NEUTROPHIL-TO-LYMPHOCYTE AND PLATELET-TO-LYMPHOCYTE RATIOS ACROSS SCHIZOPHRENIA, BIPOLAR DISORDER, AND MAJOR DEPRESSIVE DISORDER: A COMPARATIVE CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Peripheral immune dysregulation has been reported across schizophrenia and mood disorders, but cross-diagnostic evidence using inexpensive complete-blood-count-derived inflammatory ratios remains inconsistent. Medication exposure may further obscure disorder-related differences.

Aim: To compare neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) among drug-naive and drug-free adults with schizophrenia, bipolar disorder, and major depressive disorder.

Methods: This hospital-based comparative cross-sectional study included 90 adults aged 18-60 years: 30 with schizophrenia, 30 with bipolar disorder, and 30 with major depressive disorder. Diagnoses were established using ICD-11 criteria. Participants were either psychotropic-drug-naive or drug-free for at least 2 months after oral medication or 3 months after depot medication. Blood was collected in EDTA tubes and analyzed using an automated hematology analyzer. NLR and PLR were derived from the complete blood count. Group differences were assessed with one-way analysis of variance; effect sizes were expressed as η^2. Pairwise Welch contrasts were multiplicity-adjusted using the Holm method.

Results: Mean NLR was 3.23 ± 0.10 in schizophrenia, 3.21 ± 0.50 in bipolar disorder, and 2.30 ± 0.10 in major depressive disorder. The overall difference was significant, $F(2,87)=77.70$, $p<0.05$, $\eta^2=0.641$. NLR did not differ between schizophrenia and bipolar disorder (adjusted $p=0.831$), whereas both groups had higher NLR than major depressive disorder (adjusted $p<0.05$). Mean PLR was 138.4 ± 2.6, 131.6 ± 3.7, and 128.2 ± 2.1, respectively, with a significant overall difference, $F(2,87)=94.60$, $p<0.05$, $\eta^2=0.685$; all pairwise PLR contrasts were significant after correction (adjusted $p<0.05$).

Conclusions: Inflammatory ratios differed across the three diagnostic groups. Schizophrenia and bipolar disorder had comparable NLR values, while major depressive disorder had lower NLR. PLR showed a graded pattern, highest in schizophrenia and lowest in major depressive disorder. These unadjusted cross-sectional findings support a transdiagnostic inflammatory signal but do not establish diagnostic specificity or causality. Replication with healthy controls, larger samples, and multivariable adjustment is required.

Keywords: Bipolar Disorder, Inflammation, Major Depressive Disorder, Neutrophil-To-Lymphocyte Ratio, Platelet-To-Lymphocyte Ratio, Schizophrenia.

INTRODUCTION

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Schizophrenia, bipolar disorder, and major depressive disorder are major contributors to disability, impaired functioning, and premature mortality worldwide [1]. Although these diagnoses are clinically distinct, they share overlapping biological features, including disturbances in stress-response systems, neuroendocrine regulation,

oxidative balance, and immune-inflammatory signaling. A cross-disorder synthesis of meta-analytic evidence has shown that several inflammatory markers are altered across major psychiatric disorders, while also emphasizing substantial heterogeneity and limited diagnostic specificity [2].

The inflammatory hypothesis is especially developed in schizophrenia. Meta-analytic evidence indicates state-dependent cytokine alterations during acute exacerbation and first-episode psychosis, with partial normalization after antipsychotic treatment [3]. In mood disorders, inflammatory activation is similarly heterogeneous and may vary with polarity, episode phase, symptom burden, metabolic state, and treatment exposure [4]. These findings support inflammation as a potentially transdiagnostic dimension rather than a single-disorder mechanism.

Cytokine assays and specialized immune panels are informative but may be costly and difficult to implement in routine psychiatric services. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are derived from a standard complete blood count and integrate information from innate immune activation, adaptive immune status, and platelet-related inflammatory processes. Healthy-population estimates vary across settings and laboratory methods [5,6], which cautions against applying a universal threshold; nevertheless, these ratios are attractive for clinical research because they are inexpensive, reproducible, and widely available.

Systematic reviews indicate that NLR is higher in non-affective psychosis and schizophrenia than in healthy controls [7,8]. A separate meta-analysis found higher NLR and PLR in mood disorders, with effect sizes influenced by clinical state and study characteristics [9]. Within affective disorders, manic episodes have frequently shown higher inflammatory ratios than bipolar depression or unipolar depression [10,11]. Large electronic-health-record and multicategory studies also suggest that elevated NLR is not confined to one diagnosis [12,13].

