81	1.626	0.200
Neutrophil (×10^9 L)[d]	5.16±0.26	4.44±0.23	4.17±0.25	4.083	**0.019**
Lymphocyte (×10^9 L)[d]	2.40±0.12	2.50±0.11	2.67±0.12	1.305	0.274
Monocyte (×10^9 L)[d]	0.70±0.03	0.60±0.03	0.57±0.03	4.128	**0.018**
Platelet (×10^9 L)[d]	257.95±9.62	261.16±8.38	248.95±9.16	0.505	0.604
WBV at LSR[d]	46.48±3.01	47.51±2.62	57.63±2.86	4.693	**0.010**
WBV at HSR[d]	16.56±0.15	16.53±0.13	17.22±0.14	8.054	**<0.001**
SII[d]	713.87±78.34	530.73±68.23	417.12±74.56	3.831	**0.024**
SIRI[d]	2.09±0.25	1.24±0.22	0.95±0.24	5.765	**0.004**
NLR[d]	2.79±0.29	2.05±0.26	1.66±0.28	3.924	**0.022**
MLR[d]	0.34±0.02	0.27±0.02	0.22±0.02	6.315	**0.002**
PLR[d]	123.96±8.43	120.85±7.34	99.21±8.02	2.850	0.061

[a]Chi-squared test; [b]Kruskal-Wallis test; [c]Mann-Whitney U; [d]adjusted levels for age with ANCOVA (mean ± standart error).
BMI: body mass index; Hct: hematocrit; HDL: high-density lipoprotein; HSR: high shear rate; LDL: low-density lipoprotein; LSR: low shear rate; MLR: monocyte/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; PANSS: Positive and Negative Syndrome Scale; PLR: platelet/lymphocyte ratio; SD: Standard deviation; SII: systemic immune-inflammation index (neutrophil×platelet to lymphocyte ratio); SIRI: systemic inflammation response index (neutrophil×monocyte to lymphocyte ratio); WBV: whole blood viscosity.
Statistical significance set at 0.05 (bold text).

Table 2. Pairwise comparisons of blood viscosity and proinflammatory markers and indexes (p values)

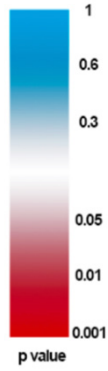
	FES vs. S-AE	FES vs. HC	S-AE vs. HC
Neutrophil (×10^9 L)	0.124	**0.018**	1.000
Monocyte (×10^9 L)	0.102	**0.018**	1.000
WBV at LSR	1.000	**0.023**	**0.031**
WBV at HSR	1.000	**0.004**	**0.001**
SII	0.252	**0.020**	0.793
SIRI	**0.040**	**0.004**	1.000
NLR	0.192	**0.019**	0.948
MLR	0.089	**0.002**	0.420

ANCOVA (analysis of covariance) test results adjusted for age with Bonferroni's post-hoc analysis.
FES: first psychotic episode of schizophrenia; HC: healthy controls; HSR: high shear rate; LSR: low shear rate; MLR: monocyte/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; S-AE: schizophrenia acute exacerbation; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; WBV: whole blood viscosity.
Statistical significance set at 0.05 (bold text).

Table 3. Correlations between serum lipids, blood viscosity and proinflammatory indexes in patients with both first psychotic episode of schizophrenia and schizophrenia acute exacerbation

r	1	2	3	4	5	6	7
1. TC	1						
2. LDL	0.26	1					
3. HDL	0.21	-0.07	1				
4. WBV at LSR	0.13	-0.11	0.07	1			
5. WBV at HSR	0.28	-0.17	0.03	0.98	1		
6. SII	-0.07	-0.07	0.13	-0.07	-0.09	1	
7. SIRI	-0.14	-0.09	0.10	-0.07	-0.07	0.92	1

HDL: high-density lipoprotein; HSR: high shear rate; LDL: low-density lipoprotein; LSR: low shear rate; r: Pearson's correlation coefficient; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; TC: total cholesterol; WBV: whole blood viscosity.



