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Serum High Mobility Group Box Protein-1 Levels in Schizophrenia During Acute Psychotic Episodes and Remission

Seda TANRIVERDİ OLUĞ[1], Özlem DEVRİM BALABAN[1], Aysu KARA[1]

[1]Department of Psychiatry, Bakirkoy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, Bakirkoy, Istanbul, Türkiye

ABSTRACT

Objective: High mobility group box-1 (HMGB1) is a non-histone protein that plays a role in neuroinflammation by inducing cytokines. We aimed to compare HMGB1 levels in patients with schizophrenia in both acute exacerbation and remission phases and in healthy controls and to determine whether HMGB1 correlates with symptom severity and C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR).

Methods: The study included 31 schizophrenia patients in remission and 31 schizophrenia patients hospitalised for acute psychotic exacerbation and 30 healthy controls. Serum HMGB1 levels were measured by enzyme-linked immunosorbent assay (ELISA). Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), and Clinical Global Impression Scale (CGI) were used to assess symptom severity.

Results: Serum HMGB1 levels were found to be significantly higher in both the remission group (140.48±63.52 pg/ml) and the acute exacerbation group (125.92±48.71 pg/ml) compared to healthy controls (57.44±13.04 pg/ml) ($p<0.05$). There was no statistically significant difference in serum HMGB1 levels between patients in remission and patients in acute psychotic exacerbation. There was no correlation between serum HMGB1 levels and severity of symptoms. No significant correlation was found between serum HMGB1 levels and other inflammatory markers. There was a statistically significant negative correlation between serum HMGB1 levels and chlorpromazine-equivalent antipsychotic doses ($r_s=-0.316$, $p=0.047$).

Conclusions: Our findings suggest that HMGB1 levels are elevated in individuals with schizophrenia, regardless of phase, which may reflect trait-like characteristics of the disorder. However, further research is needed to confirm this. Increased HMGB1 may contribute to schizophrenia pathogenesis through neuroinflammation.

Keywords: Biomarker, CRP, HMGB-1, inflammation, schizophrenia

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INTRODUCTION

Schizophrenia is a chronic and debilitating disorder characterized by positive symptoms (e.g., delusions, hallucinations, disorganized behavior and speech) and negative symptoms (e.g., social withdrawal, lack of motivation, cognitive deficits) (1). The etiology of schizophrenia and the factors affecting the course of the disease remain incompletely understood. However, schizophrenia is believed to result from a combination of factors, such as genetics, neurotransmitter system abnormalities, impaired neurodevelopmental processes, neurodegeneration, inflammation, and immune response abnormalities (2). The role of inflammation in the pathogenesis of schizophrenia has been widely investigated. Several findings support this association: elevated levels of proinflammatory cytokines, reduced levels of anti-inflammatory cytokines, increased expression of inflammatory genes, postmortem evidence of cortical inflammation, higher rates of autoimmune comorbidity, and symptom improvement with anti-inflammatory treatments (3,4).

A recent meta-analysis demonstrated that interleukin-12 (IL-12), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and IL-2R levels are elevated across both acute and remission phases of schizophrenia, whereas IL-1, IL-6, and transforming growth factor-β (TGF-β) levels are elevated only during the acute exacerbation phase (5). These findings suggest distinct phase-dependent inflammatory profiles in these two phases of schizophrenia.

Highlights

- **HMGB1 levels were higher in schizophrenia patients compared to controls.**
- **No correlation was found between HMGB1 levels and symptom severity.**
- **HMGB1 was negatively correlated with antipsychotic dosage.**
- **HMGB1 was not associated with CRP, NLR, PLR, or MLR levels.**

