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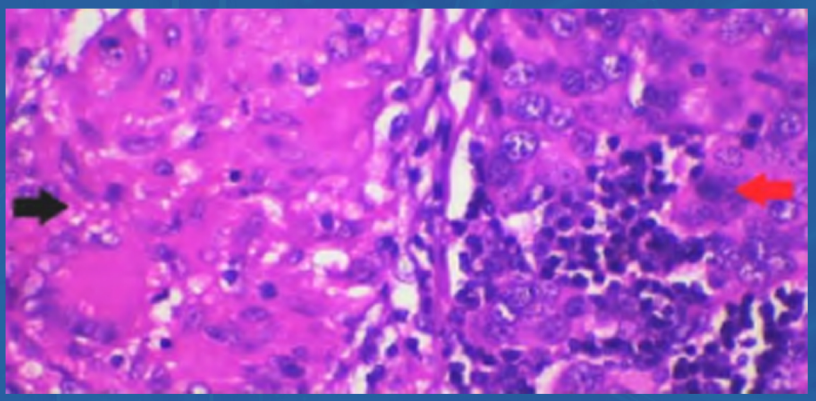
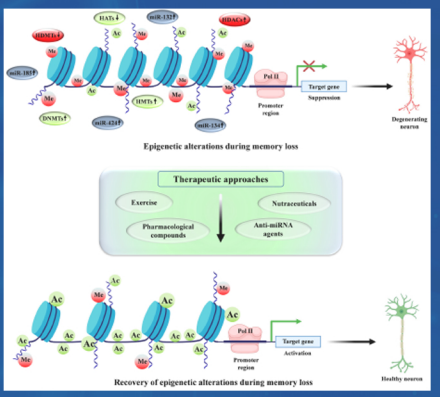


Epithelioid granuloma (black arrow) with invasive breast carcinoma (red arrow) (Haematoxylin & Eosin ×400).



Epigenetics in memory decline during aging

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Original Article

A comparative study of neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) in bipolar mania and schizophrenia

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ABSTRACT

Objectives: The role of immunological disturbance in bipolar disorder (BD) and schizophrenia has been highlighted by some studies. There are few studies available that compared the inflammatory markers between schizophrenia and BD, but only one study demonstrated the difference in terms of neutrophil/lymphocyte ratio (NLR) and Platelet/lymphocyte ratio (PLR) between them. So this study was conducted to compare the NLR and PLR values among schizophrenia, bipolar mania, and healthy controls in order to find out a potential biomarker for these disorders.

Material and Methods: Eighty consecutive patients suffering from bipolar mania, 80 suffering from schizophrenia, and 80 healthy controls were recruited in the psychiatric center situated at a tertiary care hospital. Blood samples of all groups were transferred to the laboratory for complete blood count analysis. Thereafter, all the groups were compared by applying proper statistics.

Results: Significant higher level of neutrophil count and NLR value was seen in both bipolar mania and schizophrenia groups compared to healthy controls. There was no difference observed between schizophrenia and the bipolar mania group regarding NLR, PLR, neutrophils, lymphocytes, and platelets values.

Conclusion: NLR has appeared as a potential marker in our study, and it reflects a state of low-grade inflammation in both schizophrenia and bipolar mania. BD and schizophrenia have been considered as part of one continuum, which is also supported by the findings of our study. These markers can help in the prognosis and treatment of at least a subsection of patients and also are inexpensive and easy to assess.

Keywords: Neutrophil/lymphocyte ratio; Platelet/lymphocyte ratio; Bipolar mania; Schizophrenia.

INTRODUCTION

Bipolar disorder (BD) and schizophrenia were considered in the psychotic spectrum by the psychiatric classification system until the 19th century.[1] Later, Kraepelin differentiated dementia praecox and manic-depressive disorder, setting it as a milestone in psychiatric diagnostic classification.[2] Nowadays, a continuity model has been established linking mania and psychosis and thereafter between BD and schizophrenia, which was in contrast to the conventional approach.[3] Besides this, few studies suggested that BD and schizophrenia were extensions of each other on a neurodevelopmental basis.[4]

The role of immunological disturbance in schizophrenia and bipolar illness has also been highlighted by some etiological studies.[5–7] Some studies reported alteration of peripheral inflammatory markers like cytokines, acute phase proteins, and lymphocyte cell activation in BD patients. [5,8–12] Jilma found increased neutrophils and decreased lymphocytes in general immune response to endotoxemia.[13] Thereafter, Zahorec developed the neutrophil/lymphocyte ratio (NLR) as a parameter that reflects the systemic inflammation and stress intensity in critically ill patients,[14] thus suggesting that these markers also contribute to the development of psychiatric disorders, particularly BD, and schizophrenia.

