Journal of Basic Research in Medical Sciences

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Ilam University of Medical Sciences Publications

Effect of Risperidone Treatment on Hematological Indices in Schizophrenia Patients

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Article Info

Article type:
Original Article

Article History:
Received: Jun. 07, 2026
Revised: Jul. 21, 2026
Accepted: Aug. 02, 2026
Published Online: Sep. 19, 2026

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A B S T R A C T

Introduction: Schizophrenia (SCZ) is a complex psychiatric disorder of unknown pathogenesis, characterized by a spectrum of cognitive, behavioral, and emotional dysfunctions. Recent studies have shown that SCZ is associated with immunological and hematological alterations. These alterations offer potential insights into the underlying biological mechanisms and may serve as biomarkers for diagnosis or therapeutic targets. Nonetheless, the relationship between these alterations and antipsychotic medications remains unclear. This study aimed to evaluate the effects of risperidone treatment on hematological inflammatory indices, complete blood count (CBC), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume-to-lymphocyte ratio (MPVLR) in patients with schizophrenia.

Materials & Methods: The study group consisted of 44 SCZ and 44 age- and sex-matched healthy controls. Blood samples were collected from SCZ patients before and after three months of treatment, as well as from healthy individuals. In pre-treatment, risperidone monotherapy, and healthy control groups, CBC was performed, and PLR, NLR, and MPVLR were calculated. Clinical symptoms were evaluated by the Positive and Negative Syndrome Scale (PANSS) before and after treatment.

Results: Despite the reduction of NLR and PLR ($p < 0.001$ and $p = 0.007$, respectively), PLR remained significantly higher in post-treatment patients than in the healthy control group ($p = 0.01$). Given the NLR factor, no significant difference was observed between healthy control and post-treatment groups. There were no significant differences in the MPVLR factor among the three groups.

Conclusion: The findings of this study suggest that risperidone therapy resulted in a reduction in NLR and PLR changes with improvement in symptoms, indicating its immunomodulatory effects in SCZ treatment. Such an inexpensive CBC-derived ratio may be considered a monitoring biomarker for treatment responses.

Keywords: Antipsychotic; NLR; PLR; MPVLR; Schizophrenia

➢ **Cite this paper**
Azizi E, Sharifi Z, Mozafari A, Yarhosseini A, Noori-Zadeh A, Shsrifi A, Seidkhani-Nahal A. Effect of Risperidone Treatment on Hematological Indices in Schizophrenia Patients. *J Bas Res Med Sci*. 2026; 13(4):19-28.

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Introduction

Schizophrenia (SCZ) is a complex, severe psychiatric disorder of unknown etiology, manifested by a spectrum of behavioral, emotional, and cognitive dysfunctions (1). Besides the traditional neurochemical hypotheses (2), a large body of evidence suggests critical roles of chronic inflammation and immunity dysfunction in SCZ pathogenesis (3). This inflammatory background is evidenced in the correlation of inflammatory markers with the severity of symptoms, with possible implications in cognitive impairment (4). Moreover, co-administration of antipsychotics with anti-inflammatory agents can improve the clinical outcomes, hypothesizing interplay between immune pathways and therapeutic response (5, 6). Consequently, peripheral inflammatory markers can be considered for therapeutic/diagnostic targets in SCZ.

Although cytokine measurement is often costly and time-consuming, Cell Blood Count (CBC)-derived hematological indices, particularly the Neutrophil-to-Lymphocyte Ratio (NLR) (7) and Platelet-to-Lymphocyte Ratio (PLR) (8), have been suggested as robust, inexpensive biomarkers of systemic inflammation. The NLR supports the possibility of a balance between neutrophil-mediated innate immunity and lymphocyte-mediated acquired immunity, suggesting higher stability than absolute cell counts during chronic immune dysfunction (7). In a similar manner, platelets that play a crucial role in hemostasis and inflammation regulate the recruitment of leukocytes and endothelial function (9); hence, PLR can be considered a prothrombotic and inflammatory marker.

The prognostic value of CBC-derived ratios has been emphasized in different medical conditions (10-14) with progressive investigation in psychiatric disorders (15-18). Higher levels of NLR and PLR have been reported in major depression (19), bipolar disorder (20), and SCZ (21), with a likely correlation in psychopathology severity and cognitive deficits. Of note, NLR may decrease upon antipsychotic treatment and clinical stabilization, according to some longitudinal studies (22-24). This may explain the dynamic involvement of immune-inflammatory pathways in the clinical course of SCZ, which may be modulated by pharmacotherapy.