Correspondence Address: Seda Tanrıverdi Oluğ, Department of Psychiatry, Bakirkoy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, Bakirkoy, Istanbul, Türkiye • **E-mail:** dr.sedatanriverdiolug@gmail.com
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High mobility group box-1 (HMGB1) is a non-histone nuclear protein involved in several functions such as gene regulation, recombination, DNA repair, and nucleosome organization. In addition to its nuclear roles, HMGB1 acts as a late mediator of inflammation (6). It is actively secreted by immune cells, including monocytes and macrophages, and passively released by necrotic or damaged cells in response to inflammatory stimuli. HMGB1 stimulates neutrophils to release proinflammatory cytokines such as TNF-α, IL-1, and IL-8 (7). HMGB1 secreted by cells can participate in the pathological processes of many diseases and indicate prognosis by reflecting the severity of the disease. HMGB1 is present in neurons, microglia, and astrocytes in the central nervous system (CNS) where it plays a role in neuroinflammation by inducing cytokine release. In neurological disorders, HMGB1 is a neuroinflammation and neurodegeneration biomarker and it may cause blood-brain barrier dysfunction (8). HMGB1 also facilitates neurite outgrowth and cell migration during early brain development. HMGB1 is accepted as a late mediator of inflammation with dual functions in the development of neural cells and neurodegenerative processes. Compared to controls, elevated HMGB1 levels have been observed in several neurological and psychiatric disorders, including temporal lobe epilepsy, traumatic brain injury, Alzheimer's disease, major depression, and bipolar disorder (9,10).

In recent years, clinical studies have consistently shown that serum HMGB1 levels are elevated in patients with schizophrenia compared to controls, supporting the potential involvement of HMGB1 in schizophrenia pathophysiology (11–13). Moreover, HMGB1 levels have been associated with specific symptom clusters, including delusions, hallucinations, hostility, excitement, mannerisms, and cognitive impairments such as memory and executive dysfunction (11).

Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR) are new, cost-effective, and reproducible biomarkers of systemic inflammation, easily measured in routine complete blood counts (CBC). Accumulating evidence suggests that NLR, PLR, and MLR values, which are systemic inflammatory response markers associated with chronic stress, tend to be elevated in individuals with schizophrenia. Because alterations in single leukocyte subtypes may not adequately represent the full spectrum of inflammatory responses in schizophrenia, composite indices such as NLR, PLR, and MLR provide a more comprehensive assessment of systemic inflammation (14).

C-reactive protein (CRP) is one of the most sensitive biomarkers of peripheral inflammation used in clinical practice. Its levels are higher in patients with schizophrenia compared to controls. Furthermore, recent longitudinal studies have linked high CRP levels at age 15 to an increased risk of developing schizophrenia by age 27 (15). A longitudinal study reported that CRP levels remained elevated after 8 weeks of antipsychotic treatment, suggesting that it may be indicating that CRP may function as a trait rather than a state marker (16).

However, studies assessing peripheral inflammatory markers in schizophrenia while adequately controlling for confounding variables such as age and body mass index (BMI) remain limited. Moreover, it is still unclear whether these biomarkers reflect state-related changes or trait-like characteristics of the disorder. In this study, we aimed to compare HMGB1 levels across acute exacerbation and remission phases of schizophrenia and healthy controls. Additionally, we investigated whether HMGB1 levels correlate with symptom severity and other inflammatory markers—namely CRP, NLR, MLR, and PLR—and whether these relationships differ across clinical phases. Ultimately, the aim of this study was to further elucidate the schizophrenia pathophysiology and evaluate the potential of HMGB1 as a biomarker for diagnosis and follow-up.

METHODS

This study was approved by the Ethics Committee of Health Sciences University Bakirkoy Dr. Sadi Konuk Training and Research Hospital (Date: 15.02.2021– number: 2021-04-08). Written informed consent was obtained from all participants, as well as from patients' guardians or first-degree relatives.

Participants

The sample group was selected from patients admitted to the outpatient unit and psychiatric wards of Bakirkoy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery between February 2021 and May 2021. Healthy controls were randomly recruited from the general population, namely, the family members and friends of staff, as volunteers. Informed consent was obtained from all participants. Patient diagnoses were confirmed by two psychiatry specialists according to DSM-5 criteria.

Inclusion criteria for the patient group required a diagnosis of schizophrenia, confirmed by DSM-5 criteria, with participants being male and aged between 18 and 65 years. Patients experiencing an acute psychotic episode and hospitalised due to acute exacerbation were included in the exacerbation group. Remission was defined as a Clinical Global Impression (CGI) score of 3 or lower and no hospitalisation or medication adjustments (either dose alterations or changes in the active ingredient) within the past six months. For the control group, inclusion was limited to healthy male volunteers aged 18-65 years, who had no history of psychiatric disorders.

