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Article

COVID-19 Response in Patients with Schizophrenia Spectrum Disorders: Hematological and Inflammatory Profile

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Abstract: COVID-19 cases are still of particular interest for identifying vulnerable groups. Schizophrenia is considered a high-risk factor for COVID-19 mortality, but this conclusion remains debated. This research aims to investigate the hematological and immunological response to SARS-CoV-2 in patients with schizophrenia. Data were retrieved from the medical records of 69 patients with schizophrenia and 332 mentally healthy individuals with a confirmed diagnosis of COVID-19. Immunological status was assessed by hemoglobin level, white blood cell, absolute neutrophil, absolute lymphocyte, and platelet counts. The inflammatory status was evaluated using the neutrophil-to-lymphocyte ratio; an index of systemic immune inflammation, and a platelet-to-hemoglobin ratio. Our findings showed a milder course of the disease in patients with schizophrenia compared to the controls. Notably, these patients displayed an absence of an apparent white blood cell response to SARS-CoV-2 invasion, a lower inflammatory response, except for an elevated platelet-to-hemoglobin ratio. The most intriguing result was the lack of a gender-dependent immunological reaction to COVID-19 in patients with schizophrenia, in contrast to the controls. Thus, our data revealed a different physiological response to COVID-19 in patients with schizophrenia compared to the general population, raising many questions about the complex interplay between the nature of mental diseases, medication, immune system functionality, and susceptibility to COVID-19.

Keywords: COVID-19, Schizophrenia, Inflammatory status, Hematological response

1. Introduction

Although COVID-19 is no longer classified as a pandemic, the ongoing challenges posed by the disease persist across various dimensions. The adaptation of the virus to the human-nature system diversifies the original strain the SARS-CoV-2 into lineages with distinct phenotypic characteristics, including differences in transmissibility, severity, and immune evasion, enabling its continued circulation within the global population [1,2]. This process underscores the challenges faced by the medical and scientific communities in understanding, predicting, and addressing the dangers of new COVID-19 outbreaks, both in terms of short- and long-term complications. Predictive analysis and the comparison of accumulated data on the disease's progression within and between populations serve as the foundation for developing comprehensive disease management strategies, identifying at-risk groups, and forecasting outcomes.

Within the vulnerable population, individuals with mental illnesses usually inherently form a risk group, given their distinctive biological and social backgrounds. Recently, schizophrenia has been recognized as the second most significant risk factor for COVID-19 mortality, surpassed only by advanced age [3,4].

Schizophrenia, as well as schizophrenia spectrum disorders (SSD), is a major (psychiatric) brain disorder resulting from the complex interplay between specific genetic makeup and environmental triggers [5]. The estimated global prevalence of schizophrenia is 0.3-1.25%, and only 10–15% of patients with SSD are gainfully employed. As a highly disabling lifetime disease, schizophrenia represents a multibillion-dollar economic burden for society and the state, and the World Health Organization ranks

it among the top 20 most burdensome diseases worldwide [6,7]. SSD is highly associated with psychiatric comorbidity (anxiety, depression, panic disorder, etc), physical illness (cardiovascular disease, cancer, diabetes mellitus, chronic obstructive lung disease, etc), and drug, tobacco, and alcohol abuse [8−10].

The alteration of immunophysiological homeostasis, whether underlying or concurrent with schizophrenia, may render patients with schizophrenia particularly susceptible to infectious diseases. This susceptibility has gained special interest amid and after the COVID-19 pandemic, underscoring the urgent need to identify risk groups for severe illness. According to the University of Manchester UK Biobank (UKB) cohort study, people with psychotic disorders, such as schizophrenia, had a five-fold increase in the odds of mortality from COVID-19 and were three times more likely to be hospitalized [11]. However, these findings are based on geographically restricted (UK) studies, albeit comprehensive. On a global scale, the available data is very limited and sometimes controversial: according to some research, schizophrenia was one of the most significant risk factors for dying from COVID-19, while another has shown a weak impact of mental illness on COVID-19 outcomes [3,12−14]. This discrepancy highlights the need for more extensive, diverse, and globally representative studies to reveal the true extent of the risk.

Given that, the current research aims to investigate the hematological and immunological response to COVID-19 in individuals diagnosed with SSD, compared to mentally healthy COVID-19 patients, to shed light on the basic physiological differences that may contribute to the risks associated with COVID-19 in this particular cohort of patients.

