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Assessment of Neutrophil - Lymphocyte Ratio in Psychiatric Disorders - A Retrospective Study using Medical Records

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Abstract: ***Background**: As non-specific markers of immune dysregulation, neutrophil–lymphocyte (NLR) has been consistently shown to be increased in major neuropsychiatric disorders. There is a growing amount of evidence to suggest that inflammation may have a role in the onset and prognosis of psychiatric disorders. We reviewed the literature of studies investigating neutrophil–lymphocyte ratios (NLR), a biomarker of inflammation, in both adult and youth psychiatric populations. **Aim**: To assess Neutrophil- Lymphocyte ratio in major psychiatric disorders. **Objective**: To assess Neutrophil- Lymphocyte ratio in psychiatric disorders and compare with healthy controls. **Methods**: The Study was conducted using medical records of admitted patients with a main diagnosis of Sch, BD-M, BD-D, MDD or OCD according to DSM-5. Complete blood counts (CBCs) was obtained and NLR was calculated for each patient. A control group was established from healthy donors. **Results**: Mean Neutrophil - Lymphocyte Ratio (NLR) in BP-M and Sch groups were statistically significantly more than all other groups, also the ratios in these two groups differ significantly from each other with BP-M group having significantly higher than Sch. **Conclusion**: The direct comparison of NLR between the disorders points out that the intensity of the underlying inflammation may be most prominent for BD-M, followed by Sch, MDD and BD-D. NLR may be an effective biomarker to identify these patients who may benefit from adjunctive anti-inflammatory pharmacological treatment.*

Keywords: Neutrophil-lymphocyte ratio, Psychiatric disorders, Inflammation, Biomarkers, Mental health

1. Introduction

Immune dysregulation is a key factor in the development of many neuropsychiatric disorders—a group of diagnoses thought to involve significant disruptions in brain biophysical function. Common neuropsychiatric disorders encountered in psychiatric settings include schizophrenia (Sch), bipolar disorder (BD), major depressive disorder (MDD), obsessive-compulsive disorders (OCDs), autism spectrum disorders (ASDs), and attention-deficit hyperactivity disorder (ADHD) [1]. Of these, schizophrenia, bipolar disorder, major depressive disorder, and obsessive-compulsive disorders are among the most frequent diagnoses in psychiatric inpatient units [2–4].

Recent evidence from the past decade highlights the role of immune dysregulation and inflammatory pathways in the pathophysiology of these conditions, revealing distinct mechanisms at play in both the peripheral and central nervous systems. These mechanisms encompass a range of processes, including acute neurodegeneration, reduced neurotrophic activity, blood–brain barrier dysfunction, microglial activation, and elevated oxidative stress. [5-9]

A previous review[10] indicated that anti-inflammatory and immunomodulatory drugs, such as aspirin and celecoxib, can be effective as adjunctive treatments for psychiatric disorders like depression and schizophrenia. However, the results were inconsistent across the included studies. This inconsistency may stem from the need to identify a subset of patients most likely to respond—specifically, those experiencing elevated inflammation. Therefore, there is a need for simple and accurate inflammatory markers to identify patients who may benefit from these treatments. The neutrophil–lymphocyte ratio (NLR) appears promising as one such marker.

The neutrophil–lymphocyte ratio (NLR), derived by dividing neutrophil by lymphocyte counts, has become a valuable marker in psychiatric disorders, reflecting immune and inflammatory activity. Neutrophils, part of the innate immune system, respond to bacterial infections and inflammation, while lymphocytes—key to adaptive immunity—respond primarily to viral infections. Elevated NLR can indicate inflammatory states influenced by cytokines and the hypothalamic-pituitary-adrenal axis, often presenting with neutrophilia and lymphopenia, the latter resulting from stress-related catecholamine, prolactin, and cortisol release [11]. NLR, which can be calculated from routine blood counts, serves as a cost-effective alternative to C-reactive protein (CRP) and correlates with CRP levels in psychosis[12]. Its potential to predict treatment response and outcomes in psychiatric care is increasingly recognized.