Direct comparisons among schizophrenia, bipolar disorder, and major depressive disorder remain relatively limited. Özdin and colleagues reported higher NLR and monocyte-to-lymphocyte ratio in schizophrenia than bipolar disorder [14], whereas an Indian comparative study found similar NLR and PLR values in schizophrenia and bipolar mania [15]. Differences in medication exposure, acute episode distribution, body mass index, smoking, medical comorbidity, and laboratory procedures may account for inconsistent findings.

Psychotropic medication can alter leukocyte profiles and inflammatory signaling, complicating interpretation of diagnostic differences. The present study therefore examined a balanced sample of drug-naive and drug-free patients with schizophrenia, bipolar disorder, and major depressive disorder. The primary question was whether NLR and PLR differed across diagnoses when recent psychotropic exposure and major inflammatory or metabolic comorbidity were minimized.

Aim and Objectives

Aim

To compare complete-blood-count-derived inflammatory ratios among drug-naive and drug-free adults with schizophrenia, bipolar disorder, and major depressive disorder.

Primary objectives

- To measure the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in each diagnostic group.
- To compare mean NLR and PLR across schizophrenia, bipolar disorder, and major depressive disorder.

Hypothesis

The null hypothesis was that mean NLR and PLR would not differ among the three diagnostic groups.

MATERIALS AND METHODS

Study Design, Setting, and Reporting

A hospital-based comparative cross-sectional study was conducted over 12 months at the Institute of Mental Health, Erragadda, Hyderabad, a tertiary psychiatric facility affiliated with Osmania Medical College. Both inpatients and outpatients were recruited by convenience sampling. The analytical sample comprised 90 participants, with 30 participants in each diagnostic group. Reporting was organized in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement for cross-sectional studies [27].

Participants and Diagnostic Procedure

Eligible participants were adults aged 18-60 years who met ICD-11 diagnostic criteria for schizophrenia, bipolar disorder, or major depressive disorder [21]. Diagnosis was established by clinical psychiatric assessment. The bipolar-disorder group included 23 participants with mania and 7 with a depressive episode. Participants were required to be either drug-naive, defined as having never received psychiatric medication, or drug-free, defined as being off oral psychotropic medication for at least 2 months or off a long-acting/depot preparation for at least 3 months before blood sampling. Written informed consent was obtained from all participants. Exclusion criteria were intellectual disability; harmful use of or dependence on psychoactive substances; organic or neurodegenerative disorders; current infection or fever; endocrine, inflammatory,

autoimmune, cerebrovascular, renal, cardiac, or hepatic disease; diabetes mellitus; hypertension; cancer; body mass index greater than 30 kg/m²; heavy smoking of more than 20 cigarettes per day; pregnancy or lactation; and use of nonsteroidal anti-inflammatory drugs, aspirin, corticosteroids, immunosuppressants, or antibiotics during the preceding 2 weeks.

Clinical Assessments

Sociodemographic and clinical information was recorded using a structured intake proforma. The Positive and Negative Syndrome Scale (PANSS) was administered to participants with schizophrenia; it contains 30 clinician-rated items organized into positive, negative, and general psychopathology subscales [22]. The Young Mania Rating Scale (YMRS), an 11-item clinician-rated instrument, was used for participants with bipolar mania [23]. The Hamilton Depression Rating Scale (HAM-D) was used for bipolar depressive episodes and major depressive disorder [24]. Overall illness severity was rated with the Clinical Global Impression-Severity scale (CGI-S), a 7-point clinician-rated global measure [25]. The World Health Organization Quality of Life-BREF (WHOQOL-BREF) was also administered as part of the parent study, although quality-of-life outcomes were outside the primary scope of the present diagnostic-comparison. [26].

Laboratory Assessment and Inflammatory Ratios

Peripheral venous blood was collected into ethylenediaminetetraacetic acid tubes and analyzed in the Institute of Mental Health diagnostic laboratory using an automated hematology analyzer. The complete blood count included total leukocyte count, erythrocyte count, hemoglobin, platelet count, and differential leukocyte measures. NLR was calculated from neutrophil and lymphocyte values, and PLR from platelet and lymphocyte values, using the laboratory-reported complete blood count. Height, weight, waist circumference, and body mass index were recorded.