Key questions still remain despite such promising evidence. The specific effect of individual antipsychotic medications, such as risperidone, on these hematological indices is not well-characterized. Moreover, examined patients in many studies had prior exposure to therapy, which potentially confounds the baseline inflammation. Thus, longitudinal studies are implicated to monitor the changes in NLR, PLR, and other potential indices, including the mean Platelet Volume-to-Lymphocyte Ratio (MPVLR), during a pre-treatment state to a specific period of antipsychotic treatment.

Therefore, the current study was aimed at matched case-control longitudinal analysis of NLR, PLR, and MPVLR changes in pre-treatment SCZ patients before and after a 3-month period of risperidone monotherapy. Accordingly, we sought to address possible relations between such biomarkers, SCZ pathophysiology, and immunomodulatory effects of a common antipsychotic.

Materials and methods

Study Design

This study employed a longitudinal controlled design combining a case-control comparison with a prospective pre-post assessment. Forty-four (n=44) pre-treatment patients meeting the Diagnostic and Statistical Manual of Mental Disorders (2019-2025), Fourth Edition (DSM-IV) criteria for SCZ were recruited. Diagnosis was confirmed by a panel of consulting psychiatrists. A similar number of healthy volunteers as control group (n=44). Pre-treatment patients with schizophrenia were compared with age- and sex-matched healthy controls, while longitudinal changes in

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hematological inflammatory indices were evaluated in the patient group before and after three months of risperidone monotherapy.

Setting and Participants

Forty-four (n=44) pre-treatment patients meeting the Diagnostic and Statistical Manual of Mental Disorders (2019-2025), Fourth Edition (DSM-IV) criteria for SCZ were recruited. Diagnosis was confirmed by a panel of consulting psychiatrists. A similar number of healthy volunteers as control group (n=44). Pre-treatment patients with schizophrenia were compared with age- and sex-matched healthy controls.

Control subjects were screened to ensure no personal or first-degree family history of major psychiatric disorders, no use of psychotropic medications (antidepressants, antipsychotics, mood stabilizers) within the three months preceding the study, and normal levels of C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR). Acute infection, allergic reaction, or inflammatory condition within four weeks prior to blood sampling, chronic medical illnesses known to alter immune function (e.g., autoimmune diseases, inflammatory bowel disease, immunodeficiency disorders), history of alcohol or substance abuse disorder (as per DSM-IV criteria), and use of any non-psychotropic medication with known immunomodulatory effects (e.g., corticosteroids, immunosuppressants) during the study period were exclusion criteria.

Sample Size

Forty-four (n=44) pre-treatment patients meeting the Diagnostic and Statistical Manual of Mental Disorders (2019-2025), Fourth Edition (DSM-IV) criteria for SCZ were recruited. Diagnosis was confirmed by a panel of consulting psychiatrists. A similar number of healthy volunteers as control group (n=44).

Randomization & Blinding

Pre-treatment patients with schizophrenia were compared with age- and sex-matched healthy controls, while longitudinal changes in hematological inflammatory indices were evaluated in the patient group before and after three months of risperidone monotherapy

Measurements & Validity and Reliability

Positive and Negative Syndrome Scale (PANSS)

The Positive and Negative Syndrome Scale (PANSS) was used to assess psychopathology by a trained psychiatrist at baseline (pre-treatment) and following 3 months of risperidone therapy (post-treatment).

Complete Blood Count (CBC)

Also, an automated hematology analyzer (SysMex Kx21N, USA) was used to evaluate a Complete Blood Count (CBC), including White Blood Cell count (WBC), neutrophil count, lymphocyte count, monocyte count, platelet count, Mean Platelet Volume (MPV), and Platelet Distribution Width (PDW).

Inflammatory Indices

The inflammatory indices were primarily extracted from CBC data, as follows: (a) NLR: absolute neutrophil count / absolute lymphocyte count; (b) PLR: absolute platelet count / absolute lymphocyte count; and (c) MPVLR: mean platelet volume (MPV) / absolute lymphocyte count.

Intervention

Monotherapy was initiated with risperidone (generic, Sobhan Daroo Co.) in enrolled patients. The dosage determination was relied on tolerability and clinical response, with mean of 5 mg (range: 2-8 mg) daily dose during the study period. The duration of treatment was 3 months. The Positive and Negative Syndrome Scale (PANSS) was used to assess psychopathology by a trained psychiatrist at

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baseline (pre-treatment) and following 3 months of risperidone therapy (post-treatment).