2. Material and Methods

The retrospective multicenter research utilized databases from both the Republican Psychiatric Hospital No. 1 and the Central Hospital of the State Customs Committee. The study included the medical records of 69 patients (23 males, 46 females; mean ages 52.1±13.4 and 48.7±13.9, respectively) diagnosed with schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (ICD-10: F20-F29) who were undergoing inpatient treatment at the time of their COVID-19 diagnosis.

The comparison group comprised 332 mentally healthy individuals who were patients of Central Customs Hospital (173 women and 159 men, mean age 50±14.7 and 53±14.7, respectively) and were hospitalized with either a confirmed diagnosis of COVID-19 by positive PCR results (observed in 78% of patients) or considered suspected based on specific clinical and radiological symptoms. Upon hospital admission, 93% of males and 89.9% of females were diagnosed clinically and/or radiologically (CT) with bilateral pneumonia and had typical diffuse lung ground-glass opacities with different lesion areas.

The study investigated variations in hematological parameters and their frequency, considering both inter and intra-group differences, with and without accounting for gender. Immunological status was assessed by hemoglobin level, white blood cell (WBC) count, absolute neutrophil and lymphocyte count (ANC, ALC), and platelet (Pl) count. The balance between the innate and adaptive immune responses and inflammatory status was evaluated using the following ratios:

1. Neutrophil-to-Lymphocyte Ratio (NLR): NLR = ANC/ALC
2. Systemic Immune-Inflammation Index (SII): SII = (ANC/ALC) × Pl
3. Platelet-to-Hemoglobin Ratio (PHR): PHR = Pl (per μL)/Hb (per g/dL) × 10,000

The primary data processing, which encompassed descriptive statistics as well as inter- and intra-group comparisons, was carried out using IBM SPSS Statistics 29.0. Descriptive statistics involved measures of central tendency (Mean, Standard Error of Mean, Median, Upper Quartile, and Lower Quartile) for continuous variables and absolute frequency for categorical data. To assess the normality of the distribution of quantitative indicators, coefficients of asymmetry and kurtosis were utilized. Given that the data did not follow a normal distribution, a comparative analysis was conducted employing the Mann-Whitney U-test for two groups and the Kruskal-Wallis test to compare several groups of different sizes, followed by a post-hoc analysis using Dunn's test with Bonferroni correction to identify specific group differences. Absolute frequency was determined using Fisher's exact test. The critical level of significance (p) for testing statistical hypotheses was set at 0.05.

3.Results

The obtained data are shown in Table 1.

Table 1. Comparison of hematological and inflammatory profiles of patients with and without schizophrenia

	Mental disorder (SSD)				No mental illness			
	Female		Male		Female		Male	
Number	46		23		173		159	
Age	48,7± 13,9		52,1±13,4		50±14.7		53±14.7	
	M±SEM	Me [Q1; Q3]	M±SEM	Me [Q1; Q3]	M±SEM	Me [Q1; Q3]	M±SEM	Me [Q1; Q3]
RBC ($\times 10^{12}$/L)	4.01±0.08	4.13[3.8;4.48] 1	4.00±0.13	3.97[3.58;4.44]	4.49±0.04	4.49[4.16;4.69] 1,2	4.82±0.05	4.84[4.46;5.19]
WBC ($\times 10^9$/L)	6.04±0.23	5.9[5.1;7.13]	7.01±0.63	6.1[5.4;10.5]	7.07±0.26	6.26[4.79;8.01] 2	8.08±0.32	6.7[5.08;10.34] 2
Hb (g/dL)	11.25±0.3	11.55[10.3;12.7]	12.28±0.35	11.8[11.1;14.0]	12.12±0.10	12.4[11.4;13] 2	13.77±0.14	14.2[12.8;14.9] 2
Neutrophils ($\times 10^9$/L)	3.88±0.20	3.7[2.9;4.8]	4.69±0.61	3.95 [2.25;6.5] 1	4.92±0.25	3.95 [2.90;5.58] 2	6.20±0.32	4.57[3.27;9.01] 2
Lymphocytes ($\times 10^9$/L)	1.64±0.07	1.6[1.2;2.05] 1	2.00±0.29	1.75[1.1;2.35] 1	1.51±0.05	1.4[1.0;1.87] 1,2	1.30±0.11	1.06[0.8;1.58] 1,2
Platelet ($\times 10^9$/L)	252.13±12.30	229 [199.5;302.0] 1	229.83±20.36	211 [163;284] 1	235.47±6.05	226 [175.5;278.5] 2	216.1±7.10	199 [158.0;254.0] 2
NLR	2.46±0.19	2.14[1.70;3.36] 1	3.00±0.54	2.29[1.79;3.13] 1	4.03±0.26	2.66[1.83;4.78] 1,2	7.48±0.65	3.84[2.4;10.41] 1,2
SII	600.56±60.61	489.2 [341.7;781.1] 1	719.04±178.28	472.75 [313.85;842.50] 1	989.53±77.37	609.26 [373.23;1162.91] 1,2	1730.88±160.02	817.01 [369.41;2331.52] 1,2
PHR	2.33±0.16	2.16 [1.65;2.9] 2	1.93±0.22	1.64 [1.27;2.3]	1.99±0.06	1.83 [1.44;2.39]	1.62±0.07	1.43 [1.11;1.86]