Healthy controls with a positive family history (first-degree relatives) of psychiatric disorder were excluded from the study. Exclusion criteria for all groups included female gender and a history of organic mental disorders, intellectual disability, or other psychiatric conditions, including alcohol or substance use disorders. Participants were also excluded if they had chronic systemic illnesses, immunological conditions, obesity, diabetes or other endocrinopathies, or neurological diseases including dementia or epilepsy. Additional exclusion criteria included use of medications affecting immune function (e.g., antibiotics, glucocorticoids, immunosuppressive or anti-inflammatory agents—including NSAIDs—or antioxidant supplements) within the past three months; any recent infectious illness or symptoms suggestive of infection (e.g., fever, fatigue, myalgia, sore throat, or cough); or electroconvulsive therapy within the past month.

All participants were evaluated by two psychiatry specialists to exclude additional psychiatric disorders.

A total of 81 patients with schizophrenia were initially approached for the patient groups. Of these, seven were excluded due to comorbid neurological disorders or substance use disorders. Three patients did not meet the criteria for remission, and nine patients declined participation. After these exclusions, 31 patients in remission and 31 patients experiencing acute psychotic exacerbation were included in the study. In addition, 30 healthy controls were matched with patient groups by age, gender, and BMI.

Female participants were excluded to reduce confounding effects, as hormonal changes during the menstrual cycle and biological sex differences can influence inflammatory markers and serum HMGB1 levels (17,18).

Clinical Assessments and Laboratory Measurements

Sociodemographic and clinical data were collected from all participants. BMI was calculated at the time of admission by measuring height and weight. The Brief Psychiatric Rating Scale (BPRS) (19,20), Positive and Negative Syndrome Scale (PANSS) (21,22), and Clinical Global Impression Scale (CGI) (23,24) were administered to patients diagnosed with schizophrenia according to DSM-5 diagnostic criteria.

Venous blood samples (5 mL) were collected once, between 08:00 and 10:00 am after overnight fasting to measure CRP, hemogram parameters, and serum HMGB1 levels. Blood samples were kept at room temperature for up to 2 hours or refrigerated at 4°C overnight and then centrifuged at 3000 rpm for 15 minutes to separate the serum. The serum was then transferred to Eppendorf tubes and stored at −80 °C until further analysis. Serum HMGB1 levels were measured using a human HMGB1 enzyme-linked immunosorbent assay (ELISA) kit (Fine Test, Wuhan, China, catalog no: EH0884), according to the manufacturer's protocol. The reference range for this assay was 31.25–2000 pg/mL, with a sensitivity of 18.75 pg/mL. Hemogram parameters and CRP levels were analysed in the hospital's biochemistry laboratory. NLR, MLR, and PLR were calculated based on the respective counts of neutrophils, monocytes, platelets, and lymphocytes.

Statistical Analysis

Descriptive statistical analyses were performed to assess the demographic, psychometric, clinical, and laboratory data from both the schizophrenia and control groups. Data were summarized as frequencies and percentages for categorical variables, and as means and standard deviations for continuous variables. Data normality was assessed using skewness and kurtosis (acceptable range ±1.5). Group comparisons were conducted using ANOVA or the Kruskal–Wallis test depending on distribution. Post-hoc tests (Tukey or Mann–Whitney U) were applied as appropriate. Categorical data were compared using Pearson's chi-squared test or Fisher's exact test when expected cell counts were less than 5. Spearman's rank correlation was used to assess the relationship between serum HMGB1 levels and other numerical data. Statistical significance was defined as $p < 0.05$.

To determine the adequacy of the sample size, a power analysis was conducted based on the study titled "Increased plasma levels of high mobility group box 1 protein in patients with bipolar disorder: A pilot study," which reported an effect size of 2.5 (10). However, due to differences in study design, a more conservative effect size of 1 was adopted for calculations.

With an alpha level of 0.05 and a power (1 - beta) of 0.95, the minimum required sample size was estimated at 29 participants per group (total of 87 participants) for two-tailed analyses. The present study included three groups with 31, 31, and 30 participants, respectively; thus meeting the sample size requirements suggested by the power analysis.