Statistical and Data Analysis

The SPSS statistical software was used for data analysis. The Shapiro-Wilk test was performed to assess data distribution normality. Continuous variables were expressed as mean ± standard deviation (SD) and Median±IQR. The one-way ANOVA, Student's t and chi square tests were used for baseline analysis. The Kruskal-Wallis H test followed by post-hoc Dunn's Pairwise Comparison (Bonferroni) test were used to compare three independent groups, while Wilcoxon signed-rank test was used between patient groups. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 44 pre-treatment patients with schizophrenia and 44 age- and sex-matched healthy controls were enrolled in the study. Baseline demographic characteristics, including age and sex distribution, as well as PANSS scores before and after treatment, are presented in Table 1. No significant differences were observed between patients and healthy controls regarding age or sex, confirming appropriate matching between the two groups. Changes in PANSS scores following risperidone treatment are presented in Table 1. Significant reductions were observed in the Positive, Negative, General Psychopathology, and Total PANSS scores after three months of treatment compared with baseline (all $P < 0.05$), suggesting a marked improvement in clinical symptoms.

Table 1. Baseline demographic characteristics of study participants and clinical characteristics (PANSS scores) of patients with schizophrenia before and after risperidone treatment.

Characteristic	Patients Before Treatment (n=44)	Patients After Treatment (n=44)	Healthy Controls (n=44)	P value
Demographic characteristics				
Age (years), Mean ± SD	29.40 ± 5.80	29.40 ± 5.80	29.49 ± 5.21	0.951
Male, n (%)	31 (70.45)	31 (70.45)	29 (65.91)	0.617
Female, n (%)	13 (29.55)	13 (29.55)	15 (34.09)	----
Clinical characteristics (PANSS)				
Positive score	22.72 ± 4.60	15.03 ± 5.30	—	<0.001
Negative score	19.43 ± 4.10	13.93 ± 5.07	—	0.002
General psychopathology score	42.45 ± 6.55	30.11 ± 5.45	—	<0.001
Total PANSS score	84.60 ± 15.28	59.04 ± 15.85	—	<0.001

Quantitative and qualitative variables were presented as mean ± SD and number (percent), respectively. Quantitative and qualitative variables were compared between three groups using one-way ANOVA, Student's t, and chi-square tests, respectively. The significance level was considered 0.05. PANSS, Positive and Negative Syndrome Scale; SD, Standard Deviation.

The complete hematological profile and inflammatory indices for pre- and post-treatment groups as well as the control group are tabulated in Table 2. It was noteworthy that pre-treated patients had the highest median (IQR) values for NLR and PLR (Table 2).

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Table 2. Hematological Parameters and Inflammatory Indices Across Study Groups (n=44).

Variable	Pre-treatment, (Median±IQR) [b]	Post-treatment, (Median±IQR)	Healthy Controls (Median±IQR)	p-value*
WBC (10^3/µl)	7.46 ± 2.15	5.80 ± 1.80	6.00 ± 90	<0.001
Neutrophil	4.90 ± 2.08	3.49 ± 1.21	3.80 ± 0.88	<0.001
Lymphocyte	1.90 ± 0.53	2.03 ± 0.67	1.99 ± 0.18	0.31
Platelet [a], (mean±SD)	242.14 ± 49.65	207.18 ± 54.00	240.36 ± 34.00	<0.001
MPV (fl)	7.86 ± 2.13	9.10 ± 0.77	8.84 ± 1.92	<0.001
NLR	2.49 ± 0.85	1.70 ± 0.71	1.95 ± 0.48	<0.001
PLR	127.86 ± 78.10	97.70 ± 55.12	124.52 ± 23.86	0.01
MPVLR	4.09 ± 1.74	4.55 ± 1.89	4.41 ± 0.96	0.09

*Variables were compared between three groups using Kruskal-Wallis test.
a Variable was compared between three groups using one-way ANOVA. b Interquartile range

Risperidone monotherapy for 3 months caused a statistically remarkable reduction in the examined inflammatory indices, including NLR (P = 0.002) and PLR (P = 0.04). This resulted from a substantial reduction in absolute neutrophil (P = 0.002) and platelet count (P = 0.004), with a non-significant elevation in lymphocyte number (P = 0.32). Also, a remarkable increase in MPV was reported (P < 0.001) (Table 3).