Various studies proposed the role of NLR value as a poor prognostic sign in some medical illnesses like pancreatitis, malignancy, and coronary heart disease.[15–17] Later on, scholars tried to find out its role in psychiatric illness as well. Many studies that have been done on patients with BD and schizophrenia tried to find out levels of NLR and PLR.[18–31] Better treatment response has been suggested in

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patients suffering from schizophrenia who had normal initial neutrophil and lymphocyte numbers and poor response in those who had lower lymphocyte and higher neutrophil count.[32]

Based on our current understanding and available information, we found that only a single study tried to ascertain the difference between schizophrenia and BD with respect to NLR and PLR. This study demonstrated a significantly higher NLR level in schizophrenia than BD (mania) patients.[20] In India, no study has been done on this subject so far. Therefore, we planned to conduct this study in a tertiary care center in India.

The main objective of this study was to assess and compare the levels of NLR and PLR among bipolar mania patients, schizophrenia patients, and healthy controls in order to find out a potential biomarker for these disorders. Our a priori hypothesis for this study was that the NLR and PLR values are higher among the subjects with mania and schizophrenia in comparison to healthy controls.

MATERIAL AND METHODS

The study was conducted as a cross-sectional and observational research in the Department of Psychiatry at a tertiary care hospital in North India. Ethical permission was taken from the ethics committee of the institute. The enrolment criteria were male or female participants aged greater than 18 years, who expressed a willingness to participate in the research and gave their written consent. The exclusion criteria for bipolar mania and schizophrenia groups included having any pre-existing chronic medical conditions and treatments, substance use including heavy smoking (>15 cigarettes per day),[21] clinical evidence related to active infections, as well as active or chronic inflammatory or autoimmune diseases among the participants, obesity (body mass index (BMI) >30 kg/m^2), taking immunosuppressive or anti-inflammatory medications, and the presence of clinically significant abnormalities during the baseline assessment (such as tachycardia, tachypnea, or fever) or abnormality in a laboratory test (e.g. anemia, leukocytosis, leukopenia, and thrombocytosis).[21] The exclusion criteria for healthy controls included any pre-existing psychiatric illness and treatment and parameters that were applicable to the bipolar and schizophrenia groups. The sample size for the study was determined based on a desired study power of 80% and a significance level (α-error) of 0.05, assuming a standard deviation of 1.0 as per the results of the reference article.[20] For a minimum detectable difference in means of 0.5 (NLR), 80 subjects were required as the sample size in each group. The patients who met both the inclusion as well as exclusion criteria were included in the study until the intended sample size was reached.

A total of 80 consecutive patients diagnosed with bipolar mania and 80 consecutive patients diagnosed with schizophrenia, according to the ICD-10 "(International Classification of Disease 10th Revision)", were recruited. The diagnosis of each patient was confirmed by two senior psychiatrists who were not part of the study. In addition, 80 healthy controls, preferably individuals accompanying the patients, were also included in the study. Psychiatric illnesses were ruled out in the healthy control group using the "ICD-10 symptom checklist for mental disorders."[33] Individuals who willingly participated in the study, provided written consent and met the inclusion criteria. Blood samples were collected from the antecubital vein of all subjects using vacutainer tubes containing ethylenediamine tetraacetic acid (EDTA) as an anticoagulant. The samples were collected in the morning hours (9 am–11 am) after overnight fasting and were sent to the laboratory for complete blood count (CBC) by a three-part blood cell counter manufactured by Sysmex (XP-100). Among CBC parameters, we included neutrophil, lymphocyte, and platelet counts for our study as they are involved in the inflammatory process. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Similarly, the PLR (platelet to lymphocyte ratio) was determined by dividing the absolute platelet count by the absolute lymphocyte count.

