RESEARCH ARTICLE

Blood viscosity and inflammatory indices in treatment-resistant schizophrenia: A retrospective cross-sectional study

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ABSTRACT

Objective: Alterations in blood flow and inflammation may be associated with the treatment response of psychotic disorders. However, changes in blood viscosity in patients with treatment-resistant schizophrenia (TRS) have yet to be studied. We examined whether blood viscosity and systemic inflammatory status varied between patients with TRS, remitted schizophrenia, and healthy subjects.

Method: Forty patients with TRS, 40 remitted schizophrenia patients, and 43 age- and gender-matched healthy controls were enrolled in this retrospective file review study. Whole blood viscosity (WBV) was calculated according to de Simone's formula at low and high shear rates (LSR and HSR, respectively). Complete blood count (CBC) markers of inflammation were recorded through screening data at admission.

Results: In patients with TRS, WBV at both LSR and HSR was significantly decreased, whereas all CBC markers of inflammation were significantly increased compared to controls. Remitted patients had significantly decreased WBV at HSR than controls. There was no significant correlation between blood viscosity and CBC markers in patients. According to the regression models, the systemic immune-inflammation index (β=0.578) and monocyte-to-lymphocyte ratio (β=1.844) were significantly associated with WBV at LSR in multivariate analyses, whereas the Positive and Negative Syndrome Scale (PANSS) Positive subscale (β=-0.330) was significantly associated with WBV at HSR in univariate analyses in the patient sample.

Conclusion: TRS, associated with decreased blood viscosity and increased inflammatory status, may not fully explain such a relationship. Prospective studies would help establish the extent to which hemorheological and inflammatory characteristics reflect the pathophysiological process underlying treatment responsiveness as well as cardiovascular morbidity.

Keywords: Antipsychotics, blood viscosity, cardiovascular risk, inflammation, psychosis

INTRODUCTION

Antipsychotics are the mainstay of treatment for schizophrenia, but over a third of patients fail to respond significantly to appropriate pharmacotherapy with antipsychotics (1). Such patients are generally defined as having treatment-resistant schizophrenia (TRS), which is considered a distinct, more severe, and homogenous subtype of the illness (2). The clinical importance of TRS stems from the fact that patients with TRS have poor outcomes, including worse achievement of social and occupational functioning milestones, as well as persistent positive, negative, and cognitive symptoms that lead to reduced quality of life (3).

Despite the significant variability in inclusion criteria for defining treatment-resistant patients, previous studies have focused on identifying biomarkers of TRS to aid in early prediction, enhance our understanding of the biological basis of TRS, and inform the development of future treatments (4). Alterations in redox homeostasis and immune architecture (5–7), polymorphisms or mutations in specific molecules, altered expression of certain proteins (8, 9), and changes in the endocrine system (10,11) have recently been studied as potential biological interfaces of treatment resistance or responsiveness in schizophrenia.

Specific immune-inflammatory biomarker profiles have been associated with TRS, where elevated levels of inflammatory markers leading to neuronal damage may contribute to treatment resistance in this patient group (4). Conversely, treatment resistance is linked to increased all-cause morbidity and mortality, independent of clozapine's side-effects (12). Chronic inflammation is considered a common physiological process involved in the pathogenesis of both schizophrenia and cardiometabolic-vascular diseases (13). Blood viscosity, which is influenced by proinflammatory status, is another variable associated with an increased risk of cardiovascular diseases. Taken together, a substantial body of evidence supports the notion that both increased proinflammatory status and blood viscosity are associated with an increased risk of cardiovascular diseases (14).

Parameters related to blood circulation, such as blood viscosity, are influenced by inflammation-induced changes in the surrounding milieu, psychophysiological alterations, and metabolic abnormalities (15). Psychophysiological stress can cause changes in hemorheology measures such as hemoglobin, hematocrit (Hct), total protein (TP), and blood viscosity (16,17). TRS is associated with impaired functions of endothelial neurotrophic proteins, such as vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF), whose decreased levels lead to disrupted functions of monoamine receptors located on neuronal membranes (18). Altered endothelial growth factors may contribute to pathophysiological processes of psychotic disorders by reducing synaptic plasticity and modifying treatment responses to antipsychotics. They also have the potential to influence blood viscosity through alterations in endothelial functions. Thus, changes in blood viscosity may reflect changes in receptor functions in neuronal membranes.