RESULTS

Table 1 presents the sociodemographic and clinical characteristics of the participants in the three study groups. There were no statistically significant differences between the groups with regard to age and BMI ($F=0.24$, $p=0.784$). However, the acute exacerbation group had significantly more hospitalizations ($Z=-3.45$, $p = 0.001$) and psychotic exacerbations ($Z=-2.50$, $p = 0.012$) compared to the remission group. In addition, no significant differences were found between the two schizophrenia subgroups in age at onset ($t = -0.87$, $p = 0.286$) or illness duration ($t = 1.29$, $p = 0.201$) (Table 1).

As illustrated in Figure 1A, serum HMGB1 levels were significantly higher in patients compared to control subjects ($p<0.001$). Additionally, serum CRP levels ($p=0.012$), MLR ($p=0.017$), and lymphocyte counts ($p=0.001$) differed significantly across the three groups (Table 2). Pairwise comparisons revealed that CRP ($p = 0.003$), HMGB1 ($p < 0.001$), and MLR ($p = 0.014$) were significantly higher in the remission group compared to healthy controls. In contrast, lymphocyte counts were significantly lower in this group ($p = 0.001$). Similarly, in the acute exacerbation group, HMGB1 ($p < 0.001$) and MLR ($p = 0.013$) were significantly elevated compared to controls, while lymphocyte counts were significantly reduced ($p = 0.018$). No significant differences were found groups for NLR, PLR, neutrophil count, leukocyte count, monocyte count, or platelet count (Table 2).

Effect size analysis revealed that HMGB1 levels showed a large effect size ($\eta^2 = 0.58$), with pairwise comparisons indicating very large differences between patient groups and healthy controls (*Cohen's d* = 1.81 and 1.95, respectively). CRP, MLR, and lymphocyte levels also showed medium effect sizes across groups ($\eta^2 = 0.078$, 0.069, and 0.103, respectively), supporting the clinical relevance of these findings beyond statistical significance.

Spearman's analysis showed a significant negative correlation between HMGB1 levels and both leukocyte and neutrophil counts in healthy controls ($r_s = -0.485$ and -0.482, $p = 0.007$). However, no other significant correlations were found between HMGB1 levels and age, BMI, or hematological parameters in other groups ($p > 0.05$) (Table 3).

Only one participant used typical antipsychotics; therefore, this group was excluded from analysis. HMGB1 levels were compared between those receiving atypical antipsychotics (n = 31) and those receiving a combination therapy (n = 8) using the Mann–Whitney U test. No statistically significant difference was observed between the groups ($U=80.0$, $p=0.126$).

Across all schizophrenia patients, HMGB1 levels were negatively correlated with chlorpromazine-equivalent antipsychotic dose ($r_s = -0.316$, $p = 0.047$). No significant correlations were found between HMGB1 and illness duration, age at onset, number of hospitalizations or exacerbations, and scale scores (PANSS, BPRS, CGI) ($p>0.05$) (Table 4).

DISCUSSION

In the present study, HMGB1, an inflammatory marker, was evaluated in patients with schizophrenia during acute exacerbation and remission phases, as well as in healthy controls. HMGB1 serum levels have been shown to vary in relation to age and have a positive correlation with BMI (25). Therefore, all three groups were matched for age and BMI. The principal finding was that serum HMGB1 levels were significantly elevated in patients with schizophrenia—irrespective of phase—compared to healthy controls, while no significant difference was observed between the acute exacerbation and remission groups. Effect size analyses in the present study enabled a more nuanced interpretation of the clinical implications of the results. In particular, the observed difference in HMGB1 levels was supported by a substantial effect size ($\eta^2 = 0.58$; Cohen's d = 1.81–1.95), suggesting that HMGB1 is a strong candidate biomarker for schizophrenia not only from a statistical perspective but also in terms of clinical applicability.

Our finding that patients with schizophrenia have an elevated HMGB1 serum level is is consistent with previous research. Al-Dujaili et al. reported elevated HMGB1 levels in schizophrenia patients compared to healthy controls but found no significant differences between treatment-resistant and partial-response groups (11). In line with these findings, a study conducted in Turkey by Yılmaz et al. reported increased HMGB1 levels in schizophrenia patients relative to healthy controls, without distinguishing between the acute and remission phases (12). Kozlowska et al. also demonstrated increased HMGB1 levels in patients with paranoid schizophrenia compared to healthy controls, proposing HMGB1 as a potential biomarker for schizophrenia (18).