2. Methods

This is a retrospective hospital based cross sectional study conducted at Department of Psychiatry, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan.

The Study was conducted using medical records of patients admitted in the inpatient section of Department of Psychiatry, Mahatma Gandhi Medical college, Jaipur between the duration of May 2022 and April 2023 with a main diagnosis of Sch, BD-M, BD-D, MDD or OCD according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) criteria.

We focused on non-geriatric patients to avoid the confounding influence of higher medical comorbidity and the prevalence of organic conditions in older adults, which can resemble psychiatric disorders. For the major depressive

disorder (MDD) group, we excluded patients with psychotic features to ensure greater diagnostic consistency, as previous research indicates that MDD with psychotic features may overlap etiologically and patho-physiologically with other neuropsychiatric conditions, such as bipolar disorder (BD), schizophrenia (Sch), schizoaffective disorder, and neurocognitive disorders [13-17]. Additionally, we excluded patients with known psychiatric comorbidities or differential diagnosis, including anxiety disorders, somatoform disorders, dissociative disorders, substance use disorders, borderline personality disorder, and schizoaffective disorder.

Other exclusion criteria involved medical conditions potentially impacting inflammatory markers, such as autoimmune diseases, blood disorders, liver or kidney failure, active infections, obesity (BMI > 30 kg/m²), and recent treatment with anti-inflammatory or immunosuppressive medications. Out of 200 inpatients reviewed, 100 were primarily diagnosed with one of the five neuropsychiatric disorders of interest. A control group of 100 non-psychiatric outpatients with comparable demographics and no psychiatric history was retrospectively recruited from the healthy donors who presented to the Blood Bank using similar selection criteria. The study protocol was approved by the ethical committee of Mahatma Gandhi medical College & Hospital, Jaipur.

Complete blood counts (CBCs) were obtained for each patient through retrospective screening of the hospital's medical database, considering only the CBCs taken at the time of admission. As part of standard procedure, blood samples were collected within 24 hours of each patient's initial admission to the clinic. The neutrophil–lymphocyte ratio (NLR) was then calculated for each patient using absolute cell counts.

Data analysis was conducted using SPSS (version 24.0; SPSS Inc., Chicago, IL). Descriptive statistics, including means (M), standard deviations (SD), and percentages (%), were used to present demographic and selected characteristics of the participants. The Kolmogorov–Smirnov and Shapiro–Wilk tests assessed normality of the data distribution. Group comparisons were conducted using the Kruskal–Wallis test or one-way ANOVA. Analysis of covariance (ANCOVA) was applied to control for age and gender in evaluating group differences. A two-tailed p-value of $< .05$ was considered statistically significant.

3. Results

Sample characteristics

The final sample in this study consisted of 200 participants, comprising 117 men and 83 women, distributed across various diagnostic groups. Of these participants, 32 were diagnosed with schizophrenia (Sch), 33 with bipolar disorder (BD), including 12 with bipolar depression (BD-D) and 21 with bipolar mania (BD-M), 20 with major depressive disorder (MDD), 15 with obsessive-compulsive disorder (OCD), and 100 were healthy controls (HC). Notably, the gender distribution varied significantly among the groups. The bipolar depression (BD-D) group had the highest proportion of females, with women making up 100% of this subgroup. In contrast, the schizophrenia (Sch) group had the lowest rate of female participants, with only 40.6% being women. This variation in gender distribution across groups highlights demographic differences that may be relevant to the interpretation of results, particularly in understanding how gender may impact the findings in relation to psychiatric conditions and inflammation markers.