Viscosity is defined as the thickness and stickiness of the blood and 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) (19). Whole blood viscosity (WBV), a primary determinant of endothelial shear stress, is a physiological parameter that is considered a reliable tool for the assessment of blood fluidity in various patient groups (20).

A recent study by our group reported that initial and subsequent episodes of schizophrenia are associated with decreased blood viscosity (21). This relationship could be attributed to psychotic relapses and their effect on biological systems. Furthermore, although heightened inflammation is associated with altered blood viscosity, cardiovascular morbidity, which patients with schizophrenia suffer from, might be related to distinct contributory pathways led by changes in both blood viscosity and inflammation. To our knowledge, no clinical studies have investigated WBV in patients with TRS, leading to a lack of clear and sound postulations on the association between inflammatory indices, hemorheology, and treatment responsiveness of schizophrenia. Therefore, we examined both blood viscosity and complete blood count (CBC) markers of inflammation in both treatment-resistant and remitted schizophrenia patients. In the current study, WBV was calculated according to the *de Simone* formula. Based on previous studies (21), we hypothesized that blood viscosity would be decreased in patients with TRS compared to remitted patients and healthy controls, while increased inflammatory status would be found more prominently in TRS compared to remitted schizophrenia patients and healthy subjects.

METHODS

Study Design, Sample and Procedure

This retrospective file review study included data from male and female patients (aged 18-65 years) with schizophrenia who were admitted to either the psychiatric inpatient or outpatient units providing mental health services at Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery (Istanbul, Turkiye) between October 2022 and March 2023. All patients were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) by senior attending psychiatrists. Within the study timeframe, 110 patients with schizophrenia in remission were identified. The systemic operational remission criteria, as conceptualized by Andreasen et al. (2005), (22) were followed to determine remission during outpatient follow-up or at predischarge evaluation. This criterion is based on a clinical examination by a senior psychiatrist who considers specific items of the Positive and Negative Syndrome Scale (PANSS). The criteria posit that all eight symptoms (P1, P2, P3, N1, N4, N6, G5, G9) in the PANSS should score three or lower for at least six months for remission to be considered. Additionally, during the same period, 68 patients with schizophrenia,who met the criteria for treatment-resistant schizophrenia defined by the Treatment Response and Resistance in Psychosis (TRIPP) working group consensus (23) were identified. According to the consensus, the determination of TRS requires a mitigation of symptoms by <20% despite the use of at least two antipsychotic drugs with a total daily dose equivalent to 600 mg of chlorpromazine for 12 weeks.

Following previous work (24), we considered an increase in positive psychotic symptoms and global, behavioral or functional deterioration at a moderate to high level determined through clinical evaluation, as well as the requirement of hospitalization, as a proxy of relapse. Patients with a relapse at the index admission in which blood sampling was performed were excluded. Other exclusion criteria for patients included the presence of a comorbid neurological or psychiatric illness, substance use disorder which was excluded by a urine testing and psychiatric evaluation, the presence of a systemic disease that may influence rheological properties of blood and inflammatory state 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) since it affects inflammatory parameters, use of anti-inflammatory or immunosuppressive medication, documented laboratory findings of liver or renal pathology, abnormal blood screening results such as neutropenia and electrolyte imbalances, nutritional deficiencies, and not having a laboratory screening at admission. Despite no clear evidence existing that antipsychotics modulate plasma proteins (25), patients with no change in the antipsychotic treatment regimen within the last month were recruited to rule out any possible indirect effects on circulating blood proteins.