Table 3. Pre- and Post-Treatment Comparison in Schizophrenia Patients (n=44).

Variable	Pre-treatment (Median±IQR) [a]	Post-treatment (Median±IQR)	p-value*
NLR	2.49 ± 0.05	1.69 ± 0.68	0.002
PLR	127.86 ± 78.10	97.55 ± 54.09	0.04
MPVLR	4.09 ± 1.74	4.55 ± 1.87	0.04
Neutrophil	4.90 ± 2.08	3.48 ± 1.15	0.002
Platelet	242.14 ± 49.65	207.18 ± 53.99	0.004**
MPV	7.86 ± 2.13	9.10 ± 0.80	<0.001

*Wilcoxon signed-rank test. ** paired t test. a Interquartile range

Significant differences were observed among the experimental groups for both NLR (χ^2 = 24.73, p < 0.001) and PLR (χ^2 = 8.83, p = 0.01), based on the Kruskal-Wallis test, while it was non-significant for MPVLR (χ^2 = 4.80, p = 0.09) (Table 4).

Table 4. Pairwise Comparisons of NLR and PLR Between Groups using Dunn's Pairwise Comparison (Bonferroni).

Comparison	Z-statistic	p-value (Adjusted)
NLR: Pre-treatment vs. Post-treatment	4.05	<0.001
NLR: Pre-treatment vs. Control	4.63	<0.001
NLR: Post-treatment vs. Control	-0.67	0.51
PLR: Pre-treatment vs. Post-treatment	2.70	0.007
PLR: Pre-treatment vs. Control	0.70	0.48
PLR: Post-treatment vs. Control	-2.57	0.01

Regarding NLR and upon post-hoc pairwise comparison, significantly higher levels were reported in pre-treated patients than in post-treatment and healthy controls (P < 0.001). With respect to PLR, the pre-treatment group showed remarkably higher PLR, comparable to the post-treatment group (P = 0.007). Moreover, unlike NLR, post-treatment PLR was substantially higher than in

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the control (P = 0.04). Pre-treatment and control showed no statistically significant difference (P = 0.48).

Discussion

The aim of this study was to evaluate the effects of risperidone monotherapy on inflammatory hematological indices in patients with schizophrenia. Principal results included: (1) there was a significant drop in both the NLR and the PLR; (2) the NLR decreased to the same levels seen in healthy controls, but although the PLR was lower than before, it had higher levels than those seen among healthy people; and (3) there was no difference in the MPVLR. These findings further support the association between systemic inflammation and schizophrenia (25, 26), but they also suggest that the immunomodulatory effects of risperidone may differ from those of other antipsychotic medications.

The elevated NLR and PLR observed in untreated patients are consistent with multiple studies that have associated the SCZ with inflammation (27, 28). The mean value of NLR (2.49 ± 0.73) in our study was in line with previously published studies reporting high levels of NLR in SCZ patients when compared to controls (29). The most significant finding was that NLR levels decreased to healthy control levels after three months of risperidone treatment.

This finding is consistent with previous longitudinal studies reporting reductions in NLR following antipsychotic treatment (30, 31). In the present study, the decrease in NLR after risperidone treatment was associated with reductions in absolute neutrophil count and the normalization of NLR toward healthy control levels. These findings suggest a potential influence of risperidone treatment on systemic inflammatory status; however, the study design does not allow confirmation of direct anti-inflammatory effects.

The trajectory of PLR indicates that the results are subtler than anticipated. While risperidone lowered PLR values during treatment, they remained significantly higher than those seen in healthy controls after treatment. The persistence of elevated PLR levels after treatment, compared with healthy controls, suggests that certain pro-inflammatory or pro-thrombotic pathways reflected by platelet-related inflammatory indices may be less responsive to short-term antipsychotic treatment. Platelets are active participants in the inflammatory process and can release cytokines and chemokines that have the potential to alter endothelial cell and immune function (32). Our findings are consistent with evidence suggesting that platelets exhibit altered activation in individuals with schizophrenia (32) and that PLR may relate to a different aspect of immune dysregulation than NLR. The persistent alteration in PLR may relate to the increased incidence of cardiovascular disease that occurs in individuals with schizophrenia and merits further study.