and MLR (F=6.315, p=0.002). The SII values were 713.87±78.34, 530.73±68.23, and 417.12±74.56 for the first psychotic episode of schizophrenia, schizophrenia-acute exacerbation, and healthy control groups, respectively (pairwise comparisons; first psychotic episode of schizophrenia vs. schizophrenia-acute exacerbation [p=0.252], first psychotic episode of schizophrenia vs. healthy controls [p=0.020], schizophrenia-acute exacerbation vs. healthy controls [p=0.793]). The SIRI values were 2.09±0.25, 1.24±0.22, and 0.95±0.24 for the first psychotic episode of schizophrenia, schizophrenia-acute exacerbation, and healthy control groups, respectively (pairwise comparisons; first psychotic episode of schizophrenia vs. schizophrenia-acute exacerbation [p=0.040], first psychotic episode of schizophrenia vs. healthy controls [p=0.004], schizophrenia-acute exacerbation vs. healthy controls [p=1.000]). Neutrophil/lymphocyte ratio values were 2.79±0.29, 2.05±0.26, and 1.66±0.28 for the first psychotic episode of schizophrenia, schizophrenia-acute exacerbation, and healthy control groups, respectively (pairwise comparisons; first psychotic episode of schizophrenia vs. schizophrenia-acute exacerbation [p=0.192], first psychotic episode of schizophrenia vs. healthy controls [p=0.019], schizophrenia-acute exacerbation vs. healthy controls [p=0.948]). Monocyte/lymphocyte ratio values were 0.34±0.02, 0.27±0.02, and 0.22±0.02 for the first psychotic episode of schizophrenia, schizophrenia-acute exacerbation, and healthy control groups, respectively (pairwise comparisons; first psychotic episode of schizophrenia vs. schizophrenia-acute exacerbation [p=0.089], first psychotic episode of schizophrenia vs. healthy controls [p=0.002], schizophrenia-acute exacerbation vs. healthy controls [p=0.420]) (Table 2).

We then evaluated the correlation between serum lipids, WBV at LSR, WBV at HSR, SII and SIRI between the patients (Table 3). Total cholesterol (TC) and WBV at HSR were positively and significantly correlated (r=0.28, p<0.05). As expected, both low-density lipoprotein (LDL) (r=0.26, p<0.05) and high-density lipoprotein (HDL) (r=0.21, p<0.05) were positively correlated with TC, whereas WBV at LSR was correlated with WBV at HSR (r=0.98, p<0.001) and SII was correlated with SIRI (r=0.92, p<0.001).

Multivariate linear regression analyses were performed to identify potential predictors of WBV at both LSR and HSR in patients with either first psychotic episode of schizophrenia or acutely exacerbated schizophrenia (Table 4). A significant model was obtained (F=2.770, p=0.048, adjusted R^2 of 0.094) when age (β=-0.152, p=0.289), SIRI (β=0.032, p=0.813) and TC were included in the model for the prediction of WBV at LSR. TC (β=0.309, p=0.006) was significantly associated with WBV at LSR in the first psychotic episode of schizophrenia group. However, the model (F=2.110, p=0.111, adjusted R^2 of 0.061) was not significant for predicting WBV at HSR in the same patient group when including age (β=-0.178, p=0.223), SIRI (β=0.013, p=0.092), and TC (β=0.356, p=0.018). In the schizophrenia-acute exacerbation group, age (β=-0.007, p=0.959), SIRI (β=-0.201, p=0.104), and TC (β=-0.112, p=0.379) could not significantly predict WBV at LSR (F=1.085, p=0.362, adjusted R^2 of 0.004). Whole blood viscosity at HSR was also not significantly predicted in the model (F=0.866, p=0.463, adjusted R^2 of -0.006) when age (β=0.012, p=0.925), SIRI (β=-0.170, p=0.171), and TC (β=-0.124, p=0.333) were included as independent variables.

Table 4. Multivariate linear regression analyses of clinical features and biological indexes for each WBV at LSR and at HSR in patients with either first psychotic episode of schizophrenia or schizophrenia acute exacerbation