Table 1. Comparison of sociodemographic and clinical characteristics between the groups

		Group						Statistical analysis	P
		Patients with schizophrenia in remission phase		Patients with schizophrenia in acute exacerbation		Healthy Controls			
		Mean/n	SD./%	Mean/n	SD./%	Mean/n	SD./%		
Age (years)		39.06	9.18	38.23	10.74	37.40	7.65	F=0.24 [a]	0.784
BMI (kg/m^2)		25.99	2.85	24.10	3.46	25.31	2.76	F=3.06	0.052
Education Status	Primary school graduate	11*	35.5	15*	48.4	1	3.3	χ^2=29.19 [b]	<0.001
	Middle school graduate	4*	12.9	5*	16.1	2	6.7		
	High school graduate	12*	38.7	3*	97	11	36.7		
	University graduate or above	4*	12.9	8*	25.8	16	53.3		
Marital status	Married	5*	16.1	4*	12.9	20	66.7	χ^2=25.25 [b]	<0.001
	Single	26*	83.9	27*	87.1	10	33.3		
Having children	Yes	5*	16.1	7*	22.6	18	60.0	χ^2=15.90 [c]	<0.001
	No	26*	83.9	24*	77.4	12	40.0		
Household	Spouse and/or children	5*	16.1	4*	12.9	20	66.7	χ^2=29.40 [a]	<0.001
	Parents/Sibling	24*	77.4	22*	71.0	6	20.0		
	Alone	2*	6.5	5*	16.1	4	13.3		
Working Status	Working	13**	41.9	3*	9.7	30	100.0	χ^2=60.80 [b]	<0.001
		18**	58.1	28*	90.3	0	0.0		
Family History of Psychiatric Disease	No	26**	83.9	17*	54.8	30	100.0	χ^2=20.47 [b]	<0.001
	Yes	5**	16.1	14*	45.2	0	0.0		
Smoking (pcs/day)	No	15*	48.4	9*	29.0	14	46.7	χ^2=5.69 [b]	0.464
	Light smoker (<15 adet)	3*	9.7	1*	3.2	1	3.3		
	Modarete smoker (15-25)	8*	25.8	13*	41.9	11	36.7		
	Heavy smoker (>25)	5*	16.1	8*	25.8	4	13.3		
Antipsychotic Use	Typical antipsychotic	0***	%0	1***	%3.2	-	-	***	***
	Atypical antipsychotic	24	%77.4	7	%22.6	-	-		
	Typical + Atypical	7	%22.6	1	%3.2	-	-		
	No antipsychotic use	0	%0	22	%71	-	-		
Age at onset of disease		23.84 ± 7.66		25.84 ± 10.19		-	-	t=-0.87	0.386
Duration of illness (years)		15.19 ± 8.12		12.39 ± 8.95		-	-	t=1.29	0.201
Number of hospitalisations		1.81 ± 1.00		4.84 ± 3.00		-	-	Z=-3.45	**0.001**
Number of psychotic exacerbations		2.68 ± 2.00		5.03 ± 4.00		-	-	Z=-2.50	**0.012**

[a]One-Way ANOVA Analysis; [b]Fisher's Exact Test; [c]Pearson Chi-Square Analysis
BMI: Body Mass Index; Med: Median; SD: Standard deviation; t: Independent Groups t Test; Z: Mann Whitney U Test.
p<0.05 was considered statistically significant.
*p<0.05 (compared to healthy control group)
**p<0.05 (compared to schizophrenia group in acute episode and healthy control group)
***Statistical comparisons of antipsychotic types between groups were not conducted due to low cell counts in some subgroups.