Table : Sample Characteristics

Group	Male		Female		Total	Age			
	N	%	N	%		Min.	Max.	Mean	± SD
Healthy Controls	65	65.0	35	35.0	100	21	50	31.52	7.114
Schizophrenia	19	59.4	13	40.6	32	19	44	28.00	6.227
Bipolar Mania	17	81.0	4	19.0	21	20	32	24.76	4.358
Bipolar Depression	-	-	12	100.0	12	32	41	36.33	2.570
MDD	9	45.0	11	55.0	20	25	48	34.65	6.175
OCD	7	46.7	8	53.3	15	22	50	33.73	9.098
Total	117	58.5	83	41.5	200	19	50	31.02	7.230

Comparison between Sch, BD-M, BD-D, MDD, OCD and HC

The mean Neutrophil to Lymphocyte Ratio (NLR) values for each group reveal notable differences across psychiatric conditions and the healthy control group. Specifically, the mean NLR for individuals with schizophrenia (Sch) is 3.121, with a standard deviation (SD) of 0.646, while those in the bipolar mania (BD-M) group have an even higher mean NLR of 3.513, with a larger SD of 0.882, indicating greater variability within this group. In contrast, individuals with bipolar depression (BD-D) exhibit a lower mean NLR of 2.096 (SD = 0.288), which is similar to the mean NLR of 2.151 (SD = 0.283) observed in individuals with major depressive disorder (MDD). The obsessive-compulsive disorder (OCD) group has a mean NLR of 1.946, with a standard deviation of 0.273, while the healthy control (HC) group shows the lowest mean NLR of 1.863, with an SD of 0.231.

These values suggest that NLR levels are generally elevated in schizophrenia and bipolar mania groups compared to other psychiatric conditions and healthy controls, indicating a potentially heightened inflammatory response in these groups. To ensure normality of the data distribution, the raw NLR values were log-transformed before statistical analysis. Log transformation is a common technique used in data

analysis to manage skewness, stabilize variances, and make data more suitable for parametric testing. This transformation helps ensure that statistical comparisons between groups are reliable, allowing for more accurate interpretation of differences in NLR values across these conditions.

Table : Mean values of Neutrophils, Lymphocytes and Neutrophil Lymphocyte Ratio among groups

Group	Neutrophil		Lymphocyte		Neutrophil Lymphocyte Ratio	
	Mean	± SD	Mean	± SD	Mean	± SD
Healthy Controls	56.41	5.983	30.62	4.177	1.863	0.231
Schizophrenia	69.66	6.842	23.03	4.076	3.121	0.646
Bipolar Mania	71.05	6.209	21.14	4.269	3.513	0.882
Bipolar Depression	59.92	5.915	28.92	3.397	2.096	0.288
MDD	56.85	6.063	26.60	2.137	2.151	0.283
OCD	57.20	6.050	29.73	3.575	1.946	0.273
F value#	37.539		33.023		77.426	
P value#	P<0.001**		P<0.001**		P<0.001**	

#One-Way ANOVA: **p<0.001; Highly significant

Differences in NLR

The table shows that the mean Neutrophil to Lymphocyte Ratio (NLR) is statistically significantly higher in the Bipolar Mania (BP-M) and Schizophrenia (Sch) groups compared to all other groups, including healthy controls, bipolar depression, major depressive disorder (MDD), and obsessive-compulsive disorder (OCD). This indicates that individuals with BP-M and Sch tend to have elevated NLR levels, suggesting a distinct inflammatory response or immune profile in these conditions.

Additionally, there is a statistically significant difference in NLR between the BP-M and Sch groups themselves, with the BP-M group showing a considerably higher mean NLR than the Sch group. This further highlights a unique aspect of the immune response in bipolar mania compared to schizophrenia, despite both groups having higher NLRs than other psychiatric and control groups.

In contrast, the remaining groups—healthy controls, bipolar depression, MDD, and OCD—do not show statistically significant differences in their NLRs. This suggests that these groups have similar mean NLRs, with no clear distinction in inflammatory profile based on this metric alone.

