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ORIGINAL RESEARCH

Correlation Between Monocyte Count, Monocyte–Lymphocyte Ratio, and Other Inflammatory Cells With Sleep and Psychiatric Symptoms in First-Episode Schizophrenia Patients

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Background: More and more evidence shows that infection and immune abnormality are closely related to the increased severity of schizophrenia symptoms. This study aimed to explore the correlation between inflammatory cell counts, sleep quality, and psychiatric symptoms in first-episode schizophrenia patients.

Methods: A total of 103 first-episode schizophrenia patients (patient group) admitted to the Anhui Provincial Mental Health Center from November 2021 to August 2022 were included in the study, while 57 healthy individuals (control group) who met the criteria were recruited as the study subjects. The Positive and Negative Symptom Scale (PANSS) and Pittsburgh Sleep Quality Index (PSQI) were used to evaluate the mental symptoms and sleep status of the patients. Blood analysis results were used to determine the peripheral blood white blood cells (WBC) and lymphocytes of the two groups. Count neutrophils, monocytes, and platelets (PLT) of the two groups. The neutrophil lymphocyte ratio (NLR), monocyte lymphocyte ratio (MLR), and platelet lymphocyte ratio (PLR) were calculated. Differential, correlation, and regression analysis were performed on survey data using SPSS 26.0.

Results: Results showed WBC, neutrophils, monocytes, NLR, MLR higher in case vs control group ($p<0.05$). Correlation analysis found monocytes negatively correlated with sleep time ($rs=-0.205$, $p=0.037$) and MLR with arousal factor ($rs=-0.204$, $p=0.039$). Linear regression showed that MLR positively affected arousal score ($B=7.196$, $t=2.781$, $p=0.006$) and monocytes negatively affected sleep time score ($B=-0.851$, $t=-2.157$, $p=0.033$). ROC analysis revealed high sensitivity and specificity of WBC, neutrophils, monocytes, NLR, MLR for SCZ symptom prediction.

Conclusion: The study concluded that elevated WBC, neutrophils, monocytes, NLR, and MLR levels in the case group were significantly associated with increased severity of schizophrenia symptoms, particularly affecting sleep and arousal factors, and demonstrated high predictive validity for SCZ symptoms.

Keywords: schizophrenia, inflammatory cells, mental symptoms, sleep, arousal factor, ROC analysis

Introduction

Schizophrenia (SCZ) is a severe mental illness characterized by unknown etiology, cognitive symptoms and emotional dysregulation.[1] It is often associated with a poor prognosis compared to many other mental disorders[2,3] and significantly impacts patients' lives. The disease burden associated with schizophrenia ranks among the highest of all diseases.[3] Previous research underscores the role of inflammation in SCZ pathology, with infection and immune irregularities closely linked to its symptoms.[4] For instance, reduced levels of brain-derived neurotrophic factor (BDNF) and elevated C-reactive protein (CRP) are associated with cognitive impairment and negative symptoms in SCZ patients.[5,6] The

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genetic inflammation vascular hypothesis posits[7] that chronic systemic inflammation can impair the microvasculature of the central nervous system, disrupting blood flow regulation and the blood–brain barrier, ultimately precipitating mental illness. Despite the predominant focus on inflammatory factors in existing research, biomarkers such as serum white blood cell count[8] and other inflammatory cell counts, along with their ratios like the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR),[9,10] warrant attention as indicators of inflammation. Previous studies have demonstrated elevated NLR in patients with schizophrenia, major depressive disorder, and bipolar disorder compared to healthy controls.[11] In patients with schizophrenia, female patients have higher NLR and PLR than males, and they are positively correlated with antipsychotic dose and negatively correlated with cognitive function.[12] In addition, NLR, SII and PAR values and CRP level might be a state biomarker of inflammation in bipolar patients in a manic phase.[13]

Sleep is a crucial and intricate process essential for maintaining physiological homeostasis.[14] Alterations in sleep patterns are frequently observed among psychiatric patients.[15] Inadequate sleep can induce changes in inflammatory markers and mediators such as neutrophils, monocytes, and the neutrophil lymphocyte ratio (NLR),[16] contributing to a chronic inflammatory state and fatigue,[17] which can exacerbate psychiatric symptoms such as cognitive symptoms.[18,19] Existing research indicates that in patients with schizophrenia, total sleep duration is negatively correlated with NLR and platelet lymphocyte ratio (PLR), while sleep efficiency correlates negatively with neutrophil count and NLR. Conversely, the latency to sleep onset, total activity during sleep, number of awakenings after sleep onset, and total awakenings are positively correlated with white blood cell and neutrophil counts. Additionally, the average duration of awakenings correlates positively with NLR and PLR.[20] Compared with previous studies, this study innovatively focuses on patients with first-episode schizophrenia and provides insights into the fine-grained correlations of key inflammatory markers with sleep duration and psychiatric symptoms, which provides new biomarker perspectives for early identification and intervention of schizophrenia and has important clinical applications.