Table 2. Comparison of biochemical values between the groups

	Group									
	Patients with schizophrenia in remission phase		Patients with schizophrenia in acute exacerbation		Healthy controls					
	Mean	SD	Mean	SD	Mean	SD	Analysis	p	P1	P2
HMGB1 (pg/ml)	**140.48**	**63.52**	**125.92**	**48.71**	**57.44**	**13.04**	**χ^2=53.62**	**<0.001**	**<0.001**	**<0.001**
CRP (mg/L)	**4.83**	**4.07**	**3.07**	**2.58**	**2.29**	**2.38**	**χ^2=8.93**	**0.012**	**0.003**	0.243
NLR	2.83	2.03	2.41	1.77	2.09	.96	χ^2=3.34	0.189	0.083	0.920
Leukocyte (10^3/µL)	7.79	1.76	8.55	2.45	8.72	1.95	χ^2=4.49	0.117	0.043	0.526
Neutrophil (10^3/µL)	4.89	1.37	5.51	2.35	6.90	9.73	χ^2=0.84	0.656	0.363	0.897
Platelet (10^3/µL)	248.74	62.36	241.23	51.72	264.73	52.22	F=1.41	0.249	0.504	0.231
MLR	**.24**	**.10**	**.25**	**.10**	**.19**	**.05**	**χ^2=8.11**	**0.017**	**0.014**	**0.013**
PLR	121.97	44.07	112.62	40.88	100.23	29.43	χ^2=3.90	0.142	0.048	0.254
Monocyte(10^3/µL)	.48	.09	.55	.18	.52	.15	χ^2=2.23	0.316	0.344	0.588
Lymphocyte (10^3/µL)	**2.15**	**.61**	**2.34**	**.74**	**2.82**	**.80**	**χ^2=11.19**	**0.004**	**0.001**	**0.018**

F=One-Way ANOVA Analysis; χ^2=Kruskal Wallis H test
BMI: Body mass index; CRP: C-reactive protein; HMGB1: High Mobility Group Box 1; MLR: Monocyte/lymphocyte ratio; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; SD: Standard Deviation.
p: Significance value for overall comparison among the three groups (one-way ANOVA or Kruskal-Wallis test). p<0.05 was considered statistically significant.
p1: Pairwise comparison between remission schizophrenia group and healthy controls (post-hoc analysis)
p2: Pairwise comparison between acute schizophrenia group and healthy controls (post-hoc analysis)

Table 3. Correlations of serum HMGB1 levels to age, BMI and, biochemical values of the groups

		Patients with schizophrenia in remission phase	Patients with schizophrenia in acute exacerbation	Healthy controls	Total patients with schizophrenia
Age (years)	r_s	-0.081	0.344	-0.212	0.141
	p	0.666	0.058	0.262	0.276
BMI (kg/m$^{2)}$	r_s	0.021	-0.112	0.223	-0.012
	p	0.910	0.550	0.236	0.925
CRP (mg/L)	r_s	-0.190	0.001	-0.011	-0.071
	p	0.306	0.995	0.953	0.586
NLR	r_s	-0.169	-0.232	-0.017	-0.153
	p	0.364	0.209	0.927	0.234
Leukocyte (10^3/µL)	r_s	-0.055	-0.060	**-0.485**	-0.073
	p	0.768	0.748	**0.007**	0.575
Neutrophil (10^3/µL)	r_s	-0.099	-0.184	**-0.482**	-0.167
	p	0.596	0.320	**0.007**	0.196
Platelet (10^3/µL)	r_s	0.156	-0.202	-0.315	-0.003
	p	0.402	0.276	0.090	0.979
MLR	r_s	0.124	0.047	0.213	0.077
	p	0.505	0.801	0.259	0.551
PLR	r_s	0.097	-0.106	0.081	0.022
	p	0.603	0.572	0.672	0.863
Monocyte (10^3/µL)	r_s	0.233	0.004	-0.034	0.089
	p	0.206	0.981	0.859	0.492
Lymphocyte (10^3/µL)	r_s	0.084	0.023	-0.317	0.033
	p	0.654	0.903	0.088	0.802

Spearman Correlation Analysis was used. BMI: Body mass index; CRP: C-reactive protein; HMGB1: High Mobility Group Box 1; MLR: Monocyte/lymphocyte ratio; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio. p<0.05 was considered statistically significant.