Table : Pairwise Difference between groups using Post-Hoc Tukey Test

Group	Neutrophil			Lymphocyte			Neutrophil Lymphocyte Ratio		
	Mean	± SEm	P value	Mean	± SEm	P value	Mean	± SEm	P value
HC vs Sch	-13.246	1.251	<0.001**	7.589	0.799	<0.001**	-1.258	0.089	<0.001**
HC vs BP-M	-14.638	1.479	<0.001**	9.477	0.944	<0.001**	-1.650	0.105	<0.001**
HC vs BP-D	-3.507	1.882	0.428	1.703	1.201	0.716	-0.232	0.134	0.511
HC vs MDD	-0.440	1.509	1.000	4.020	0.963	0.001*	-0.288	0.107	0.084
HC vs OCD	-0.790	1.706	0.997	0.887	1.089	0.965	-0.083	0.121	0.984
Sch vs BP-M	-1.391	1.730	0.966	1.888	1.104	0.527	-0.392	0.123	0.021*
Sch vs BP-D	9.740	2.085	<0.001**	-5.885	1.331	<0.001**	1.026	0.148	<0.001**
Sch vs MDD	12.806	1.756	<0.001**	-3.569	1.121	0.021*	0.970	0.125	<0.001**
Sch vs OCD	12.456	1.928	<0.001**	-6.702	1.230	<0.001**	1.175	0.137	<0.001**
BP-M vs BP-D	11.131	2.229	<0.001**	-7.774	1.423	<0.001**	1.418	0.159	<0.001**
BP-M vs MDD	14.198	1.925	<0.001**	-5.457	1.229	<0.001**	1.362	0.137	<0.001**
BP-M vs OCD	13.848	2.083	<0.001**	-8.590	1.329	<0.001**	1.567	0.148	<0.001**
BP-D vs MDD	3.067	2.249	0.749	2.317	1.436	0.591	-0.056	0.160	0.999
BP-D vs OCD	2.717	2.386	0.865	-0.817	1.523	0.995	0.149	0.170	0.951
MDD vs OCD	-0.350	2.104	1.000	-3.133	1.343	0.186	0.205	0.150	0.746

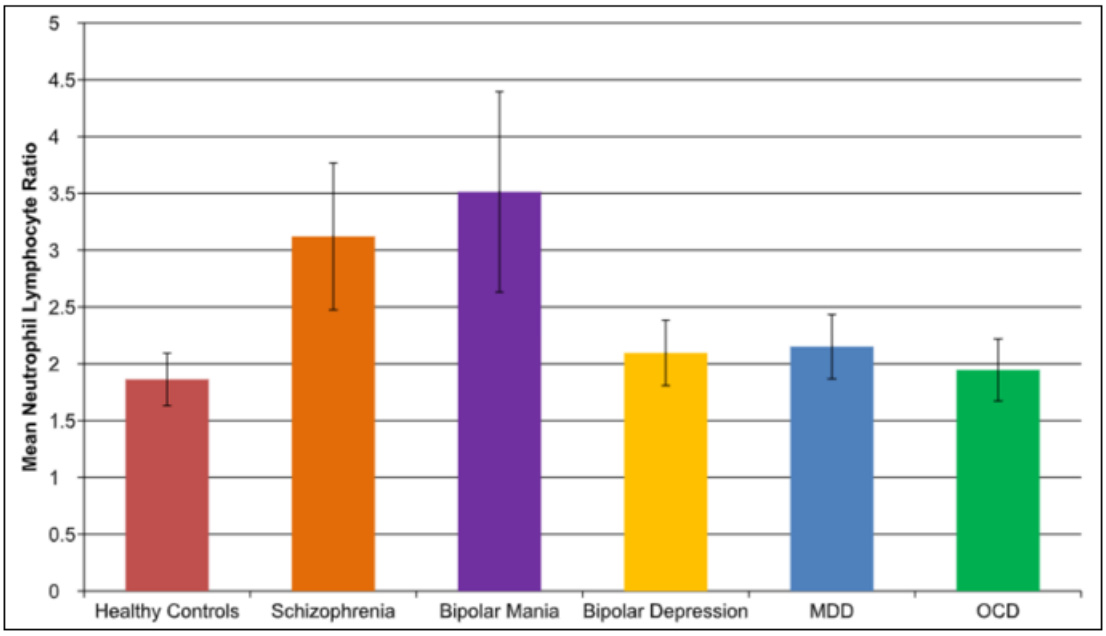

Figure 1

This bar chart (Figure-1) illustrates the "Mean Neutrophil to Lymphocyte Ratio" (NLR) across various groups, including healthy controls and individuals with different psychiatric disorders. Here's a breakdown of the findings:

1) **Healthy Controls**: The mean NLR for healthy individuals is around 2, with a relatively small error margin.
2) **Schizophrenia**: The mean NLR for people with schizophrenia is higher than that of healthy controls, approximately 3, with a moderate error margin.
3) **Bipolar Mania**: This group has the highest mean NLR, nearing 4, with a larger error margin, indicating greater variability within this group.
4) **Bipolar Depression**: The mean NLR in this group is slightly above 2, comparable to healthy controls but somewhat elevated.
5) **MDD (Major Depressive Disorder)**: The mean NLR for individuals with MDD is slightly above 2, similar to the bipolar depression group, with a moderate error margin.
6) **OCD (Obsessive-Compulsive Disorder)**: The NLR for individuals with OCD is also slightly above 2, resembling MDD and bipolar depression, with a moderate error margin.

Overall Findings:

- The highest NLR is observed in the bipolar mania group.
- Healthy controls have one of the lowest mean NLRs.
- Schizophrenia shows a significantly higher NLR than other psychiatric groups, though lower than bipolar mania.
- There is notable variability, represented by error bars, particularly in the schizophrenia and bipolar mania groups.

These results suggest that NLR, an indicator potentially linked to inflammation, differs across psychiatric conditions, with bipolar mania and schizophrenia displaying notably elevated levels compared to the other groups. This may indicate an association between these disorders and inflammatory processes.

4. Discussion

Over the past two decades, immunological mechanisms in the pathophysiology of neuropsychiatric disorders have garnered increasing research interest. Building on the theoretical foundations of prior studies, the objective of our current research was to provide a direct comparison of the inflammatory profiles of the most common neuropsychiatric conditions observed in psychiatric inpatient settings, using the Neutrophil to Lymphocyte Ratio (NLR) as a marker and including a comparison with healthy controls (HCs).

Our findings provide further evidence for the involvement of inflammatory processes in the pathophysiology of major neuropsychiatric disorders. The elevated NLR observed across multiple disorders, with the highest levels in bipolar mania, suggests a common inflammatory thread underlying these conditions. This aligns with previous research demonstrating increased levels of inflammatory markers in various psychiatric disorders.[18-19]

The significant difference in NLR between bipolar mania and other disorders is intriguing. It suggests that the inflammatory response may be more pronounced in the manic phase of bipolar disorder, potentially contributing to the heightened energy, impulsivity, and psychotic symptoms characteristic of this state. This finding underscores the need for further investigation into the specific inflammatory pathways involved in bipolar mania and how they may be targeted therapeutically.

While NLR offers a promising biomarker for identifying patients with elevated inflammation, it is important to acknowledge its limitations. NLR is a simple and accessible marker, but it reflects a general systemic inflammatory response rather than specific neuroinflammatory processes. Future research should explore more specific biomarkers, such as cytokine levels or neuroimaging markers of inflammation, to gain a deeper understanding of the underlying mechanisms.[20-21]

Furthermore, the relationship between NLR and clinical symptoms warrants further investigation. Longitudinal studies are needed to determine whether changes in NLR precede or follow symptom fluctuations. Additionally, the impact of different treatments, including pharmacological and psychological interventions, on NLR levels should be examined. This information could help identify patients who may benefit from adjunctive anti-inflammatory therapies and optimize treatment strategies.[22]

5. Conclusion

Our research reinforces the link between inflammation and major neuropsychiatric disorders. We found that individuals with bipolar mania exhibit the highest levels of systemic inflammation, followed by schizophrenia, major depressive disorder, and bipolar depression. This suggests that inflammation may be a common factor across these disorders, rather than specific to any one.

The Neutrophil to Lymphocyte Ratio (NLR) could be a valuable biomarker to identify patients who might benefit from anti-inflammatory treatments. Future studies should explore how NLR changes before and after treatment to better understand the role of inflammation in symptom severity and progression.

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