Materials and Methods

Subjects

This study selected first-time schizophrenia patients who were hospitalized at the Anhui Provincial Mental Health Center from November 2022 to August 2023. Inclusion criteria: (1) individuals who meet the diagnostic criteria for DSM-5 schizophrenia; (2) first onset, no use of antipsychotic drugs (including sedative and hypnotic drugs); (3) age range from 18 to 60 years old. Exclusion criteria: (1) individuals with diseases that may lead to abnormal peripheral blood count results (such as chronic obstructive pulmonary disease, cardiovascular disease, hematological abnormalities, malignant tumors, etc); (2) those who have a history of head injury, nervous system diseases, or other chronic diseases (such as infectious diseases, diabetes, hypertension, autoimmune diseases, etc); (3) those who take drugs that may interfere with peripheral blood levels (such as glucocorticoids, nonsteroidal anti-inflammatory drugs, antibiotics); (4) Leukocytosis (>11 × 10^9/L), leukopenia (<4 × 10^9/L), thrombocytosis (>450 × 10^9/L), thrombocytopenia (<150 × 10^9/L). A total of 103 first-time psychiatric patients were included in this study, including 52 male patients (50.4%) and 51 female patients (49.6%) aged 18–58. Additionally, there were 57 healthy controls.

This study was reviewed and approved by the Medical Ethics Committee of the Affiliated Psychological Hospital of Anhui Medical University (Ethics Number: HFSY-IRB-YJ-KYXM-ZXL). All participants had a clear understanding of the research purpose and signed informed consent forms.

Research Design

General Data Collection

Collect demographic data of enrolled individuals, including gender, age, height, weight, body mass index (BMI), years of education, and course of illness.

Peripheral Blood Cell Testing

Fasting venous blood samples were collected from the enrolled subjects the next day at 6–8 am and tested at the Laboratory of Anhui Provincial Mental Health Center. Blood routine analysis was performed using an automatic blood

analyzer (Mindray BC-2800, Shenzhen, China). We obtained serum white blood cell count (WBC), lymphocyte count, neutrophil count, monocyte count, and platelet count (PLT) data, and calculated: NLR=neutrophil count/lymphocyte count, PLR = platelet count/lymphocyte count.

Clinical Assessment

The Positive and Negative Syndrome Scale (PANSS) was used for evaluation, and a 5-factor model analysis was performed, including cognitive factors (P2, N5, N7, G10, G11), excitatory factors (P4, P7, G4, G8, G14), depressive factors (G2, G3, G6), negative factors (N1-N7), and positive factors (P1-P7). The evaluation was conducted by two psychiatric clinical physicians who have undergone consistency training; the higher the score, the greater the severity of the symptoms.

The Pittsburgh Sleep Quality Index (PSQI) was used, which was developed by psychiatrists at the University of Pittsburgh in 1989.[21] It consists of 9 questions, divided into 7 dimensions: sleep quality, sleep onset time, duration of sleep, sleep efficiency, sleep disorders, use of sleep medication, and daytime functional impairment. Each dimension is scored from 0 to 3, with a total score of 21 points. The higher the score, the lower the sleep quality.[22]

Data Analysis

SPSS 26.0 was used for statistical analysis. Normally distributed data were represented as mean ± standard deviation (x ±s), while skewed distribution data were represented as median (P25, P75). Measurement data that followed a normal distribution were compared between two groups using independent sample *t*-tests, while measurement data that did not follow a normal distribution were compared using Mann–Whitney *U*-tests. Count data were compared using chi-square tests, expressed as [n (%)]. The receiver operating characteristic (ROC) curve was used to predict the influencing factors on the prognosis of first-episode schizophrenia. A 95% confidence interval was used, and a difference of $P < 0.05$ was considered statistically significant.

Results

Comparison of General Information Between the Patient Group and the Control Group

The results showed that there was no significant difference in gender, age, BMI, and years of education between the patient group and the control group (all $P>0.05$), as shown in Table 1.

Comparison of Inflammatory Cells Between the Patient Group and the Control Group

The number of white blood cells, neutrophils, monocytes, NLR, and MLR in the patient group was significantly higher than those in the control group, and the differences were statistically significant (all $P<0.05$). The results are shown in Table 2.