Statistical Analysis

The data collected in this study were entered into a Microsoft Excel 2007 worksheet and organized into a master chart. The data were then classified and analyzed according to the study's aims and objectives. The Pearson's chi-square test was used to analyze categorical variables. The normality of the data distribution was assessed using the "Shapiro–Wilk test." For normally distributed data, one-way Analysis of Variance (ANOVA) test was utilized, while for data that did not follow a normal distribution, the "Kruskal–Wallis post hoc Dunn's test" was applied. Statistical significance was considered at a p-value of less than 0.05 ($p < 0.05$).

RESULTS

Characteristics of participants

Bipolar mania, schizophrenia, and the healthy control groups were found to be comparable in terms of age, BMI, and distribution of gender.

The mean age of bipolar mania patients, schizophrenia patients, and healthy controls was 28.5 ± 5.5 years, 27.8 ± 6.2 years, and 28.11 ± 5.3 years ($p = 0.746$), respectively, and mean BMI was 24.6 ± 1.8 Kg/M^2, 24.5 ± 1.9 Kg/M^2, and 24.01 ± 1.9 Kg/M^2 ($p = 0.103$), respectively. In all the groups, there was an equal distribution of males and females (1:1) [Table 1].

Laboratory findings of various groups

There was a significant increase in the mean value of neutrophil count and NLR in bipolar mania than control subjects (5.32 ± 1.30 v/s 4.58 ± 1.18; p = 0.001 and 2.55 ± 1.13 v/s 1.93 ± 0.59; p < 0.001, respectively). Similarly, higher neutrophil and NLR mean values were observed in the schizophrenia group than the healthy control (5.26 ± 1.28 v/s 4.58 ± 1.18; p = 0.001 and 2.52 ± 1.07 v/s 1.93 ± 0.59; p < 0.001, respectively) [Table 2].

When a comparison was made between schizophrenia and bipolar groups, no significant difference of mean neutrophil count and NLR was observed between them (p = 1.00 for both neutrophil count and NLR) [Table 2].

According to the study findings, there were no significant differences observed in the mean values of lymphocyte count, platelet count, and PLR among all the groups (p = 0.058, p = 0.870, and p = 0.094, respectively) [Table 2].

DISCUSSION

The study findings reveal a significant increase in the value of neutrophils and NLR in both bipolar mania and schizophrenia groups compared to the control group. These results show an association of BD and schizophrenia with inflammatory parameters. Most of the studies that have been done so far are consistent on a higher NLR level in schizophrenia and BD while inconclusive over the neutrophil levels.[18–31]

BD and schizophrenia groups do not differ significantly when considering lymphocytes, neutrophil count, and NLR as a parameter of inflammation in the study. As per our knowledge, there is only a single study available till now that compared these markers in BD and schizophrenia. It showed a contradictory result of significantly higher NLR level in schizophrenia than BD (mania) patients.[20]

The NLR serves as an indicator of the balance between the innate immune response (neutrophils) and the adaptive immune response (lymphocytes).[34] Neutrophils, as the first line of defense, play a role in phagocytosis and apoptosis, releasing various inflammatory mediators like cytokines, which can lead to cellular DNA damage.[35] Lymphocytes play a crucial role in the immune system as they have protective and regulatory functions. Lymphopenia, which refers to a decrease in lymphocyte count, can be an indicator suggesting compromised overall health and physiological stress.[36,37] Considering that NLR represents an integrated parameter of these two immune pathways, it has the potential to be more predictive as a biomarker for BD during manic states and schizophrenia than using either parameter alone.[34] Therefore, NLR could serve as a valuable indicator and biomarker for these psychiatric conditions.

Indeed, the relationship between mental disorders and platelet parameters has been acknowledged for a considerable time. The PLR has shown promise in predicting the inflammatory response in affective disorders. Platelets serve

Table 1: Characteristics of participants.