Outcomes

The prespecified primary outcomes were NLR and PLR. The primary exposure was diagnostic group: schizophrenia, bipolar disorder, or major depressive disorder. Sociodemographic characteristics, illness duration, age at onset, body mass index, and symptom-severity measures were used to characterize the sample.

Statistical Analysis

The original study analysis was performed in IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean and standard deviation; categorical variables were summarized as frequency and percentage. One-way analysis of variance was used for continuous comparisons across the three diagnostic groups, and chi-square tests were used for categorical variables. Omnibus ANOVA results are reported with numerator and denominator degrees of freedom. Eta squared was derived from the reported F statistic as an omnibus effect-size estimate [28].

For statistical completion, pairwise group contrasts for NLR and PLR were calculated from the reported group sample sizes, means, and standard deviations using Welch independent-samples t tests. Mean differences, 95% confidence intervals, Satterthwaite degrees of freedom, and Hedges g were calculated. The three pairwise comparisons within each biomarker were adjusted using the Holm procedure. These calculations were performed in Python 3.13.5 using NumPy 2.3.5 and SciPy 1.17.0. All tests were two-sided, and $p<0.05$ was considered statistically significant.

Ethics

The study received approval from the Ethics Committee of Osmania Medical College before recruitment. Participants received information about the study and provided written informed consent.

RESULTS

Sample Characteristics

The final analytical sample included 90 participants: 30 with schizophrenia, 30 with bipolar disorder, and 30 with major depressive disorder. The mean ages were 32.6 ± 5.6, 31.7 ± 4.0, and 34.0 ± 3.2 years, respectively, with no significant difference in continuous age, $F(2,87)=2.10$, $p=0.129$. Each group included 15 men and 15 women. Illness duration, age at onset, and body mass index differed across diagnoses. The bipolar-disorder group included 23 participants with mania and 7 with bipolar depression.

Table 1. Sociodemographic and clinical characteristics by diagnostic group

Characteristic	Schizophrenia (n=30)	Bipolar disorder (n=30)	Major depressive disorder (n=30)	Statistical comparison
Age, years	32.6 ± 5.6	31.7 ± 4.0	34.0 ± 3.2	F(2,87)=2.10; p=0.129
Male sex	15 (50.0%)	15 (50.0%)	15 (50.0%)	χ^2=0.00; p=1.000
Married	27 (90.0%)	24 (80.0%)	26 (86.7%)	χ^2=1.25; p=0.530

Characteristic	Schizophrenia (n=30)	Bipolar disorder (n=30)	Major depressive disorder (n=30)	Statistical comparison
Rural domicile	27 (90.0%)	27 (90.0%)	24 (80.0%)	χ^2=1.70; p=0.420
Lower socioeconomic status	27 (90.0%)	26 (86.7%)	28 (93.3%)	χ^2=0.70; p=0.690
Unemployed	21 (70.0%)	8 (26.7%)	12 (40.0%)	Overall occupation: χ^2=19.60; p=0.030
Duration of illness, years	6.4 ± 5.6	6.9 ± 3.9	0.7 ± 0.2	F(2,87)=22.70; p<0.05
Age at illness onset, years	26.2 ± 6.2	24.6 ± 4.3	34.0 ± 3.2	F(2,87)=32.80; p<0.05
Body mass index, kg/m²	24.0 ± 0.3	26.0 ± 1.5	24.1 ± 0.5	F(2,87)=38.70; p<0.05
Current mood polarity	Not applicable	Mania: 23 (76.7%); depression: 7 (23.3%)	Depressive episode: 30 (100%)	Descriptive only

Primary inflammatory outcomes

Both biomarkers differed significantly across diagnoses. NLR showed a large omnibus group effect, F(2,87)=77.70, p<0.05, η^2=0.641. Mean NLR was almost identical in schizophrenia and bipolar disorder, while the major-depressive-disorder group had a lower mean. PLR also showed a large group effect, F(2,87)=94.60, p<0.05, η^2=0.685, with a descending pattern from schizophrenia to bipolar disorder to major depressive disorder.

Table 2. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio across diagnoses

Outcome	Schizophrenia (n=30)	Bipolar disorder (n=30)	Major depressive disorder (n=30)	Omnibus ANOVA	Eta squared
NLR	3.23 ± 0.10	3.21 ± 0.50	2.30 ± 0.10	F(2,87)=77.70; p<0.05	0.641
PLR	138.4 ± 2.6	131.6 ± 3.7	128.2 ± 2.1	F(2,87)=94.60; p<0.05	0.685

Pairwise Diagnostic Contrasts

Holm-adjusted pairwise comparisons showed no evidence of an NLR difference between schizophrenia and bipolar disorder. Schizophrenia and bipolar disorder each had higher NLR than major depressive disorder. For PLR, all three diagnostic groups differed significantly, with the largest contrast between schizophrenia and major depressive disorder.