Table 1 Comparison of General Information Between Patient Group and Control Group

Project	Patient Group	Control Group	P-value
Gender (eg male/female)	52/51	26/31	0.206
Age (years $\overline{X} \pm S$),	33.79 ± 10.18	32.75 ± 9.86	0.536
BMI (kg/m^2, $\overline{X} \pm S$)	22.37 ± 3.65	22.19 ± 2.80	0.726
Education years (years $\overline{X} \pm S$)	12.05 ± 3.67	12.82 ± 3.89	0.212
Disease duration (months $\overline{X} \pm S$)	4.37 ± 3.50	-	-

Note: - represents the absence of this data.
Abbreviation: BMI, the body mass index.

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Table 2 Comparison of Peripheral Blood Cell Differences Between the Patient Group and the Control Group

Group	Example Count	Peripheral Blood Cells [*M* (P_{25}, P_{75}), ^{109}]							
		WBC	Neutrophil Count	Lymphocyte Count	Monocyte Count	PLT	NLR	MLR	PLR
Patient group	103	7.47 (5.93,9.13)	4.84 (3.5,5.68)	1.97 (1.53,2.35)	0.49 (0.36,0.57)	213.29 (172,260)	2.68 (1.74,3.05)	0.28 (0.19,0.3)	117.91 (85.66140.78)
Control group	57	5.57 (4.49,6.28)	3.19 (2.38, 3.72)	1.91 (1.48,2.27)		210.12 (186,245)	1.77 (1.40,2.02)	0.17 (0.14,0.2)	188.53 (90.96136.48)
Z-value		−5.068	−5.831	−0.390	−6.585	−0.362	−4.762	−6.091	−5.068
P-value		<0.001**	<0.001**	0.696	<0.001**	0.718	<0.001**	<0.001**	0.547

Note: ** p<0.01.
Abbreviations: WBC, white blood cell count; PLR, platelet count; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Correlation Analysis Between WBC, Neutrophil Count, Monocyte Count, NLR, MLR, PANSS, and PSQI Scores in the Patient Group

The Spearman rank correlation results showed a negative correlation between monocyte count and sleep time factor (rs=−0.205, P=0.037), and MLR and excitatory factor (rs=−0.204, P=0.039), as shown in Table 3.

Multiple Linear Regression Analysis of Factors Affecting Excitability and Sleep Time in the Patient Group

Using variables with significant correlation in correlation analysis, ie, dividing excitatory factors as the dependent variable and MLR as the independent variable; PSQI sleep time is the dependent variable, and monocyte count is the independent variable. The results showed that MLR had a positive effect on excitatory factor scores (β=7.196, t=2.781, P=0.006); The number of monocytes has a negative impact on the sleep time factor score (β=−0.851, t=−2.157, P=0.033), as shown in Table 4.

Table 3 Correlation Between PANSS Scale, PSQI Scale and Peripheral Inflammatory Cells in Patient Group

group	NLR	MLR	WBC	Neutrophil Count	Monocyte Count
PANSS total score	−0.061	−0.190	0.138	0.104	−0.008
Cognitive factors	−0.010	−0.098	0.067	0.067	−0.011
Excitatory factor	−0.163	−0.204a	0.113	0.040	−0.007
Depressive factors	−0.138	−0.158	−0.069	−0.093	−0.179
Positive factors	−0.126	−0.102	0.117	0.057	0.100
Negative factors	0.106	−0.061	0.032	0.067	−0.092
PSQI total score	0.116	−0.041	0.050	0.056	−0.130
Sleep quality	0.046	−0.049	0.159	0.114	0.031
Sleep time	0.030	−0.045	−0.108	−0.086	−0.170
Sleep time	0.114	−0.039	−0.055	−0.013	−0.205 *
Sleep efficiency	0.040	0.002	−0.070	−0.056	−0.112
Sleep disorders	0.135	0.030	0.052	0.065	−0.081
Daytime Dysfunction	0.013	−0.024	0.075	0.049	−0.009

Note: *p<0.05;
Abbreviations: WBC, white blood cell count; L, lymphocyte count; PLR, platelet count; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 4 Multiple Linear Regression Analysis of Factors Affecting Excitability and Sleep Time in the Patient Group

Dependent Variable	Independent Variable	B	SE	β	T-value	P-value
Excitatory factor	Constant	7.807	2.632	-	2.966	0.003**
	MLR	7.196	2.588	0.24	2.781	0.006**
Sleep time	Constant	1.061	0.180	-	5.909	<0.001**
	Monocyte count	−0.851	0.395	−0.169	−2.157	0.033*