	First psychotic episode of schizophrenia†				Schizophrenia acute exacerbation††			
	Beta	**t**	**Sig.**	**[95% CI]**	**Beta**	**t**	**Sig.**	**[95% CI]**
WBV at LSR								
Age	-0.152	-1.073	0.289	[-1.110 – 0.337]	-0.007	-0.052	0.959	[-0.667 – 0.663]
SIRI	0.032	0.238	0.813	[-1.726 – 2.189]	-0.201	-1.649	0.104	[-9.887 – 0.944]
TC	0.309	2.869	**0.006**	[0.054 – 0.307]	-0.112	-0.886	0.379	[-0.208 – 0.080]
Constant		2.094	0.042	[1.073 – 53.076]		4.079	0.000	[33.219 – 96.947]
	First psychotic episode of schizophrenia‡				Schizophrenia acute exacerbation‡‡			
	Beta	**t**	**Sig.**	**[95% CI]**	**Beta**	**t**	**Sig.**	**[95% CI]**
WBV at HSR								
Age	-0.178	-1.234	0.223	[-0.057 – 0.014]	0.012	0.094	0.925	[-0.032 – 0.035]
SIRI	0.013	0.092	0.092	[-0.091 – 0.099]	-0.170	-1.385	0.171	[-0.475 – 0.086]
TC	0.356	2.450	0.018	[0.001 – 0.014]	-0.124	-0.974	0.333	[-0.011 – 0.004]
Constant		25.343	0.000	[14.650 – 17.174]		21.044	0.000	[15.741 – 19.042]

Results from multivariate linear regression (enter), model summary.
†F=2.770; p=0.048; adjusted R^2 of 0.094; ††F=1.085, p=0.362; adjusted R^2 of 0.004; ‡F=2.110, p=0.111; adjusted R^2 of 0.061; ‡‡F=0.866, p=0.463; adjusted R^2 of -0.006.
CI: Confidence interval; HSR: high shear rate; LSR: low shear rate; SIRI: systemic inflammation response index; TC: total cholesterol; WBV: whole blood viscosity. p<0.05 statistically significant (bold text).

DISCUSSION

In the current study, whole blood viscosity and four out of five peripheral inflammatory indexes were lower in patients experiencing a first psychotic episode of schizophrenia compared to healthy individuals. This suggests that the onset of schizophrenia is likely to be closely linked to acute psychophysiological events that may cause alterations in hemorheology and inflammatory status. Since altered blood viscosity and inflammation are associated with impaired cardiometabolic and cardiovascular outcomes, our results may support previous findings that patients with the first psychotic episode of schizophrenia are at short- and long-term risk for cardiovascular diseases (5). It is known that WBV at an LSR is a better discriminator of cardiovascular risk than WBV at an HSR (19). Correspondingly, our finding that total cholesterol and WBV at LSR are closely related in patients with the first psychotic episode of schizophrenia may partially explain the increased risk of cardiovascular diseases in this patient group.

Two previous studies have demonstrated increased erythrocyte aggregation and hypercoagulability in response to stress in psychotic patients (20,21). However, blood viscosity levels at different acute stages of schizophrenia have not been reported, precluding any direct comparisons with the available literature. A few studies have evaluated blood rheology in psychiatric disorders such as bipolar disorder (22), major depressive disorder (23), neuroleptic malignant syndrome (24) and panic disorder (25). These studies argued that blood fluidity was affected in psychiatric disorders in both short and long terms.

SIRI, a novel integrated indicator based on peripheral neutrophil, monocyte and lymphocyte counts, has been recognized as a reliable tool to indicate increased systemic inflammatory status (26). In the current study, SIRI was higher in patients with the first psychotic episode of schizophrenia compared to both acutely exacerbated schizophrenia patients and healthy controls. An imbalance favoring a proinflammatory state has been reported to be involved in the pathogenesis of schizophrenia; both in the disease predisposition process and in the early stages, such as the high-risk state for psychosis (27). However, other indexes of peripheral inflammation used in the current study were not different between the first psychotic episode of schizophrenia and schizophrenia-acute exacerbation groups, supporting previous findings that increased proinflammatory status is rather a function of the presence of initial or subsequent exacerbations and may not differentiate between early and later stages of the disorder (7).

Systemic inflammation and related oxidative stress can affect labile groups in plasma proteins and the erythrocyte's cytoskeleton. The subsequent modification of plasma and membrane proteins and lipids may increase blood viscosity and erythrocyte aggregation and decrease microcirculation (4,28). However, the association between inflammatory indexes and WBV did not reach statistical significance. Since blood viscosity may be affected by many components, our data suggest that in addition to the inflammatory status, parameters such as blood lipids can also affect blood viscosity. These factors may interact with each other to ensure homeostasis (29). Acute psychophysiological stress was also reported to alter the fluid balance in the body (30); thus, an imbalance in fluid homeostasis may also contribute to decreased plasma viscosity in patients with a first psychotic episode of schizophrenia.