After applying the exclusion criteria, we enrolled 40 treatment-resistant schizophrenia patients (35 males, 5 females) and 40 patients with remitted schizophrenia (33 males, 7 females). A comparison group of healthy controls consisted of 43 individuals (34 males, 9 females), who visited our outpatient unit for pre-employment health check-ups or employee medical examinations during the study period and were subjected to the same exclusion criteria as the patients. Control subjects were matched by gender and smoking status with both patient groups. The study protocol was reviewed and approved by the Scientific Research Ethics Committee of the University of Health Sciences, Hamidiye Faculty of Medicine [IRB: 10.03.2023—5/21], and was conducted according to the principles stated in the Helsinki Declaration. Since the data of the individuals were retrieved anonymously without any accessible personal identifying information and the file review was made retrospectively by the researchers, informed consent was not applicable.

Variables of Interest

The sociodemographic and clinical characteristics of the patients, such as age, gender, duration of illness, chlorpromazine equivalent dose, and PANSS scores at the time of admission, were recorded. PANSS is a 30-item clinician-rated tool based on scoring symptom severity in psychotic disorders (26). It consists of 30 items, with 7 on the positive symptoms subscale, 7 on the negative symptoms subscale, and 16 on the general psychopathology subscale, and each item has a 7-point Likert-type assessment. The total score is calculated by adding the scores of all items. Its Turkish validity and reliability were assessed by Kostakoglu et al. (1999) (27). At our institution, PANSS is administered by a senior psychiatrist or trained psychiatry resident at admission.

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 "WBV (208 sec-1)=(0.12×Hct)+[0.17×(TP−2.07)]" (28). In addition, the 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 the index admission.

Statistical Analysis

The minimum required sample size (N=111) to achieve statistical significance in WBV at HSR between groups was calculated with G*Power software V. 3.1.9.2, considering an α-error of 0.05, power of 0.80, and effect size of 0.3. Statistical Package for Social Sciences 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. Chi-Squared, Mann-Whitney U, Independent Samples t Test, Kruskal-Wallis Test, and Analysis of Variance (ANOVA) were used for comparisons of categorical and continuous variables between the groups. Bonferroni-corrected Mann-Whitney U Test was used for post hoc pairwise comparisons of Kruskal-Wallis Test results. Turkiye Honestly Significant Difference (HSD) was used as a post hoc analysis for pairwise comparisons of ANOVA results. Pearson's correlation coefficient was used to examine the relationship between blood viscosity parameters and Complete Blood Count (CBC) markers of inflammation. Univariate and multivariate linear regression analyses using the enter method were used to identify potential predictors of WBV at both LSR and HSR in the patient sample consisting of both TRS and remitted schizophrenia patients (n=80). Potential predictors were determined as independent variables that are predicted to have a clinical impact on WBV at both LSR and HSR. A p-value<0.05 was considered significant.

RESULTS

Descriptive characteristics and comparisons of laboratory parameters between the study groups are presented in Table 1. The mean age in years of the treatment-resistant schizophrenia group was 35.40±9.28, 35.92±9.61 for the remitted group, and 33.51±9.67 for the control group. There was no significant statistical difference in mean age between the groups

(F=1.876, p=0.391). The study groups did not show a significant difference in gender (χ^2=1.048, p=0.592), body-mass index (F=2.219, p=0.189), or duration of illness (F=-1.372, p= 0.272). Significant differences were observed for the Total, Positive, Negative, and General subscale scores of PANSS, which were significantly higher in the treatment-resistant schizophrenia group compared to the remitted schizophrenia group (Z=-7.543, p<0.001; Z=-7.682, p<0.001; Z=-7.474, p<0.001; Z=-6.639, p<0.001, respectively).

Statistically significant differences were observed in WBV at both LSR and HSR between the three groups (F=3.845, p=0.024 and F=9.375, p=0.009, respectively). The WBV values at LSR were 47.88±19.16, 50.34±21.04, and 59.34±19.49 for the treatment-resistant schizophrenia, remitted schizophrenia, and control groups, respectively (pairwise comparisons; treatment-resistant vs. remitted [p=0.846], treatment-resistant vs. control [p=0.027], remitted vs. control [p=0.103]). The WBV values at HSR were 15.54±3.39, 16.76±1.03, and 17.19±0.93 for the treatment-resistant schizophrenia, remitted schizophrenia, and control groups, respectively (pairwise comparisons; treatment-resistant vs. remitted [p=0.184], treatment-resistant vs. control [p=0.004], remitted vs. control [p=0.048]).

