ORIGINAL RESEARCH PAPER
Volume-8 | Issue-10 | October - 2019 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ASSESSMENT OF PLATELET LYMPHOCYTE RATIO, NEUTROPHIL LYMPHOCYTE RATIO AND MEAN PLATELET VOLUME IN BIPOLAR AFFECTIVE DISORDER: A CROSS-SECTIONAL STUDY

Clinical Research

Mukesh Kumar Jatoliya Senior Resident (M.D.), Department of Psychiatry, American International Institute Of Medical Sciences Udaipur, Rajasthan, India.

Sushil Kherada Senior Professor and Head Of Department, Department of Psychiatry, RNT Medical College and hospital, Udaipur, Rajasthan, India. *Corresponding Author

Suresh Gocher Assistant Professor, Department of Psychiatry, RNT Medical College and hospital, Udaipur, Rajasthan, India.

Meenakshi Kumari Post Graduation in Psychology, Mohan Lal Sukhadiya University Udaipur, Rajasthan, India.

ABSTRACT

OBJECTIVES: The objectives of the study is to assess peripheral inflammatory indices-neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), mean platelet volume (MPV) in bipolar affective disorder (BPAD) and healthy controls (HCs)

SUMMARY : Consecutive drug-naive patients or not on any concomitant medicine for last 6 months with 72 Bipolar affective disorder (52 with manic episode and 20with depressive episode) and 91 Healthy Controls were studied. Neutrophils, lymphocytes, monocytes, platelets, NLR, PLR and MPV were measured and unpaired student's t- test used for statistical analysis. The BPAD patients had statistically significant elevated neutrophils, monocytes, platelets, NLR, PLR, MPV and lower lymphocytes compared to the Healthy Control group. BPAD is associated with higher level of inflammatory indices compared to Controls.

KEYWORDS

Inflammatory Indices, PLR, NLR, BPAD

INTRODUCTION

Inflammation is a biological phenomenon characterized by cytokine cascades, cellular immune responses, higher levels of acute phase proteins and complement factors.[1,2] It is protective response involving immune cells, blood vessels, and various molecular mediators .Neuro-inflammation is inflammation of the nervous tissue. It may be started in response to a variety of condition, including infection, traumatic brain injury, toxic metabolites, or autoimmunity. Including the brain and spinal cord, microglia are the resident innate immune cells that are activated in response to these cues, in the CNS. [3] Multiple reviews clearly demonstrate that depression, schizophrenia and bipolar disorder are associated with a disturbed regulation of immune responses as reflected by the observed abnormal profiles of inflammatory cytokines in affected patients. [4]

Bipolar affective disorder (BPAD) can be counted among the psychiatric diseases in which chronic cellular stress plays a role in the etiology of illness.[5,6] Stress leads to impair regulation of leukocyte functions by the hypothalamic-pituitary-adrenal axis and causes persistent low-grade inflammation response.[6,8] The peripheral pathophysiology of BPAD seems to be related to systemic inflammatory mechanisms.[7] Cytokines are produced by immune cells and have important roles in cell signaling, causes changes in lymphocyte, neutrophil and platelet level.[9]

There are only a few psychiatric illnesses studies that have examined the neutrophil lymphocyte ratio (NLR) and the platelet lymphocyte ratio (PLR), both of which are considered inflammatory indices. [8-12]

A study revealed that patients with bipolar disorder have statistically significant elevated NLR than healthy subjects, elevated levels of NLR may be involved in inflammatory pathophysiology of bipolar disorder (Ugur C et al April 2015) [15]

The findings of a study reveal that NLR tends to be higher in patients with Major Depressive Disorder(MDD) and a high NLR value supports the view that inflammation is a critical factor in the etiology of MDD (Suleyman D. et al Aug 2015) [16]

Higher NLR and MLR values were found in schizophrenia patients compared to bipolar disorder. Findings of their study supported the inflammation hypothesis for schizophrenia and bipolar disorder. (Ozdin S, et al June 2017) [13]

First Episode of Depression(FED) and recurrent depression are associated with lower serum concentration of BDNF and higher IL-2 & no significant correlation was found between severity of depression and serum concentration of CRP, BDNF, and IL-2 in both the groups (Jeenger J et al 2018) [19]

A positive correlation has been reported between suicidal behavior in bipolar disorder and NLR. [7] Pro-inflammatory cytokines have been reported to increase and anti-inflammatory cytokines to decrease in the manic period compared to a control group. (Leboyer M et al 2012)[8]

In clinical practice, it has been reported that haemogram parameters such as the mean platelet volume (MPV), NLR, and PLR can be used as markers of inflammation in different disease. There are only a few psychiatric disorder studies that have examined the neutrophil lymphocyte ratio (NLR) and the platelet lymphocyte ratio (PLR), both of which are considered inflammatory indices. We also aided MPV along with NLR and PLR in our Current research emphasis is on the biological markers that can be used in the diagnosis and can offer therapeutic options.