Table 3. Pairwise contrasts for inflammatory ratios

Outcome and contrast	Mean difference	95% confidence interval	Welch t (df)	Holm-adjusted p	Hedges g
NLR: schizophrenia vs bipolar disorder	0.02	-0.17 to 0.21	0.21 (31.3)	0.831	0.05
NLR: schizophrenia vs major depressive disorder	0.93	0.88 to 0.98	36.02 (58.0)	<0.05	9.18

Outcome and contrast	Mean difference	95% confidence interval	Welch t (df)	Holm-adjusted p	Hedges g
NLR: bipolar disorder vs major depressive disorder	0.91	0.72 to 1.10	9.77 (31.3)	<0.05	2.49
PLR: schizophrenia vs bipolar disorder	6.80	5.14 to 8.46	8.24 (52.0)	<0.05	2.10
PLR: schizophrenia vs major depressive disorder	10.20	8.98 to 11.42	16.72 (55.5)	<0.05	4.26
PLR: bipolar disorder vs major depressive disorder	3.40	1.84 to 4.96	4.38 (45.9)	<0.05	1.12

Clinical characterization

Among participants with schizophrenia, mean PANSS positive, negative, general psychopathology, and total scores were 25.0 ± 1.42, 20.0 ± 1.43, 18.0 ± 1.50, and 63.0 ± 4.31, respectively. Among the 23 participants with bipolar mania, 8 (34.8%) had mild and 15 (65.2%) had moderate symptoms on the YMRS. In bipolar depression, 3 of 7 participants (42.9%) had mild and 4 (57.1%) had moderate HAM-D severity; in major depressive disorder, 14 of 30 (46.7%) had mild and 16 (53.3%) had moderate HAM-D severity. CGI-S distributions were: schizophrenia, 15 moderately ill and 15 markedly ill; bipolar disorder, 3 mildly ill, 14 moderately ill, and 13 markedly ill; and major depressive disorder, 12 mildly ill, 10 moderately ill, and 8 markedly ill.

DISCUSSION

Principal findings

This comparative cross-sectional study identified distinct unadjusted patterns of complete-blood-count-derived inflammatory ratios across schizophrenia, bipolar disorder, and major depressive disorder in a sample selected to minimize recent psychotropic exposure. NLR was similar in schizophrenia and bipolar disorder but lower in major depressive disorder. PLR demonstrated a graded pattern, with the highest mean in schizophrenia, an intermediate mean in bipolar disorder, and the lowest mean in major depressive disorder. The large omnibus effect sizes indicate substantial separation of the reported group distributions; however, the magnitude of the standardized pairwise effects was amplified by very small reported within-group standard deviations and requires confirmation from the raw dataset.

The finding of comparable NLR in schizophrenia and bipolar disorder is consistent with the comparative study by Goyal and colleagues, which found no significant difference between schizophrenia and bipolar mania despite higher NLR in both groups than healthy controls [15]. This pattern supports the possibility that NLR captures a shared state of low-grade systemic immune activation across severe psychotic and affective illness rather than a diagnosis-specific signal. By contrast, Özdin and colleagues reported higher NLR in schizophrenia than bipolar disorder [14]. Differences in episode phase, prior treatment, disease duration, comorbidity, smoking, and laboratory methods may explain the discrepancy.

The lower NLR observed in major depressive disorder is broadly compatible with affective-disorder studies in which mania shows greater inflammatory activation than unipolar depression. Koureta and colleagues reported higher NLR in mania than unipolar depression [10], and Wei and colleagues found higher NLR in bipolar disorder, particularly manic episodes, than in major depressive disorder [11]. The present bipolar group was predominantly manic, with 23 of 30 participants in a manic episode, which may have contributed to its higher NLR relative to major depressive disorder. This composition should be considered when interpreting the result as a diagnostic difference.