The current study has several limitations. Due to the cross-sectional design of the study, we were unable to obtain follow-up data on the patients with subsequent cardiovascular diseases. The inclusion of schizophrenia patients in remission would have provided more accurate information on the association between blood viscosity and the pathophysiology of schizophrenia, but they were not included in the study. Although de Simone's formula is widely acknowledged for determining blood viscosity, a more sensitive viscometer would provide more accurate results.

The replication of this study with larger patient samples can support the role of hemorheological characteristics in the pathogenesis of cardiovascular morbidity in schizophrenia. Such studies would also help establish to what extent these characteristics reflect the ongoing pathophysiological process in psychotic episodes. Extrapolation of whole blood viscosity with a simple, bedside formulated evaluation tool using hematocrit and total protein level may provide a new tool

for risk stratification of short- and long-term cardiovascular diseases in newly diagnosed schizophrenia patients. Identification of changes in blood viscosity and inflammatory status may help facilitate the development of personalized or precision clinical approaches to psychosis by helping stratify patients and implement biologically tailored pharmacological and psychological interventions to reduce any cardiovascular and cardiometabolic risk at the early stages of the disease.

Ethics Committee Approval: The study protocol was reviewed and approved by the Scientific Research Ethics Committee of the University of Health Sciences, Hamidiye Faculty of Medicine (Approval Date: 11.03.2022, Approval Number: 22/142) and was conducted according to the principles stated in the Helsinki Declaration.