The absence of a statistically significant difference in MPVLR between groups suggests that this composite index was not markedly affected during the study period. Although MPV increased after treatment despite a reduction in platelet count, this finding should be interpreted with caution because MPV is an indirect marker of platelet characteristics and does not necessarily indicate increased platelet reactivity. In addition, the observed changes may have been influenced by biological variability or unmeasured confounding factors. Therefore, the present findings should be considered observational and hypothesis-generating rather than evidence of a causal effect of risperidone on platelet function.

A practical advantage of NLR and PLR is that they can be readily calculated from routine CBCs at minimal cost compared with cytokine assays (33). In addition, the reduction in these indices accompanied the improvement in PANSS scores, suggesting that they may serve as accessible state-dependent biomarkers of psychopathology. These indices are

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clinically relevant because they have been associated with key features of schizophrenia.

NLR has been related to negative symptom severity and cognitive impairment (34, 35), while PLR has been related to cognitive impairment in both psychiatric and neurologic disorders (36).

There are both strengths and limitations in the current study. The strengths of this study include its longitudinal retrospective design, the inclusion of pre-treatment baseline measurements, the use of standardized antipsychotic monotherapy, and a well-matched healthy control group.

The main limitations include the relatively small sample size and the short follow-up period of three months. Furthermore, risperidone dosage was individualized according to clinical response rather than standardized across participants, which may have contributed to variability in treatment effects. Moreover, no formal adjustment for multiple comparisons was performed; therefore, the statistical findings should be interpreted with appropriate caution. A longer follow-up period would help determine whether PLR eventually returns to baseline or whether the changes are maintained throughout longer observation periods. We also did not measure inflammatory cytokines such as IL-6 and TNF-α to see whether they correspond to the hematological indices, nor did we control for some possible confounding variables, such as diet, smoking, or physical exercise, which can affect inflammatory markers. Finally, because only risperidone was evaluated in this study, the results may not be generalizable to other antipsychotics that have a different receptor profile than risperidone. The significant reduction in PANSS scores observed after three months of risperidone treatment indicates a marked improvement in clinical symptom severity. The concurrent reduction in NLR and PLR suggests that these readily available hematological inflammatory indices may parallel clinical improvement and could serve as practical biomarkers for monitoring treatment response in schizophrenia. However, larger prospective studies are needed to confirm their clinical utility.

Limitations and Strengths

The discussion is systematic, properly links the study's results to previous evidence and provides a balanced assessment of the different response patterns of NLR and PLR to risperidone treatment. It also considers the limitations of the observational design. Furthermore, the clinical importance of cheap inflammatory indices obtained from the complete blood count (CBC) is clearly highlighted. However, the discussion is focused on the potential role of NLR and PLR, as biomarkers of treatment response, without evidence of causality or predictive analyzes. Moreover, the possible impact of important confounding factors like smoking, BMI, metabolic status and lifestyle, do not sufficiently support the interpretation of the findings, and therefore many mechanistic explanations about immune modulation and platelet activation are still speculative. This is because inflammatory cytokines and platelet function were not directly measured.

Conclusion

Risperidone monotherapy for three months was associated with significant reductions in NLR and PLR in pre-treatment patients with schizophrenia, whereas the changes in MPVLR were not statistically significant. These findings support the presence of altered inflammatory status in schizophrenia and suggest that selected CBC-derived inflammatory indices may be useful for monitoring immune-inflammatory changes during antipsychotic treatment. Larger prospective studies with longer follow-up and comprehensive clinical assessments are needed to further clarify the clinical significance of these biomarkers.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The study was funded by the Ilam University of Medical Sciences, Iran.

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CRediT authorship contribution statement

Conceptualization, Methodology, Validation: EA, ZS, AM, Formal Analysis, Investigation, Resources, Software: AN, AS, Data Curation, Writing–Original Draft Preparation, Writing–Review & Editing, Visualization, Supervision, Project Administration: EA, ASN.

Declaration of Generative AI and AI-assisted technologies in the writing process

Artificial intelligence was not used in any of the stages of design, implementation, calculations, interpretation, conclusion, or writing of this work.

Conflict of interest

All authors declare that they have no conflict of interest.

Ethical considerations

This study was adhered to the principles of the Declaration of Helsinki and ethically approved by the Vice Chancellor for Research of Ilam University of Medical Sciences (IR.MEDILAM.REC.1399.082).

Data availability statement

The associated data could be available by a reasonable request from scientists by sending email to the corresponding author.

Acknowledgements

Authors would like to thanks all participants in this study.

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