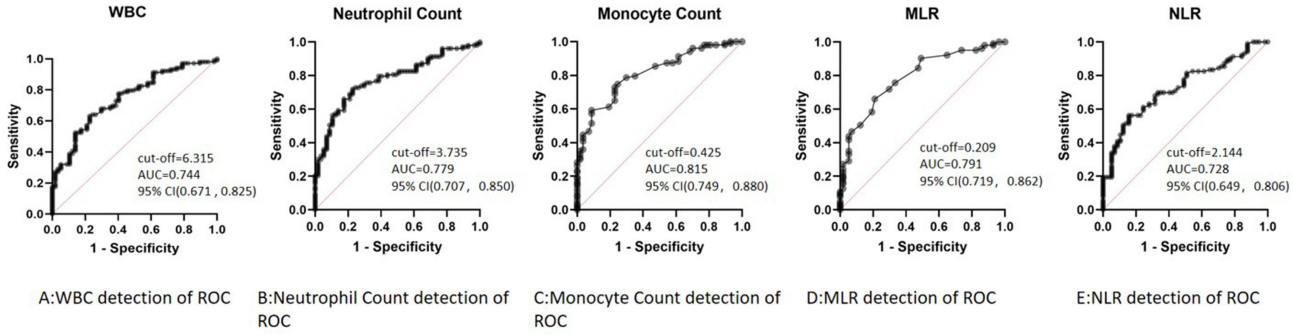
Notes: *p<0.05;** p<0.01.

ROC Curve Analysis of WBC, Neutrophil Count, Monocyte Count, NLR, and MLR in Predicting the Prognosis of SCZ

The number of white blood cells, neutrophils, monocytes, NLR, and MLR in the patient group was significantly higher than those in the control group. The ROC curve was used to evaluate these inflammatory cells that may affect the prognosis of SCZ. WBC was detected separately, with a cut-off value of 6.315, AUC=0.744, sensitivity of 0.631, and specificity of 0.768, 95% confidence interval (0.671, 0.825); neutrophil Count was detected separately, with a cut-off value of 3.735, AUC=0.779, sensitivity of 0.718, and specificity of 0.772, 95% confidence interval (0.707, 0.850); NLR detection alone, cut-off value 2.144, AUC=0.728, sensitivity 0.563, specificity 0.542, 95% confidence interval (0.649, 0.806); MLR alone detection, cut off value 0.209, AUC 0.791, sensitivity 0.650, specificity 0.807, 95% confidence interval (0.719, 0.862); monocyte count alone detection, cut-off value 0.425, AUC 0.815, sensitivity 0.592, specificity 0.912, 95% confidence interval (0.749, 0.880), as shown in Figure 1.

Discussion

Previous studies have focused on the role of inflammatory cells in the pathogenesis of schizophrenia, but less attention has been paid to their direct correlation with patients' sleep and psychiatric symptoms. The present study systematically investigated for the first time the correlation between monocyte count, MLR, and other inflammatory cell indices with sleep quality and psychiatric symptoms in patients with first-episode schizophrenia, filling a research gap in this field. Extensive research[23,24] has highlighted the pivotal role of inflammation in the pathophysiology of schizophrenia, where inflammatory factors are closely linked to alterations in brain structure and function.[25] Immune cell counts in peripheral blood are included in routine blood tests and represent an indicator of systemic immunity. The study of the relationship between peripheral immune cells in routine blood tests and the symptoms of schizophrenia can, on the one hand, strengthen the immune hypothesis of schizophrenia and, on the other hand, is simple and easy to perform, with good clinical application value.[26] Recent studies have reported elevated levels of white blood cells, neutrophils, lymphocytes, and monocytes in SCZ patients compared to healthy controls,[27] consistent with findings from our study. However, unlike previous studies, we further analyzed the correlation of these inflammatory cellular markers with patients' sleep quality and psychiatric symptoms and found that monocyte count and MLR were significantly correlated with patients' sleep disturbances and psychiatric symptom



A:WBC detection of ROC B:Neutrophil Count detection of ROC C:Monocyte Count detection of ROC D:MLR detection of ROC E:NLR detection of ROC

Figure 1 ROC curve analysis of leukocytes, neutrophils, monocytes, NLR and MLR to predict prognosis in SCZ.

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severity. These results not only complement existing studies on the role of inflammatory cells in schizophrenia but also provide new perspectives for understanding the potential link between inflammation and clinical symptoms.