Variables		Bipolar mania (n = 80)	Schizophrenia (n = 80)	Healthy control (n = 80)	P-value
Age	(Mean ± SD)	28.45 ± 5.53	27.76 ± 6.21	28.11 ± 5.25	0.746*
	Median	29 Yrs	27 Yrs	28 Yrs	
BMI (Kg/M^2) (Mean ± SD)		24.59 ± 1.76	24.50 ± 1.86	24.01 ± 1.87	0.103*
Sex	Male	40 (50%)	40 (50%)	40 (50%)	1.00†
N (%)	Female	40 (50%)	40 (50%)	40 (50%)	

*One way ANOVA; †chi square test; SD – Standard deviation; BMI – Body mass index; N – Number

Table 2: Laboratory findings of various groups.

Variables	Bipolar mania (n = 80) Mean ± SD	Schizophrenia (n = 80) Mean ± SD	Healthy control (n = 80) Mean ± SD	H(2)	P1	P2	P3
Neutrophil (µl)	5.32 ± 1.30	5.26 ± 1.28	4.58 ± 1.18	17.7	**0.001**	**0.001**	1.00
Lymphocyte (µl)	2.28 ± 0.65	2.26 ± 0.60	2.47 ± 0.57	5.7		0.058	
Platelet (µl)	225.18 ± 81.82	224.14 ± 71.90	219.55 ± 73.65	0.28		0.870	
NLR	2.55 ± 1.13	2.52 ± 1.07	1.93 ± 0.59	20.8	**<0.001**	**<0.001**	1.00
PLR	105.80 ± 43.50	106.40 ± 41.77	93.96 ± 37.61	4.7		0.094	

Kruskal–Wallis H test post-hoc Dunn's test; SD – Standard deviation; P1 – Bipolar mania v/s Healthy Control; P2 – Schizophrenia v/s Healthy Control; P3 – Bipolar mania v/s Schizophrenia; NLR – neutrophil/lymphocyte ratio; PLR – Platelet/lymphocyte ratio; H(2) – Test statistics; Bold value signifies the significant difference among the groups (P < 0.05).

as specific first-line inflammatory markers and play a role in regulating various parameters, including neutrophil and macrophage recruitment as well as endothelial permeability.[26] A meta-analysis has reported that patients with BD exhibit higher PLR values compared to controls.[26] Indeed, platelets are known to contain significant amounts of glutamate and serotonin within their dense granules. Serotonin and glutamate are neurotransmitters that play crucial roles in various physiological processes, including mood regulation.[38] In this study, no significant differences were observed in PLR values and platelet count among the groups being compared. Similarly, a study done by Ozdin *et al.* didn't find any significant difference in the PLR level between BD and schizophrenia groups.[20] The findings regarding platelet count and activation in psychiatric disorders have been contradictory and inconclusive in various studies.[18–19,24,29–31,39,40] Considering the inconsistent findings, it is important to acknowledge that PLR may not be a consistent and reliable marker for BD and schizophrenia.

In the study, the age distribution, BMI, and distribution of gender in all the groups (bipolar mania, schizophrenia, and control groups) were compared, and no significant differences were found among these variables. This suggests that the study groups were well-matched in terms of age, BMI, and gender distribution, which reduces the potential confounding effects of these factors on the study results.

Our study has the following limitations: Since this study is conducted in a cross-sectional manner, it is not possible to establish causal relationships. Other indicators of inflammation like cytokines, interferon-gamma, C-reactive proteins, acute phase proteins, and lymphocyte cell activation have not been studied. The patients were on different psychotropic drugs, which can influence blood cell count. Any lifestyle factors or levels of psychological distress were not assessed, which may affect NLR levels.

CONCLUSION

The NLR has emerged as a promising indicator, and it reflects a state of low-grade inflammation in both schizophrenia and bipolar mania. BD and schizophrenia have been considered as part of one continuum, proven by the fact that no significant differences were observed in the levels of neutrophils, lymphocytes, platelets, NLR, and PLR between these disorders. These markers can help in the prognosis and treatment of at least a subsection of patients and also are inexpensive and easy to assess.

More such studies are required in the future to definitively establish the role of inflammatory markers in psychiatric illnesses. The longitudinal study is required to ascertain whether the markers are state- or trait-specific markers. This will open the gate for new treatment strategies.

Ethical approval

The research/study is approved by the Ethics Committee at SMS Medical College and attached hospitals Jaipur, number 46/MC/EC/2020, dated 23 January 2020.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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