Informed Consent: Following a thorough explanation of the study procedure, all participants or their legal representatives/guardians (where necessary) provided written informed consent to participate in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- YHB, UHY; Design- YHB, HG; Supervision- MNN; Resource- HG, UHY; Materials- HG, UHY; Data Collection and/or Processing- HG; Analysis and/or Interpretation- YHB; Literature Search- YHB; Writing- YHB; Critical Reviews- HG, MNN.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Marder SR, Cannon TD. Schizophrenia. N Engl J Med. 2019;381:1753–1761. [Crossref]
2. Emul M, Kalelioglu T. Etiology of cardiovascular disease in patients with schizophrenia: Current perspectives. Neuropsychiatr Dis Treat. 2015;11:2493–2503. [Crossref]
3. Balõtšev R, Koido K, Vasar V, Janno S, Kriisa K, Mahlapuu R, et al. Inflammatory, cardio-metabolic and diabetic profiling of chronic schizophrenia. Eur Psychiatry. 2017;391–310. [Crossref]
4. Gyawali P, Richards RS. Association of altered hemorheology with oxidative stress and inflammation in metabolic syndrome. Redox Rep. 2015;20:139–144. [Crossref]
5. Russell A, Ciufolini S, Gardner-Sood P, Bonaccorso S, Gaughran F, Dazzan P, et al. Inflammation and metabolic changes in first episode psychosis: Preliminary results from a longitudinal study. Brain Behav Immun. 2015;49:25–29. [Crossref]
6. Piotrowski P, Kotowicz K, Rymaszewska J, Beszłej JA, Plichta P, Samochowiec J, et al. Allostatic load index and its clinical correlates at various stages of psychosis. Schizophr Res. 2019;21073–21080. [Crossref]
7. Borovcanin M, Jovanovic I, Radosavljevic G, Dejanovic SD, Bankovic D, Arsenijevic N, et al. Elevated serum level of type-2 cytokine and low IL-17 in first episode psychosis and schizophrenia in relapse. J Psychiatr Res. 2012;46:1421–1426. [Crossref]
8. Brun JF. Hormones, metabolism and body composition as major determinants of blood rheology: Potential pathophysiological meaning. Clin Hemorheol Microcirc. 2002;26:63–79.
9. Allen MT, Patterson SM. Hemoconcentration and stress: a review of physiological mechanisms and relevance for cardiovascular disease risk. Biol Psychol. 1995;41:1–27. [Crossref]
10. Patterson SM, Marsland AL, Manuck SB, Kameneva M, Muldoon MF. Acute hemoconcentration during psychological stress: Assessment of hemorheologic factors. Int J Behav Med. 1998;5:204–212. [Crossref]
11. Kensey KR. The mechanistic relationships between hemorheological characteristics and cardiovascular disease. Curr Med Res Opin. 2003;19:587–596. [Crossref]
12. Nader E, Skinner S, Romana M, Fort R, Lemonne N, Guillot N, et al. Blood rheology: Key parameters, impact on blood flow, role in sickle cell disease and effects of exercise. Front Physiol. 2019;10:1329. [Crossref]
13. First MB. Structured Clinical Interview for the DSM (SCID). In: The Encyclopedia of Clinical Psychology. John Wiley & Sons, Ltd; 2015. p. 1–6. [Crossref]
14. Elbir M, Alp Topbaş Ö, Bayad S, Kocabaş T, Topak OZ, Çetin Ş, et al. Adaptation and reliability of the structured clinical interview for DSM-5-disorders - clinician version (SCID-5/CV) to the Turkish language. Turk Psikiyatr Derg. 2019;30:51–56. [Crossref]
15. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261–276. [Crossref]
16. Kostakoglu E, Batur S, Tiryaki A, Göğüş A. Reliability and Validity of the Turkish version of the Positive and Negative Syndrome Scale. Turkish J Psychol. 1999;14:23–34.
17. de Simone G, Devereux RB, Chien S, Alderman MH, Atlas SA, Laragh JH. Relation of blood viscosity to demographic and physiologic variables and to cardiovascular risk factors in apparently normal adults. Circulation 1990;81(1):107–117.
18. Kalelioglu T, Karamustafalioglu N, Genc A, Kocabiyik M. Serum osmolarity in male patients with bipolar disorder manic episode. Exp Physiol. 2017;102:1264–1268. [Crossref]
19. Ciuffetti G, Schillaci G, Lombardini R, Pirro M, Vaudo G, Mannarino E. Prognostic impact of low-shear whole blood viscosity in hypertensive men. Eur J Clin Invest. 2005;35:93–98. [Crossref]
20. Levine J, Luby E, Rauch A, Yesner R. Blood viscosity of psychotics and nonpsychotics under stress. Psychosom Med. 1954;16:398–403. [Crossref]
21. Barshtein G, Ponizovsky AM, Nechamkin Y, Ritsner M, Yedgar S, Bergelson LD. Aggregability of red blood cells of schizophrenia patients with negative syndrome is selectively enhanced. Schizophr Bull. 2004;30:913–922. [Crossref]
22. Kalelioglu T, Kocabiyik M, Kok B, Unalan P, Sozen S, Yuksel O, et al. Does blood flow change according to mood? Blood rheology in bipolar disorder. Clin Psychopharmacol Neurosci. 2018;16:310–315. [Crossref]
23. Wong ML, Dong C, Esposito K, Thakur S, Liu W, Elashoff RM, et al. Elevated stress-hemoconcentration in major depression is normalized by antidepressant treatment: Secondary analysis from a randomized, double-blind clinical trial and relevance to cardiovascular disease risk. PLoS One. 2008;3:e2350. [Crossref]
24. Kalelioglu T, Karamustafalioglu N, Celikel G, Genc A, Emul M. Serum osmolarity and blood viscosity as a potential explanation for the pathophysiology of neuroleptic malignant syndrome. Int J Psychiatry Clin Pract. 2019;23:307–310. [Crossref]
25. Le Melledo JM, Perez-Parada J, Morrow J, Bellavance F, Lara N, Jahandar F, et al. Pentagastrin-induced hemoconcentration in healthy volunteers and patients with panic disorder: Effect of pretreatment with ethinyl estradiol. J Psychopharmacol. 2011;25:71–77. [Crossref]
26. Qi Q, Zhuang L, Shen Y, Geng Y, Yu S, Chen H, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. Cancer. 2016;122:2158–2167. [Crossref]
27. Cannon TD. Brain biomarkers of vulnerability and progression to psychosis. Schizophr Bull. 2016;42:S127–S132. [Crossref]
28. Richards RS, Nwose EU. Blood viscosity at different stages of diabetes pathogenesis. Br J Biomed Sci. 2016;67:67–70. [Crossref]
29. Cetin MS, Ozcan Cetin EH, Balci KG, Aydin S, Ediboglu E, Bayraktar MF, et al. The association between whole blood viscosity and coronary collateral circulation in patients with chronic total occlusion. Korean Circ J 2016;46:784–790. [Crossref]
30. Lv S-Y, Yang Y-J, Chen Q. Regulation of feeding behavior, gastrointestinal function and fluid homeostasis by apelin. Peptides. 2013;44:87–92. [Crossref]