Table 4. Correlation between serum HMGB1 levels, and clinical and psychometric characteristics of patient groups

		Patients with schizophrenia in remission phase	**Patients with schizophrenia in acute exacerbation**	**Total patients with schizophrenia**
Age at onset of disease	r_s	0.051	0.248	0.137
	p	0.784	0.178	0.288
Duration of illness (years)	r_s	-0.330	0.029	-0.105
	p	0.069	0.877	0.415
Number of hospitalisations	r_s	-0.315	-0.118	-0.219
	p	0.084	0.528	0.087
Number of psychotic exacerbations	r_s	-0.059	-0.085	-0.080
	p	0.752	0.649	0.536
Chlorpromazine-equivalent antipsychotic doses	r_s	-0.329	-0.373	**-0.316**
	p	0.071	0.323	**0.047**
CGI	r_s	-0.320	0.050	-0.155
	p	0.079	0.791	0.230
PANSS-positive symptoms	r_s	0.052	0.290	-0.013
	p	0.783	0.113	0.920
PANSS-negative symptoms	r_s	-0.033	-0.012	-0.106
	p	0.859	0.950	0.411
PANSS-general psychopathology	r_s	0.013	0.138	-0.056
	p	0.944	0.459	0.666
PANSS-total	r_s	-0.029	0.155	-0.064
	p	0.877	0.406	0.621
BPRS	r_s	-0.030	0.111	-0.076
	p	0.872	0.554	0.556

Spearman Correlation Analysis was used. BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression; HMGB1: High Mobility Group Box 1; PANNS: Positive and Negative Symptoms Rating Scale. p<0.05 was considered statistically significant.

In schizophrenia, cytokines are classified into two categories: 'state markers,' which fluctuate with symptom severity and typically normalize during remission, and 'trait markers,' which remain consistently altered throughout the disease course and differ from healthy individuals. Trait markers reflect underlying biological processes that predispose individuals to psychiatric disorders, whereas state markers reflect the current status of clinical symptoms. Therefore, focusing on trait markers offers greater understanding of the genetic and neurobiological underpinnings of schizophrenia (3). Consistent with prior literature, our findings show that HMGB1 is elevated in both acute exacerbation and remission phases compared to healthy controls, reinforcing its candidacy as a stable inflammatory biomarker associated with schizophrenia.

In the present study, a negative correlation was identified between antipsychotic doses and HMGB1 levels. Similarly, Zhu et al. observed that serum HMGB1 levels decreased following six months of risperidone treatment but remained higher than those of healthy controls. Notably, the reduction in HMGB1 levels did not align with the degree of symptom improvement (13). Collectively, these findings imply that HMGB1 might serve as a marker of disease recovery, though the precise mechanisms underlying these changes remain unclear. Although this study attempted to compare different antipsychotic medications in terms of their effects on HMGB1 levels, the small subgroup sizes (e.g., 31 vs. 8 patients) limited statistical power. Consequently, no significant differences were detected. Therefore, while antipsychotic treatment in general may influence HMGB1 levels, the potential differential effects of specific antipsychotic agents remain unclear. Future studies with larger and more balanced samples are needed to elucidate to better understand the distinct effects of various antipsychotics on HMGB1 regulation.

In a similar vein, although the groups were matched for smoking status (light, moderate, and heavy smokers) to minimize confounding, the small sample sizes in these subgroups prevented meaningful statistical comparison. Given the well-established pro-inflammatory effects of smoking and its potential to elevate HMGB1 levels, future studies with larger and more balanced samples are warranted to better clarify the impact of smoking intensity on HMGB1 in schizophrenia.

In the present study, CRP levels were significantly higher in schizophrenia patients in the remission group compared to healthy controls. While CRP levels in the acute exacerbation group were also elevated relative to healthy controls, the increase did not reach statistical significance. A meta-analysis conducted in 2022 reported that CRP levels were generally higher in schizophrenia patients than in healthy controls and were higher during acute exacerbation than remission; however, this difference was not observed in patients receiving antipsychotic treatment (26). Studies indicate that antipsychotic drugs influence CRP levels, with clozapine known to induce an acute phase reaction (27). Although some studies argue that antipsychotic drugs do not affect CRP levels (28), other findings suggest that CRP levels may increase after the initiation of antipsychotic treatment in schizophrenia patients (26). The significantly higher CRP levels observed in the remission group in this study may reflect more consistent antipsychotic use compared to the acute exacerbation group.

In various pathologies such as appendicitis, PCOS, and cholecystitis, HMGB1 and CRP have been shown to correlate positively. However, HMGB1 has often been regarded as a more sensitive and clinically meaningful biomarker, particularly in conditions like coronary artery disease, obesity, and ischemia (10). Kozlowska et al. found no significant correlation between HMGB1 and CRP levels in schizophrenia patients (18). In the present study, no correlation was observed between HMGB1 levels and CRP, NLR, PLR, or MLR, which are acute-phase markers. As these markers are non-specific inflammatory biomarkers, this may indicate that HMGB1-related inflammatory mechanisms are more closely linked to the neurobiology of schizophrenia, as opposed to general systemic inflammation.