In this study, there was a notable correlation between MLR and symptoms. MLR, reflecting the ratio of monocytes to lymphocytes, is particularly significant due to the role of lymphocytes in physiological stress and their regulatory function in the immune system.[28] Recent research has implicated B lymphocytes in the pathogenesis of schizophrenia,[29] with correlations identified between CD19+ and CD20+ B lymphocytes and schizophrenia.[30] These associations may be linked to the major histocompatibility complex (MHC) region on chromosome 6.[31] A recent international study involving 200 schizophrenia patients found positive correlations between MLR and NLR and negative symptoms, with a specific positive correlation with PRL in male patients.[27,32] The study revealed significantly higher counts of white blood cells, neutrophils, monocytes, NLR, and MLR in the patient group compared to the control group. Further investigation explored whether these inflammatory markers serve as predictive factors for schizophrenia. ROC curve analysis demonstrated that the AUC values for WBC, neutrophil count, monocyte count, NLR, and MLR were all greater than 0.7, indicating their potential to predict SCZ prognosis and further supporting the association between schizophrenia and inflammation.[9,33,34] The study focuses on patients with first-episode schizophrenia, a group with unique pathophysiologic characteristics and treatment responses during the disease process. Compared to chronic patients, studies of first-episode patients can reveal more clearly the relationship between inflammation and clinical symptoms in the early stages of the disease, providing new targets and ideas for early intervention and treatment. This study not only focuses on the quantitative analysis of inflammatory cells but also combines the detailed analysis of sleep quality assessment and psychiatric symptoms. Through the comprehensive multidimensional assessment, we revealed the potential link between inflammatory cells and clinical symptoms, providing new perspectives for understanding the complex pathomechanisms of schizophrenia.

Sleep impairment in SCZ patients is also related to the inflammatory hypothesis.[35] Studies have shown that reduced sleep time and sleep deprivation can increase inflammatory markers in SCZ patients.[36] Maintaining regular sleep habits and sufficient sleep can help improve the clinical status of SCZ patients by regulating their inflammatory response. Approximately, 46% of patients with mental disorders experience sleep abnormalities, such as early awakening, difficulties falling asleep, and reduced sleep quality.[37,38] Sleep deprivation can further exacerbate symptoms of schizophrenia, such as positive symptoms.[39] A recent study found that insomnia and inflammation were significantly associated among SCZ patients, with insomnia significantly correlated with elevated levels of interleukin-6 (IL-6) and leptin.[40] In this study, the monocyte count was found to be negatively correlated with sleep duration, consistent with previous findings linking elevated peripheral blood monocytes to changes in dopamine neurons in the brain, potentially contributing to rapid eye movement sleep behavior disorder (RBD) and impacting sleep duration.[41] Sleep and immunity share a bidirectional relationship,[42] immune system activation can influence sleep patterns, which in turn affects our body's innate and adaptive defense mechanisms. Disruptions in sleep can trigger abnormal increases in inflammatory responses,[43] illustrating the interplay between these two factors. It might be helpful to integrate the findings into particular neurobiological models, such as dopaminergic or cytokine-mediated pathways. It may be helpful to incorporate findings into specific neurobiological models, such as dopaminergic-mediated pathways. For example, sleep deprivation induces dopaminergic pathways that control mood,[44] and dopamine signaling in the basolateral amygdala initiates rapid eye movement sleep in mice.[45] Inflammation can affect dopamine release,[46] suggesting a complex interaction between inflammation and the dopaminergic system that may regulate sleep and mood states by affecting dopamine synthesis and release.

Several limitations of the present study are worth noting. First, all the data in this study came from peripheral blood cell counts without other inflammatory markers. Inflammatory factors (eg, C-reactive protein, interleukin, tumor necrosis factor, etc.) are more intuitively reflective of a patient's inflammatory state than inflammatory cells, and we will add these data to subsequent studies, which may provide more information about the link between sleep and inflammation. Second, the present study was a cross-sectional study, and it was not possible to observe the pattern of change with disease duration between immune indicators and symptoms and sleep, obvious correlations do not guarantee causality, and further studies can be conducted subsequently to illustrate the dynamic pattern of change among the three. Third, a limitation of this study was the inadequate sample size; the smaller sample size may have limited the statistical efficacy of the findings, thus affecting the significance level of certain analyses; future studies need to expand the sample size to validate the findings of this study and to further explore the relationship between inflammatory cellular markers and clinical symptoms.