Between the three groups, significant differences were identified for SII (F=10.963, p=0.004), SIRI (F=7.351, p=0.025), NLR (F=12.451, p=0.002), MLR (F=8.286, p=0.016), and PLR (F=7.994, p=0.018). The SII values were 691.01±571.70, 634.87±363.21, and 421.78±210.89 for the treatment-resistant schizophrenia, remitted schizophrenia, and control groups, respectively (pairwise comparisons; treatment-resistant vs. remitted [p=0.847], treatment-resistant vs. control [p=0.009], remitted vs. control [p=0.002]). The SIRI values were 2.12±2.64, 1.43±1.09, and 0.98±0.47 for the treatment-resistant schizophrenia, remitted schizophrenia, and control groups, respectively (pairwise comparisons; treatment-resistant vs. remitted [p=0.356], treatment-resistant vs. control [p=0.008], remitted vs. control [p=0.079]). NLR values were 2.94±2.64, 2.41±1.27, and 1.68±0.69 for the treatment-resistant schizophrenia, remitted schizophrenia, and control groups, respectively (pairwise comparisons; treatment-resistant vs. remitted [p=0.577], treatment-resistant vs. control [p<0.001], remitted vs. control [p=0.009]). MLR values were 0.37±0.42, 0.26±0.12, and 0.22±0.07 for the treatment-resistant schizophrenia, remitted schizophrenia, and control groups, respectively (pairwise comparisons; treatment-resistant schizophrenia vs. remitted [p=0.106], treatment-resistant schizophrenia vs. control [p=0.004], remitted vs. control [p=0.270]). PLR values

Table 1: Descriptive variables and comparison of blood viscosity and proinflammatory markers and ındices between study groups

	TRS (n=40) Mean±SD n (%)	Remitted (n=40) Mean±SD n (%)	Controls (n=43) Mean±SD n (%)	Test statistic	p
Gender (male/female)[a]	35/5	33/7	34/9	1.048	0.592
Age[b]	35.40±9.28	35.92±9.61	33.51±9.67	1.876	0.391
BMI (kg/m²)[b]	25.54±2.07	24.65±2.08	24.42±2.15	2.219	0.189
Duration of illness (years)[b]	12.42±9.78	13.59±8.05	–	-1.372	0.272
PANSS positive[c]	27.45±7.28	10.82±1.79	–	-7.682	**<0.001**
PANSS negative[c]	24.02±7.15	11.05±2.05	–	-7.474	**<0.001**
PANSS general[c]	36.20±12.04	20.70±3.08	–	-6.639	**<0.001**
PANSS total[c]	87.67±18.38	42.57±6.25	–	-7.543	**<0.001**
CED (mg)[d]	694.15±8.13	692.70±8.46	–	0.781	0.437
Hct (%)[b]	42.87±4.51	43.55±4.23	44.34±3.46	1.558	0.459
Hemoglobin (g/dL)[b]	14.21±1.69	14.54±1.56	14.87±1.16	3.214	0.200
Total protein (g/L)[e]	69.60±4.26	69.92±4.77	71.91±4.85	3.047	0.051
Neutrophil (×10⁹ L)[b]	5.15±2.35	5.12±1.92	4.31±1.27	4.236	0.120
Lymphocyte (×10⁹ L)[b]	2.17±0.98	2.38±0.76	2.75±0.82	13.666	**<0.001**
Monocyte (×10⁹ L)[b]	0.65±0.29	0.58±0.25	0.59±0.21	1.739	0.419
Platelet (×10⁹ L)[e]	236.87±62.15	261.00±57.23	249.54±51.35	1.796	0.170
WBV at LSR[e]	47.88±19.16	50.34±21.04	59.34±19.49	3.845	**0.024**
WBV at HSR[b]	15.54±3.39	16.76±1.03	17.19±0.93	9.375	**0.009**
SII[b]	691.01±571.70	634.87±363.21	421.78±210.89	10.963	**0.004**
SIRI[b]	2.12±2.64	1.43±1.09	0.98±0.47	7.351	**0.025**
NLR[b]	2.94±2.64	2.41±1.27	1.68±0.69	12.451	**0.002**
MLR[b]	0.37±0.42	0.26±0.12	0.22±0.07	8.286	**0.016**
PLR[b]	126.88±55.31	121.88±49.88	97.53±33.06	7.994	**0.018**

a: Chi-squared test; b: Kruskal-Wallis test; c: Mann-Whitney U; d: Independent Samples T-test (mean±standard error); e: Analysis of Variance (ANOVA); 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; 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 values).