M ± SEM: Mean ± Standard Error of the Mean; Me [Q1; Q3]: Median [Lower Quartile; Upper Quartile]; RBC: red blood cells; WBC: white blood cells; Hb: hemoglobin; NLR: neutrophil to lymphocyte ratio; SII: systemic immune inflammation index; PHR: platelet to hemoglobin ratio

1 – gender-dependent differences are significant in inter-group comparisons, $p<0.05$

2– gender-dependent differences are significant in intra-group comparisons, $p<0.05$

3.1 Red Blood Cell Parameters

At the time of COVID-19 diagnosis, patients without mental pathology had higher levels of red blood cell indicators (erythrocyte and hemoglobin levels) compared to patients with SSD:

4.61 [4.3; 4.97] versus 4.09 [3.8; 4.4], $p < 0.01$ for erythrocytes, and 12.9 [11.9; 14.2] versus 11.8 [10.6; 12.9], $p < 0.01$ for hemoglobin. It is interesting to note that in patients with SSD, gender dependency in those indicators was not observed, contrasting with statistically significant differences among mentally healthy individuals. Comparing patients with and without mental disorders, a notable gender difference was also evident (Table 1).

3.2 Leukocytes

There was no statistically significant difference in white blood cell (leukocyte) counts between individuals with SSD and mentally healthy patients affected by COVID-19: 6 [5.2; 7.3] vs 6.35[4.98; 9.29]. Notable disparities in this parameter were only observed between male and female COVID-19 patients without SSD, although these differences had a small effect size (Table 1). Meanwhile, the prevalence of leukocytosis was nearly three times higher among mentally healthy patients compared to those with SSD (28% vs. 8.7%, $p<0.01$) and was significantly more frequent in males. Leukopenia was registered at almost similar frequency in both SSD patients (14.5%) and the control group of COVID-19 patients (10.2%).

3.2.1 Neutrophils

A statistically significant difference was observed in neutrophil count between both compared groups of patients: 3.8 [2.95; 5.0] in SSD patients versus 4.23[3.09; 7.12], $p<0.03$. Neutropenia was significantly more frequently spotted among patients with SSD compared to the control group (14.3% vs. 5.1%, respectively, $p<0.01$). Conversely, cases of high ANC were encountered about four times as often in patients without mental disorders (22.9% vs. 6.3%, $p<0.01$). Stratifying by gender eliminated differences in ANC between groups, making it noticeable only inside the control group of COVID-19 patients. Notably, high ANC was observed in men nearly twice as often as in women (31.4% vs 16.2%, respectively, $p<0.01$). Among female patients with SSD, cases of neutrophilia were not registered at all, whereas among males, both high and low levels of ANC accounted for 20% and 25% of cases, respectively. Overall, patients with SSD showed a tendency toward a predominance of normal to low ANC.

3.2.2 Lymphocytes

The most substantial disparity in hematological parameters among the patient groups pertained to ALC (Table 1). Notably, patients with SSD did not exhibit a pronounced lymphocyte reaction to SARS-CoV-2 infection: cases of low ALC were rare, observed in only 9% of male patients, and there were no deviations in lymphocyte levels among female patients. Conversely, among mentally healthy patients with COVID-19, 45.9% of males and 23.1% of females experienced reduced lymphocyte counts ($p<0.01$). This suggests a robust gender-dependent response to COVID-19 within the control group of patients.

3.3 Platelet Count

Differences in platelet levels between the group of schizophrenia patients and control subjects were statistically significant, although the standardized effect size was small ($p<0.01$). Patients with schizophrenia tended to have higher platelet levels than their control peers: 228.5[192;285] vs 213[165; 270]. Stratification by sex revealed certain gender-dependent differences in platelet response to COVID-19 among the control group of patients: in women, this indicator was higher than in male patients (Table 1). A similar trend was observed in the group of SSD patients, but it was not statistically significant.