This study found that improving the inflammatory response in patients with schizophrenia may help control symptoms and treat insomnia, which has important implications for the prevention and treatment of the disorder.[47] Future research can explore several promising directions. For instance, longitudinal studies can help elucidate the temporal relationships between inflammation, sleep, and schizophrenia symptoms, providing insights into the potential causality. Additionally, investigating pro-inflammatory cytokine levels, which are known to be altered in schizophrenia,[48] can offer a more detailed understanding of the inflammatory processes involved.[49,50] This could include studying how changes in cytokine levels over time correlate with symptom fluctuations and sleep quality. These future directions hold the potential to deepen our understanding of the complex interplay between sleep, inflammation, and schizophrenia, ultimately leading to more effective prevention and treatment strategies.

Conclusion

In summary, significant differences in peripheral blood cells exist between patients with schizophrenia and healthy controls, which may contribute to psychiatric symptoms and disturbances in sleep patterns among SCZ patients. Enhancing the management of inflammatory responses in individuals with schizophrenia could potentially mitigate symptoms and address insomnia, thereby offering substantial implications for disease prevention and treatment strategies.

Abbreviations

SCZ, schizophrenia; WBC, white blood cell count; N, neutrophil count; L, lymphocyte count; M, monocyte count; PLR, platelet count; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Data Sharing Statement

The data that support the findings of this study are available from Hefei Fourth People's Hospital but restrictions apply to the availability of those data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Hefei Fourth People's Hospital. To obtain the data in this study, the researchers may be contacted at dn980409@163.com.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of The Anhui Mental Health Centre. Informed consent was obtained from all the subjects. The trial registration number was HFSY-IRB-YJ-KYXM-ZXL. All procedures carried out in studies conformed to the 1964 helsinki Declaration and its subsequent amendments or similar ethical standards.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest.