were 126.88±55.31, 121.88±49.88, and 97.53±33.06 for the treatment-resistant schizophrenia, remitted schizophrenia, and control groups, respectively (pairwise comparisons; treatment-resistant vs. remitted [p=0.693], treatment-resistant vs. control [p=0.011], remitted vs. control [p=0.023]) (Table 2).

There was no significant correlation between WBV at both LSR and HSR and SII, SIRI, NLR, MLR, and PLR (r=-0.05 to 0.15) in all patients. Univariate and multivariate linear regression analyses were performed to identify potential predictors of WBV at each LSR and HSR in the patient sample consisting of TRS and remitted schizophrenia subjects (Table 3). Initially, age, gender (male vs. female), patient group (treatment-resistant vs. remitted), PANSS subscales, SII, SIRI, NLR, MLR, and PLR were entered into univariate analyses as independent variables.

Table 2: Pairwise comparisons of blood viscosity and proinflammatory markers and ındices (p-values)

	TRS vs. remission	TRS vs. HC	Remission vs. HC
Lymphocyte (×10⁹ L)[a]	0.073	**<0.001**	0.079
WBV at LSR[b]	0.846	**0.027**	0.103
WBV at HSR[a]	0.184	**0.004**	**0.048**
SII[a]	0.847	**0.009**	**0.002**
SIRI[a]	0.356	**0.008**	0.079
NLR[a]	0.577	**<0.001**	**0.009**
MLR[a]	0.106	**0.004**	0.270
PLR[a]	0.693	**0.011**	**0.023**

a: Kruskal-Wallis test results with Bonferroni corrected post-hoc analysis (p<0.017 was set as statistical significance; bold values); b: Analysis of variance (ANOVA) test results with Tukey HSD (p<0.05 was set as statistical significance; bold values); TRS: Treatment-resistant schizophrenia; HC: Healthy controls; HSR: High shear rate; LSR: Low shear rate; WBV: Whole blood viscosity; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; NLR: Neutrophil/lymphocyte ratio; MLR: Monocyte/lymphocyte ratio; PLR: Platelet/lymphocyte ratio.

Table 3: Univariate and multivariate linear regression analyses of clinical features and ınflammatory ındices for each WBV at LSR and HSR in patients with both treatment-resistant and remitted schizophrenia (n=80)

WBV at LSR	Univariate			Multivariate†		
	Beta	Sig.	[95% CI]	Beta	Sig.	[95% CI]
Age	-0.151	0.183	[-0.796–0.154]	-0.099	0.386	[-0.682–0.267]
Gender (ref=male)	-0.206	0.069	[-24.332–0.925]	-0.204	0.104	[-25.605–2.440]
Group (ref=TRS)	0.062	0.587	[-6.501–11.417]	0.341	0.055	[-0.270–27.118]
PANSS positive	-0.064	0.572	[-0.586–0.326]		NI	
PANSS negative	0.083	0.467	[-0.340–0.736]	0.352	0.058	[-0.028–1.698]
PANSS general	0.043	0.707	[-0.312–0.458]		NI	
PANSS total	0.021	0.854	[-0.155–0.186]		NI	
SII	0.149	0.186	[-0.003–0.016]	1.263	**0.049**	[0.001–0.104]
SIRI	0.128	0.258	[-0.938–3.454]	-1.768	0.050	[-34.143– -0.023]
NLR	0.139	0.218	[-0.810–3.490]	0.139	0.707	[-5.635–8.266]
MLR	0.095	0.401	[-8.148–20.140]	1.335	**0.039**	[4.441–161.043]
PLR	0.060	0.599	[-0.063–0.109]	-0.636	0.067	[-0.495–0.017]
WBV at HSR	**Univariate**			**Multivariate‡**		
	Beta	Sig.	[95% CI]	Beta	Sig.	[95% CI]
Age	0.073	0.522	[-0.042–0.081]	0.050	0.669	[-0.050–0.077]
Gender (ref=male)	-0.011	0.923	[-1.757–1.595]	-0.049	0.696	[-2.215–1.486]
Group (ref=TRS)	0.238	0.034	[0.096–2.330]	-0.176	0.424	[-3.131–1.333]
PANSS positive	-0.330	**0.003**	[-0.141– - 0.030]	-0.480	0.028	[-2.242–0.028]
PANSS negative	-0.140	0.214	[-0.112–0.025]		NI	
PANSS general	-0.080	0.482	[-0.067–0.032]		NI	
PANSS total	-0.203	0.071	[-0.041–0.002]		NI	
SII	-0.002	0.986	[-0.001–0.001]	0.578	0.371	[-0.004–0.010]
SIRI	-0.050	0.656	[-0.347–0.220]	-1.260	0.171	[-3.865–0.701]
NLR	-0.010	0.931	[-0.290–0.266]	0.284	0.444	[-0.556–1.256]
MLR	-0.040	0.722	[-2.145–1.493]	1.844	0.200	[-3.669–17.253]
PLR	0.012	0.917	[-0.010–0.012]	-0.331	0.348	[-0.050–0.018]