3.4 Hematological Indexes

3.4.1 Neutrophil-to-Lymphocyte Ratio (NLR)

The research findings have indicated that the average NLR among individuals in the control group was significantly higher than in their counterparts from the psychiatric clinic ($p<0.001$). Gender stratification has revealed intergroup disparities in NLR levels, with intra-group variations observed only within the group without mental illness. In general, among patients with SSD, a high NLR (above 3) was predominantly observed in women (30.2%) and less frequently in men (22.7%). Among the controls, on the contrary, a high NLR at 59.1% was slightly more prevalent among men versus 44.5% among women. It is also worth noting that the highest level of stress among individuals with SSD did not surpass the "mild to moderate inflammatory stress" threshold, whereas 42.9% of women and 51.1% of men in the control group exhibited NLR levels within the "moderate to severe inflammatory stress" range.

3.4.2 Systemic Immune-Inflammation Index (SII)

Likewise, as with the NLR parameter, there were statistically significant intergroup differences in the SII magnitude. The average SII value among SSD patients was 639.46 ± 70.8, while it stood at 1344.58 ± 88.82 in patients without mental disorders ($p<0.01$). Upon dividing the study participants by gender, a consistent pattern emerged: statistically significant difference in the SII magnitude was observed between groups, while intra-group disparities in the indicator's level were notable only among individuals without mental disorders (Table 1). The frequency of the SII exceeding the 600-point threshold was observed in 54.5% of males and 39.5% of females with SSD and in 62.3% of males and 50.9% of females without mental disorders.

3.4.3 Platelet-to-Hemoglobin Ratio (PHR)

PHR is the only parameter that has revealed both statistically significant differences, both within and between groups (Table 1). This indicator was significantly higher in individuals with SSD than in control group patients (1.93[1.5;2.5] vs 1.65 [1.23;2.21], $p<0.01$). Upon stratifying the data by gender, a significant trend towards higher PHR levels in women compared to men became evident. Importantly, this trend was consistent for both SSD patients and the control group.

4. Discussion

It is widely acknowledged that schizophrenia is a multifactorial disorder, where immune system changes are one part of a complex interplay of genetic, neurobiological, environmental, and other systemic factors [5]. Research into the immunological aspects of schizophrenia has yielded a range of findings, some of which remain inconclusive or conflicting [15,16]. Schizophrenia has been associated with alterations in cytokine balance, shifts in immune cell activity, and instances of autoimmunity [17, 18]. Yet, it is difficult to ascertain whether these changes precede the onset of schizophrenia, are a result of the disorder, or are influenced by other factors such as medication, lifestyle, or comorbid conditions. So, despite extensive research and theories dating back over a century, the scientific community has yet to reach a definitive conclusion on whether immune system abnormalities in schizophrenia causative factors are, mere reflections of broader systemic changes, or both.

In either case, the potential immunological dysfunction backgrounding schizophrenia can compromise the ability of the body to effectively respond to COVID-19. This is one of the key reasons why patients with SSD are considered to be at risk for the severity of the course of coronavirus infection. Findings of the present study, based on a retrospective analysis of the COVID-19 outbreak among patients of a psychiatric hospital undergoing inpatient treatment showed a tendency towards a milder course of the disease compared to the general population. In most cases of laboratory-confirmed disease, the illness either had no clinical manifestation or occurred in a mild to moderate form. To gain a deeper understanding of the nature of the unique response to the infection in a cohort of patients with SSD, a comparative analysis of hematological parameters at the onset of the disease was undertaken. Our research has revealed significant disparities in the hematological profiles between patients with and without mental disorders.

In patients with schizophrenia, the study has pinpointed an absence of apparent white blood cell response to the SARS-CoV2 invasion, with all parameters staying within normal ranges to the opposite reaction seen in mentally healthy individuals, who exhibited a strong tendency toward neutrophilia and lymphocytopenia. Lymphocytopenia is the key laboratory marker, associated with disease severity and poor prognosis in COVID-19 [19, 20]. A less robust immune response and ability to maintain a normal lymphocyte count might potentially protect patients with SSD against severe disease manifestations.

Another important set of findings has emerged from the study of specific hematological indices. In our research, we assessed two WBC-derived indices (NLR and SII) and one RBC-derived index (PHR), which reflected the status of different branches of the immune-inflammatory system. The neutrophil-to-lymphocyte ratio and the systemic immune-inflammation index are both widely utilized in clinical practice for disease progression and outcome prognostication [21].