Most of the studies held out of the India and in Indian context regarding these inflammatory markers (PLR, NLR, and MPV) is the new area of study. Thus we planned a cross sectional study in Rajasthan region of India to detect role of inflammation in bipolar affective disorder.

METHOD

This study was conducted at Department of psychiatry, R.N.T. Medical College & associated hospitals, Udaipur. All investigations was done in laboratory of R.N.T. Medical College & associated hospitals, Udaipur (a tertiary care center) which is free of cost under state govt. scheme. All participants were screened, including a lifetime evaluation for psychiatric disorders using Mini-International Neuropsychiatric Interview Plus, and diagnoses of bipolar affective disorder were based on the International Classification of Diseases-10. [62, 63] Patients attending the department of psychiatry cases of bipolar affective disorder diagnosed on the basis of ICD-10 criteria, full-filling the inclusion and exclusion criteria. Healthy blood donors (biologically unrelated to cases) were included in the study those who didn't have current and past history of psychiatric illness and exclusive criteria were applied on healthy blood donor after that they were included as control subjects. These controls were included from blood bank (Blood Transfusion department) RNT Medical College Udaipur. Duration of study was From 27 October 2017 to 31August 2018 & Study design was Cross-Sectional observational.

INCLUSION CRITERIA

1. The patient/attendant should give informed consent.
2. Patient should be fulfilling the ICD-10 criteria of and Bipolar

affective disorder.
3. Age of patient: 18 years to 60 years.

EXCLUSION CRITERIA
1. Patient/attendant who would not consent
2. Age of patient less than 18 years and more than 60 years.
3. Who are on antipsychotic medication, on treatment with anti-inflammatory or Immune suppressive medication, and on concomitant drug use for any reason for last 6 months.
4. Who are having heavy smoking (more than 15 cigarettes per day), significant alcohol and other substance use.
5. Who are having any other psychiatric disorder and other acute/chronic medical condition (endocrinological, immunological and autoimmune diseases, epilepsy, diabetes mellitus, hypertension, hepatic or renal failure, heart disease, severe systemic disease, active infections, a leukocyte value suggesting infection.)
6. Obesity (body mass index ≥ 30 kg/m2).

Total 163 participant were included after applying inclusion and exclusion criteria, 72 participants were patients of Bipolar affective disorder (52 patients with manic episode and 20 with depressive episode) and 91were Healthy Controls included in our study, the blood samples were collected early from the subjects who were identified as included in our study, the specimen containers were labeled appropriately before specimen collection. Container label includes details like subject name, age and identification number, for proposed blood investigations (CBC) venous blood sample sent to our hospital laboratory and there after getting the reports data are analyzed. MLR,NLR, PLR ratios are find out by using (neutrophil % / lymphocyte %= NLR & platelet % / lymphocyte %= PLR) cells value from CBC.

Total 163 participant were included in our study after applying inclusion and exclusion criteria,out of them 72 patients were of BPAD (20 patients with depressive episode and 52 patients with manic episode) and 91were healthy controls.

INSTRUMENTS OF STUDY

Consent form: This form were written in Hindi and English language & it was given, once the patient was enrolled in the study, Screening Performa: This includes basic questions regarding the Patient's complains, history details (past, family, personal), history of questions related to the eligibility for determining the inclusion & exclusion criteria, Modified kuppuswamy scale: For socio-demographic profile, Stadiometer (for height measurement), Weight Machine, Blood pressure measuring apparatus, Material for blood collection (Disposable syringes and needles, blood Collection bottles, EDTA as an anti-coagulant, cotton, spirit and tourniquet) and Fully Auto hematology analyzer (Procan PE-6800).

STATISTICS

Data analysis Statistical analyses were done by using the Statistical Package for Social Sciences for Windows, version 16 (SPSS Inc., Chicago, IL, USA). Continuous covariates were expressed as mean with standard deviation and compared between groups using the unpaired Student's t-test. To determine the correlation between variables, Pearson's correlation coefficient was used. All statistical analysis was done at 95% confidence interval and P<0.05 considered statistically significant.