In the present study, schizophrenia patients had significantly higher MLR and lower lymphocyte counts compared to healthy controls, consistent with previous research. NLR and PLR were also higher in the patient group but the differences were not statistically significant. Recent studies demonstrated that CBC-derived biomarkers of inflammation, including NLR, PLR, and MLR, were higher, while lymphocyte counts were lower in schizophrenia patients compared to healthy individuals (14). However, another study where age, gender, smoking, and BMI were matched between the groups found no significant difference in NLR values, highlighting the potential influence of methodological differences and sample characteristics on inflammatory marker outcomes (29).

In a study published in 2020 compared schizophrenia patients in the acute and remission phases with healthy controls, reporting NLR values of 2.27±1.41, 2.09±1.17, and 1.65±0.6, respectively. This study demonstrated a significant statistical difference between the patient and control groups (4). In the present study, NLR values in the acute exacerbation group, remission group, and the control group were found to be 2.41±1.77, 2.83±2.03, and 2.09±0.96, respectively. While the patient groups in our study had higher NLR values, the control group in the other study had lower mean values compared to ours. This discrepancy may explain the lack of a statistically significant difference in NLR between schizophrenia patients and controls in our study, as the control group's mean value was higher than those reported in previous studies. Additionally, there are conflicting results in the literature regarding the effect of antipsychotic drugs on NLR. While some studies found no significant difference in NLR between patients receiving and not receiving antipsychotic treatment (30), Zhou et al. reported a significant decrease in NLR levels in patients receiving antipsychotics treatment in a study involving 1144 schizophrenia patients (31). Further studies that stratify participants by antipsychotic use are needed to resolve these inconsistencies.

In conclusion, our findings demonstrate that elevated HMGB1 levels in schizophrenia persist across both remission and acute exacerbation phases, further reinforcing its potential as a trait marker in schizophrenia. The elevated HMGB1 levels observed during inflammatory responses may contribute to schizophrenia pathogenesis by promoting neuroinflammation, highlighting its potential as a novel therapeutic target for future investigation. Although serum HMGB1 serves as a valuable biomarker across neurological and psychiatric disorders, its ability to reliably mirror CNS inflammation remains uncertain. To better define its pathophysiological role and diagnostic potential, future studies should directly measure HMGB1 in cerebrospinal fluid from schizophrenia patients and their first-degree relatives.

All patients in this study were recruited from a tertiary hospital and a community mental health center affiliated with our institution. These facilities primarily serve treatment-resistant patients with severe forms of the disorder. Consequently, the findings may not be generalized to all schizophrenia phenotypes. Additionally, as the patients were treated with various medications at different doses, the confounding effect of antipsychotic treatment on HMGB1 levels cannot be entirely ruled out. Future studies should focus on drug-naive, first-episode patients to better elucidate the relationship between HMGB1 and schizophrenia symptomatology.

Furthermore, this study does not conclusively determine whether HMGB1 is a state or trait marker. Its cross-sectional design limits the ability to assess longitudinal changes in HMGB1 levels, and the extent to which peripheral HMGB1 reflects central nervous system inflammation remains unclear**.** Additionally, HMGB1 and inflammatory cytokines were not evaluated together, representing an additional limitation of the study. The relatively high standard deviations observed in HMGB1 levels may reflect intrinsic biological variability and the presence of outliers, which could not be entirely eliminated despite exclusion criteria. This variability may also indicate the influence of other unmeasured inflammatory factors. Although the sample size was adequate for detecting between-group differences based on prior power analysis, it may not have been sufficient for more nuanced analyses—such as distinguishing whether HMGB1 acts as a state or trait marker—due to limited statistical power for within-group assessments.

Further studies with larger sample sizes and longitudinal designs are needed to clarify the dynamics of HMGB1 over time, to better understand how well this serum marker reflects neuroinflammation in schizophrenia, to determine whether HMGB1 functions as a trait or state marker, and to evaluate its potential as a novel pharmacological target in this disorder.

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