References

1. Uludag K, Wang DM, Goodman C, Chen DC, Wang L, Zhang X. Prevalence, clinical correlates and risk factors associated with Tardive Dyskinesia in Chinese patients with schizophrenia. *Asian J Psychiatr*. 2021;66:102877. doi:10.1016/j.ajp.2021.102877
2. Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. *Lancet*. 2022;399(10323):473–486. doi:10.1016/S0140-6736(21)01730-X
3. GBDMD C. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Psychiatry*. 2022;9(2):137–150.
4. Uludag K. The Relationship Between Air Pollution and Severity of Schizophrenia Symptoms. In: Moumtzoglou AS, editor. *Convergence of Population Health Management, Pharmacogenomics, and Patient-Centered Care*. Hershey, PA, USA: IGI Global; 2025:43–58.
5. Patlola SR, Donohoe G, McKernan DP. The relationship between inflammatory biomarkers and cognitive dysfunction in patients with schizophrenia: a systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psych*. 2023;121:110668. doi:10.1016/j.pnpbp.2022.110668
6. Ullah I, Awan HA, Aamir A, et al. Role and perspectives of inflammation and C-reactive protein (CRP) in psychosis: an economic and widespread tool for assessing the disease. *Int J mol Sci*. 2021;22(23):13032. doi:10.3390/ijms222313032
7. Bishop JR, Zhang L, Lizano P. Inflammation subtypes and translating inflammation-related genetic findings in schizophrenia and related psychoses: a perspective on pathways for treatment stratification and novel therapies. *Harv Rev Psychiatry*. 2022;30(1):59–70. doi:10.1097/HRP.0000000000000321
8. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. *Bratisl Lek Listy*. 2021;122(7):474–488. doi:10.4149/BLL_2021_078
9. Ozdin S, Boke O. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. *Psychiatry Res*. 2019;271:131–135. doi:10.1016/j.psychres.2018.11.043
10. Avcil S. Evaluation of the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and mean platelet volume as inflammatory markers in children with attention-deficit hyperactivity disorder. *Psychiatry Clin Neurosci*. 2018;72(7):522–530. doi:10.1111/pcn.12659
11. Bhikram T, Sandor P. Neutrophil-lymphocyte ratios as inflammatory biomarkers in psychiatric patients. *Brain Behav Immun*. 2022;105:237–246. doi:10.1016/j.bbi.2022.07.006
12. Frota IJ, de Oliveira ALB, De Lima DN Jr, et al. Decrease in cognitive performance and increase of the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios with higher doses of antipsychotics in women with schizophrenia: a cross-sectional study. *BMC Psychiatry*. 2023;23(1):558. doi:10.1186/s12888-023-05050-x
13. Korkmaz SA, Kizgin S, Oguz EF, Neselioglu S, Erel O. Thiol-disulphide homeostasis, ischemia-modified albumin, complete blood count-derived inflammatory markers and C-reactive protein from acute mania to early remission in bipolar disorder. *J Affect Disord*. 2023;339:426–434. doi:10.1016/j.jad.2023.07.079
14. Yamazaki EM, Antler CA, Lasek CR, Goel N. Residual, differential neurobehavioral deficits linger after multiple recovery nights following chronic sleep restriction or acute total sleep deprivation. *Sleep*. 2021;44(4). doi:10.1093/sleep/zsaa224
15. Kalin NH. Depression and schizophrenia: sleep, medical risk factors, biomarkers, and treatment. *Am J Psychiatry*. 2021;178(10):881–884. doi:10.1176/appi.ajp.2021.21080824
16. Yin J, Gong R, Zhang M, et al. Associations between sleep disturbance, inflammatory markers and depressive symptoms: mediation analyses in a large NHANES community sample. *Prog Neuropsychopharmacol Biol Psych*. 2023;126:110786. doi:10.1016/j.pnpbp.2023.110786
17. Zielinski MR, Systrom DM, Fatigue RNR. Sleep, and autoimmune and related disorders. *Front Immunol*. 2019;10:1827.
18. Lee EE, Ancoli-Israel S, Eyler LT, et al. Sleep disturbances and inflammatory biomarkers in schizophrenia: focus on sex differences. *Am J Geriatr Psychiatry*. 2019;27(1):21–31. doi:10.1016/j.jagp.2018.09.017
19. Mazza MG, Tringali AGM, Rossetti A, Botti RE, Clerici M. Cross-sectional study of neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in mood disorders. *Gen Hosp Psychiatry*. 2019;58:7–12. doi:10.1016/j.genhosppsych.2019.02.003
20. Fang SH, Suzuki K, Lim CL, Chung MS, Ku PW, Chen LJ. Associations between sleep quality and inflammatory markers in patients with schizophrenia. *Psychiatry Res*. 2016;246:154–160. doi:10.1016/j.psychres.2016.09.032
21. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193–213. doi:10.1016/0165-1781(89)90047-4
22. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh Sleep Quality Index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. *Sleep Med Rev*. 2016;25:52–73. doi:10.1016/j.smrv.2015.01.009
23. Sun HL, Bai W, Li XH, et al. Schizophrenia and inflammation research: a bibliometric analysis. *Front Immunol*. 2022;13:907851. doi:10.3389/fimmu.2022.907851
24. Muller N. Inflammation in schizophrenia: pathogenetic aspects and therapeutic considerations. *Schizophr Bull*. 2018;44(5):973–982. doi:10.1093/schbul/sby024
25. Williams JA, Burgess S, Suckling J, et al. Inflammation and brain structure in schizophrenia and other neuropsychiatric disorders: a Mendelian randomization study. *JAMA Psychiatry*. 2022;79(5):498–507. doi:10.1001/jamapsychiatry.2022.0407
26. Hartwig FP, Borges MC, Horta BL, Bowden J, Davey Smith G. Inflammatory biomarkers and risk of schizophrenia: a 2-sample Mendelian randomization study. *JAMA Psychiatry*. 2017;74(12):1226–1233. doi:10.1001/jamapsychiatry.2017.3191
27. Sagud M, Madzarac Z, Nedic Erjavec G, et al. The associations of neutrophil-lymphocyte, platelet-lymphocyte, monocyte-lymphocyte ratios and immune-inflammation index with negative symptoms in patients with schizophrenia. *Biomolecules*. 2023;13(2). doi:10.3390/biom13020297.
28. Waldron JA Jr, Dohring EJ, Farber LR. Primary large cell lymphomas of the mediastinum: an analysis of 20 cases. *Semin Diagn Pathol*. 1985;2(4):281–295.
29. van Mierlo HC, Broen JCA, Kahn RS, de Witte LD. B-cells and schizophrenia: a promising link or a finding lost in translation? *Brain Behav Immun*. 2019;81:52–62. doi:10.1016/j.bbi.2019.06.043
30. Printz DJ, Strauss DH, Goetz R, et al. Elevation of CD5+ B lymphocytes in schizophrenia. *Biol Psychiatry*. 1999;46(1):110–118. doi:10.1016/S0006-3223(98)00307-2
31. Khandaker GM, Dantzer R, Jones PB. Immunopsychiatry: important facts. *Psychol Med*. 2017;47(13):2229–2237. doi:10.1017/S0033291717000745