Results from multivariate linear regression analyses (enter), model summary; †: F=2.065, p=0.048, R^2 of 0.180; ‡: F=1.265, p=0.272, R^2 of 0.142, p<0.05 statistically significant (bold values). WBV: Whole blood viscosity; LSR: Low shear rate; HSR: High shear rate; TRS: Treatment-resistant schizophrenia; PANSS: Positive and Negative Syndrome Scale; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; NLR: Neutrophil/lymphocyte ratio; MLR: Monocyte/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; NI: Not included in the model.

According to univariate analyses, PANSS Positive was significantly associated with WBV at HSR in patients with both treatment-resistant and remitted schizophrenia patients. However, this association did not remain significant in the multivariate model for the prediction of WBV at HSR since the model itself did not reach statistical significance (F=1.265, p=0.272, R^2 of 0.142). In multivariate analyses, a significant model was obtained (F=2.080, p=0.048, R^2 of 0.180) for the prediction of WBV at LSR in both treatment-resistant and remitted schizophrenia patients. SII (β=1.263, p=0.049) and MLR (β=1.335, p=0.039) were significantly associated with WBV at LSR in the patient group.

DISCUSSION

To date, little is known about the relationship between treatment resistance, blood viscosity, and CBC markers as a proxy of peripheral inflammatory status in schizophrenia. This retrospective study revealed that blood viscosity was significantly decreased, and CBC indices of inflammation were significantly increased in patients with treatment-resistant schizophrenia compared to healthy controls. On the other hand, blood viscosity and inflammatory markers did not discriminate TRS and remitted schizophrenia patients. This suggests that biological differences between treatment-resistant and treatment-responsive patients are likely

to be explained by mechanisms other than immuno-inflammatory processes. Since increased inflammation is associated with impaired cardiometabolic and cardiovascular outcomes, our results support previous findings that schizophrenia patients may be at short- and long-term risk for cardiovascular diseases (29), irrespective of treatment responsiveness.

A few studies have evaluated blood rheology in psychiatric disorders such as bipolar disorder (30), major depressive disorder (31), neuroleptic malignant syndrome (32), panic disorder (33), and first-episodes and clinical exacerbations in schizophrenia (21). These studies argue that blood fluidity is affected in psychiatric disorders in both the short and long term. Labile groups in plasma proteins and the erythrocyte's cytoskeleton can be affected by systemic inflammation and related oxidative stress. The subsequent modification of plasma and membrane proteins and lipids may increase blood viscosity and erythrocyte aggregation and decrease microcirculation (14,34). In our study, decreased blood viscosity observed in patients with TRS does not seem to be completely attributable to the increased systemic inflammation, which requires further investigation.