The third index, the platelet-to-hemoglobin ratio, is relatively new in use but has already demonstrated its robustness and predictive value in cardiovascular diseases [22, 23]. Given the link between cardiovascular health and COVID-19 complications, PHR helps identify patients at higher risk of severe outcomes, including thrombotic events and acute respiratory distress syndrome (ARDS).

Comprehensively, our study has revealed a lower level of inflammatory response to COVID-19 in patients with SSD compared to control peers based on NLR and SII estimations. It diverges from the common expectation that individuals with schizophrenia always exhibit a strong pro-inflammatory background due to inherent immunological dysfunctions [24]. This observation implies that if the immune response in patients with SSD is less prone to over-activation, it could potentially reduce the risk of cytokine storm, which is a severe complication commonly associated with COVID-19. Cytokine storm is characterized by an excessive and uncontrolled release of proinflammatory cytokines, which can cause significant tissue damage and have been linked to a high fatality rate of COVID-19 [25]. Meanwhile, we observed an elevated PHR in SSD patients, which may indicate specific vascular and

respiratory issues of concern due to the clotting risks. The most intriguing result of this research was the lack of a gender-dependent immunological reaction to COVID-19 in patients with SSD, in contrast to one observed in the mentally healthy group. The gender difference in response to infection is a well-established phenomenon, determined by biological, genetic (certain immune-related genes are located on the X chromosome), hormonal (estrogens enhance immune activity; while testosterone often has an immunosuppressive effect) and behavioral aspects [26, 27]. In SSD patients, the impact of the mental disorder and its treatment on the endocrine system might mask these hormonal influences and reduce the normal differences in immune responses between genders. At the same time, in the mentally healthy group, high levels of proinflammatory activity were predominantly observed in males and exceeded the same indicator in females. The only exception was PHR, which tends to be higher in female patients compared to males. All these findings suggest a distinct immune response pattern to the virus in patients with SSD to be attributed either to intrinsic factors related to the disorder itself, such as specific immune system misbalance, or the influence of psychiatric medications, which can have immunomodulatory properties or a combination of both.

In the context of the antiviral properties associated with antipsychotic medications, it is worth noting haloperidol [28]. This drug was used in psychiatric treatment schemes at the onset of the pandemic to alleviate symptoms in patients with schizophrenia. Haloperidol usage could well explain many of the phenomena observed in patients with SSD in response to the coronavirus infection. By acting on dopamine D2 receptors, haloperidol impacts prolactin levels, which are usually associated with low levels of testosterone and estrogens. This can, to a certain degree, clarify the diminished gender-dependent response to COVID-19 in patients with SSD. Moreover, prolactin is also known for its strong cytokine-like modulatory activity within both the innate and adaptive immune systems [29]. Additionally, antiviral and immune-inflammatory mechanisms proposed for haloperidol extend beyond the central nervous system. It is a well-established fact that haloperidol exhibits its anti-inflammatory effect by increasing the levels of cytokines such as IL-4 and IL-10 and by suppressing the level of IFN-γ, which, inter alia, decreases the risk of cytokine storm development [20, 28–30].

Besides its already-known ability to block RNA virus replication, research by Gordon and others has identified the high affinity of haloperidol for sigma-1 and sigma-2 receptors, suggesting its potential to inhibit SARS-CoV-2 viral entry mechanisms [31, 32]. These data collectively explain how psychiatric drugs, in this case, haloperidol, can modulate the body's response to SARS-CoV-2 infection, by dampening the overly aggressive immune reaction.

5. Conclusion

The findings from our retrospective study have shown a notably different physiological response to COVID-19 in patients with SSD compared to the general population. In particular, there was no clear reaction of white blood cells to SARS-CoV-2, and patients with SSD exhibited a significantly lower inflammatory response to the infection, as reflected in reduced neutrophil-to-lymphocyte and systemic immune inflammation indices compared to mentally healthy individuals. Interestingly, while an elevated platelet-to-hemoglobin ratio in SSD patients suggests increased vascular risks, the clinical course of COVID-19 unfolded without apparent vascular complications. Furthermore, the absence of a gender-dependent immune response in SSD patients contrasts with the distinct gender differences observed in the control group. These findings underscore the need for further investigation into the complex interplay between schizophrenia, its treatment, immune system functionality, and susceptibility to COVID-19, with potential implications for personalized therapeutic strategies. Given the relatively small sample size, which is a limitation of this study, further research with larger cohorts is necessary to validate these findings and explore the underlying mechanisms in greater detail.

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