32. Zhou X, Wang X, Li R, et al. Neutrophil-to-lymphocyte ratio is independently associated with severe psychopathology in schizophrenia and is changed by antipsychotic administration: a large-scale cross-sectional retrospective study. *Front Psychiatry*. 2020;11:581061. doi:10.3389/fpsyt.2020.581061
33. Jackson AJ, Miller BJ. Meta-analysis of total and differential white blood cell counts in schizophrenia. *Acta Psychiatr Scand*. 2020;142(1):18–26. doi:10.1111/acps.13140
34. Juchnowicz D, Dzikowski M, Rog J, et al. The usefulness of a complete blood count in the prediction of the first episode of schizophrenia diagnosis and its relationship with oxidative stress. *PLoS One*. 2023;18(10):e0292756. doi:10.1371/journal.pone.0292756
35. Zielinski MR, Gibbons AJ. Neuroinflammation, sleep, and circadian rhythms. *Front Cell Infect Microbiol*. 2022;12:853096. doi:10.3389/fcimb.2022.853096
36. Cosgrave J, Wulff K, Gehrman P. Sleep, circadian rhythms, and schizophrenia: where we are and where we need to go. *Curr Opin Psychiatry*. 2018;31(3):176–182. doi:10.1097/YCO.0000000000000419
37. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA*. 1989;262(11):1479–1484. doi:10.1001/jama.1989.03430110069030
38. Chiu VW, Ree M, Janca A, Iyyalol R, Dragovic M, Waters F. Sleep profiles and CBT-I response in schizophrenia and related psychoses. *Psychiatry Res*. 2018;268:279–287. doi:10.1016/j.psychres.2018.07.027
39. Miller BJ, McCall WV. Meta-analysis of insomnia, suicide, and psychopathology in schizophrenia. *Curr Opin Psychiatry*. 2023;36(3):156–165. doi:10.1097/YCO.0000000000000856
40. Miller BJ, McCall WV, McEvoy JP, Lu XY. Insomnia and inflammation in Phase 1 of the clinical antipsychotic trials of intervention effectiveness study. *Psychiatry Res*. 2021;305:114195. doi:10.1016/j.psychres.2021.114195
41. Farmen K, Nissen SK, Stokholm MG, et al. Monocyte markers correlate with immune and neuronal brain changes in REM sleep behavior disorder. *Proc Natl Acad Sci U S A*. 2021;118(10). doi:10.1073/pnas.2020858118.
42. Besedovsky L, Lange T, Haack M. The sleep-immune crosstalk in health and disease. *Physiol Rev*. 2019;99(3):1325–1380. doi:10.1152/physrev.00010.2018
43. Irwin MR. Sleep and inflammation: partners in sickness and in health. *Nat Rev Immunol*. 2019;19(11):702–715. doi:10.1038/s41577-019-0190-z
44. Wu M, Zhang X, Feng S, et al. Dopamine pathways mediating affective state transitions after sleep loss. *Neuron*. 2024;112(1):141–154e148. doi:10.1016/j.neuron.2023.10.002
45. Hasegawa E, Miyasaka A, Sakurai K, Cherasse Y, Li Y, Sakurai T. Rapid eye movement sleep is initiated by basolateral amygdala dopamine signaling in mice. *Science*. 2022;375(6584):994–1000. doi:10.1126/science.abl6618
46. de Bartolomeis A, Barone A, Vellucci L, et al. Linking inflammation, aberrant glutamate-dopamine interaction, and post-synaptic changes: translational relevance for schizophrenia and antipsychotic treatment: a systematic review. *MOL NEUROBIOL*. 2022;59(10):6460–6501. doi:10.1007/s12035-022-02976-3
47. Zhang H, Zhang L, Liu Z, Ma J. Prevalence and clinical correlates of autistic features in patients with initial-treatment and drug-naive schizophrenia. *Alpha Psych*. 2024;25(5):611–616. doi:10.5152/alphapsychiatry.2024.241626
48. Na KS, Jung HY, Kim YK. The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia. *Prog Neuropsychopharmacol Biol Psych*. 2014;48:277–286. doi:10.1016/j.pnpbp.2012.10.022
49. Zhang Y, Wang J, Ye Y, et al. Peripheral cytokine levels across psychiatric disorders: a systematic review and network meta-analysis. *Prog Neuropsychopharmacol Biol Psych*. 2023;125:110740. doi:10.1016/j.pnpbp.2023.110740
50. Halstead S, Siskind D, Amft M, et al. Alteration patterns of peripheral concentrations of cytokines and associated inflammatory proteins in acute and chronic stages of schizophrenia: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2023;10(4):260–271. doi:10.1016/S2215-0366(23)00025-1