The PLR results differed from the NLR pattern because schizophrenia and bipolar disorder were clearly separated. Multicategory work by Bulut and colleagues found elevated PLR in bipolar mania, schizophrenia, and major depressive disorder relative to controls, although the relative ranking varied [12]. Platelets participate in inflammatory signaling, endothelial interactions, and serotonin storage; therefore, PLR may reflect biological processes that are not identical to those represented by NLR. Nevertheless, PLR is sensitive to hematologic, nutritional, vascular, and metabolic influences and should not be interpreted as a stand-alone psychiatric biomarker.

Evidence from schizophrenia-focused studies supports increased inflammatory ratios in at least a subgroup of patients. Meta-analyses have found higher NLR in non-affective psychosis and

schizophrenia than in controls [7,8]. Medication-naive first-episode studies have also linked higher NLR with greater psychotic symptom burden [16,17], while longitudinal data suggest that baseline NLR may relate to later remission status [18]. Studies comparing relapse and remission indicate that inflammatory ratios can vary with clinical state [19]. These observations reinforce the need to distinguish diagnosis, episode state, and severity when interpreting cross-sectional group means.

The present study has potential clinical relevance because NLR and PLR are inexpensive and available from routine hematology testing. However, their value is more likely to be adjunctive than diagnostic. Considerable overlap across psychiatric diagnoses, population-dependent reference values, and sensitivity to age, sex, body mass index, smoking, infection, stress, sleep, medication, and medical illness limit specificity [5,6,13]. The absence of a healthy control group in the current study also prevents direct estimation of the degree to which each diagnostic group differed from the local reference population.

Differences in illness duration, age at onset, body mass index, occupational status, and episode composition were present among the groups. These variables may be associated with inflammatory indices and could confound the observed diagnostic contrasts.

Strengths

- Balanced diagnostic groups with equal sample sizes and equal male-female distribution.
- Inclusion of drug-naive and adequately drug-free participants, reducing confounding from recent psychotropic exposure.
- Exclusion of several medical, inflammatory, metabolic, pregnancy-related, and medication-related factors that could alter blood counts.
- Use of inexpensive, routinely available inflammatory ratios measured within a single institutional laboratory.
- Direct three-group comparison, which is more informative than isolated pairwise reports from the same cohort.

Limitations

- Cross-sectional design, which prevents conclusions about temporal sequence, causality, or within-person change.
- Single-center convenience sample and modest group sizes, limiting external validity and precision.
- Absence of a healthy control group, preventing direct comparison with local nonpsychiatric reference values.
- No documented a priori sample-size calculation in the study record.
- Unadjusted primary comparisons despite differences in body mass index, illness duration, age at onset, occupation, and episode composition.
- No participant-level breakdown of drug-naive versus drug-free status by diagnosis in the reported results.
- Potential residual confounding from smoking below the exclusion threshold, diet, sleep, acute stress, menstrual status, subclinical infection, and prior medication exposure.
- Use of NLR and PLR without concurrent C-reactive protein, cytokines, or other immune measures.
- Unusually small reported standard deviations raise the possibility of rounding, data-entry, or transcription errors.

Future directions

- Conduct multicenter studies with larger, clinically diverse samples and matched healthy controls.
- Use prospective designs with repeated blood sampling before treatment, during acute treatment, and in remission.
- Prespecify and report multivariable models that adjust for demographic, metabolic, behavioral, and illness-related confounders.
- Stratify bipolar disorder by manic, depressive, mixed, and euthymic states and distinguish first-episode from recurrent illness.
- Combine NLR and PLR with C-reactive protein, cytokine panels, metabolic markers, and clinical outcomes to test incremental validity.
- Evaluate within-person change and prognostic performance before considering clinical thresholds or routine psychiatric use.
- Assess reproducibility across laboratories and establish population-specific reference distributions.

CONCLUSION

In this drug-naive and drug-free psychiatric sample, NLR and PLR differed significantly across schizophrenia, bipolar disorder, and major depressive disorder. NLR was comparable between schizophrenia and bipolar disorder and lower in major depressive disorder. PLR was highest in schizophrenia, intermediate in bipolar disorder, and lowest in major depressive disorder. The findings are consistent with a transdiagnostic inflammatory component but do not establish diagnostic specificity, causality, or clinical cutoffs.

Declarations

Ethics approval and consent to participate: Approval was obtained from the Ethics Committee of Osmania Medical College before recruitment, and written informed consent was obtained from all participants.

Consent for publication: Not applicable; no identifiable individual-level information is reported.

Availability of data and materials: De-identified participant-level data are held by the investigator and institution and may be considered for sharing on reasonable request, subject to ethics and institutional approval.
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