Blood viscosity may be affected by multiple components (21), which may interact with each other to maintain homeostasis (28). Acute and persistent psychophysiological stress have been reported to alter fluid balance in the body (35). Thus, an imbalance in fluid homeostasis may also contribute to changes in blood viscosity in patients with schizophrenia. In this study, the severity of positive psychotic symptoms is related to lower whole blood viscosity at a high shear rate in the univariate analysis. Moreover, WBV at HSR seems to be a trait marker for schizophrenia rather than WBV at LSR according to pairwise comparisons. These findings suggest that psychophysiological mechanisms have an impact on blood viscosity, particularly during systolic endothelial shear. Chronic, persistent, and severe psychopathology in schizophrenia may trigger biological mechanisms, such as increased vascular permeability and extravasation of solid plasma ingredients (which may also be associated with increased inflammation), escalated catabolism of circulating proteins due to oxidative stress, decreased serum lipids, and reduced negative acute phase reactants, all of which entail decreased blood viscosity. In this study, all patients were taking antipsychotic drugs. Antipsychotics were associated with inhibited platelet aggregation, increased clot formation time, and decreased clot firmness through

adenosine diphosphate receptors (36), all of which are associated with changes in blood viscosity (37).

CBC markers of inflammation in schizophrenia patients were significantly decreased in clinical remission compared to acute exacerbation (38), whilst such a decrease does not seem to be mediated simply by the effects of receiving antipsychotic medication (39). We found that inflammatory indices were not different between TRS and remission groups, suggesting that these indices may be a trait marker of the illness rather than treatment responsiveness. On the other hand, previous work has revealed that a link existed between an increased inflammatory state and poorer treatment outcomes in schizophrenia (6,40). Mondelli et al. (2015) (41) reported that patients who did not sufficiently respond to antipsychotics had higher inflammatory cytokines following treatment compared to responsive patients, suggesting TRS as a more severe and distinct biological subtype of schizophrenia. Follow-up data from large patient samples are required to clarify the role of CBC markers of inflammation as a proxy for treatment responsiveness.

The results of our study should be considered in the context of the following limitations. Due to the retrospective and cross-sectional design of the study, we were unable to obtain follow-up data on patients with subsequent cardiovascular diseases; hence, we were unable to establish a causal association between blood viscosity and future adverse cardiovascular events. Although there was no significant difference between patient groups in chlorpromazine equivalent doses, blood viscosity, and inflammatory markers could be confounded by the effect of specific antipsychotics which we did not examine. Biochemical parameters examined in this study might be affected by numerous factors such as nutrition, exercise, and sedentary lifestyle. A relatively small sample size might not be adequate for statistically significant results for WBV. Although *de Simone*'s formula is widely acknowledged for the determination of blood viscosity, a viscometer is more sensitive and would provide more accurate results.

In conclusion, TRS may be associated with decreased blood viscosity, and replication of this study with larger patient samples and a prospective design can reflect the pathophysiological processes and their influence on cardiovascular risk in treatment-resistant schizophrenia. Researchers may focus on the extrapolation of whole blood viscosity through a feasible evaluation tool using hematocrit and total protein level to demonstrate how blood viscosity may reflect endothelial dysfunction involved in pathophysiological processes in

schizophrenia. Such studies would also help establish to what extent hemorheological and inflammatory characteristics reflect biological interfaces of treatment resistance or responsiveness in schizophrenia. Determination of the alterations in blood viscosity and inflammatory status may help facilitate the development of personalized or precision clinical approaches to schizophrenia by helping stratify patients and implement biologically-tailored pharmacological and psychological interventions to reduce any cardiovascular and cardiometabolic risk in both treatment-resistant and treatment-responsive patients with schizophrenia.

Contribution Categories		Author Initials
Category 1	Concept/Design	Y.H.B., H.G., U.H.Y.
	Literature review	U.H.Y., S.S.K.B., H.G.
	Data analysis/Interpretation	Y.H.B., H.G.
Category 2	Drafting manuscript	Y.H.B.
	Critical revision of manuscript	S.S.K.B., U.H.Y
Category 3	Final approval and accountability	Y.H.B., H.G., U.H.Y, S.S.K.B.
Other	Supervision	Y.H.B., S.S.K.B.

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