RESULTS

Total 163 participants were included 72 BPAD patients (52 with manic episode and 20 with depressive episode) and 91 healthy controls. Out of 72 BPAD patients 51 (70.8%) were male and 21 (29.2%) female, in controls 64 (70.3%) were male and 27 (29.7%) female. 19 (26.4%) patients of BPAD had family history positive for psychiatric illness. 87.5% patients of BPAD and 84.6% controls were belong to rural background and 63 (87.5%) patients of BPAD and 67 (72.5%) were married. Mean age of bipolar affective disorder patients was 33.8 years and mean age of control subject was 33.6yrs.

COMPARISON OF BPAD AND CONTROL :

Result shows that mean value of neutrophils% in BPAD patients(n=72) is 63.38±8.31 that is significantly higher (p<0.05) than control subjects(n=91) 60.59±3.90, mean NLR value of BPAD patients (2.68±1.21) was also significantly higher(p<0.05) in BPAD compare to control(2.20±0.39) and mean MPV values was also significantly higher in BPAD patients (10.89±1.94) compare to control (9.61±1.64).Mean values of lymphocytes in BPAD was low, mean platelets values was high and mean PLR was also high but p value was >0.05 that was not significant.(shown in table 1)

Table 1: Comparison of various CBC parameters between Bipolar affective disorder and control

PARAMETERS	BIPOLAR AFFECTIVE DISORDER		CONTROL SUBJECTS		P value
	Mean	SD	Mean	SD	
Neutrophils(%)	63.38	8.31	60.59	3.90	.012
Lymphocytes(%)	26.47	7.01	28.24	4.90	>.05
Platelets(in lacs)	3.05	0.77	2.71	0.84	>.05
Monocytes(%)	8.60	1.22	6.76	1.66	.000
NLR	2.68	1.21	2.20	0.39	.004
PLR	158.82	82.98	143.9	63.45	>.05
MPV(fL)	10.89	1.94	9.61	1.64	.000
ESR(mm/hr)	15.57	8.08	13.67	4.55	>.05

Comparison of BPAD with depression and BPAD with mania :

Result shows that mean value of neutrophil (64.41±8.91) in BPAD with mania(n=52) was significantly higher (p<0.05) with compare to BPAD with depression(n=20) (56.97±6.08) , mean values of lymphocytes was lower in BPAD with mania then BPAD with depression but p value was not significant and no significant difference is found in NLR,PLR and MPV values.(shown in table 2)

Table 2: Comparison of various CBC parameters between BPAD with manic and BPAD with depression

PARAMETERS	BPAD(MANIA)		BPAD(DEPRESSION)		P value
	Mean	SD	Mean	SD	
Neutrophils(%)	64.41	8.19	56.97	6.08	0.00
Lymphocytes(%)	25.83	7.19	30.39	4.20	0.05
Platelets(in lacs)	3.17	3.70	2.31	0.87	0.46
Monocytes(%)	8.46	4.50	9.45	1.40	0.49
NLR	2.80	0.58	1.93	0.47	0.35
PLR	167.02	49.30	107.98	48.70	0.22
MPV(fL)	10.90	1.99	10.84	1.69	0.92
ESR(mm/hr)	15.77	8.19	14.30	7.63	0.53

DISCUSSION

Bipolar disorder (BPAD) can be counted among the diseases in which chronic cellular stress plays a role in the etiology.[5,6] Stress impairs the normal regulation of leukocyte functions by the hypothalamic-pituitary-adrenal (HPA) axis and causes persistent low-grade inflammation.[6,8]

Recent theories concerning the neurobiological etiology of BPAD that have focused on impairments in cellular energy regulation, the immune system, neuroprotective mechanisms, and epigenetic aberrations (Gardner & Boles 2011, Grande et al. 2012). These components may be central to neuro-progressive alterations in BPAD (Berk et al. 2011); dysfunction of the inflammatory system may also be a key factor in the pathophysiological mechanisms underlying psychiatric disorder (Kapczinski et al. 2008, Stertz et al. 2013).

1.)SAMPLE COLLECTION AND METHOD :

Our study was conducted in Department of psychiatry, R.N.T. Medical College & associated hospitals, Udaipur that is in southern part of Rajasthan in India.Total 163 participant were included in our study,out of them 72 patients were of BPAD (10 patients with depressive episode and 62 patients with manic episode) and 91were healthy control, in our study and mean age of bipolar affective disorder patients was 33.8 years and mean age of control subject was 33.6yrs that is similarly matched age in both group. After fulfilling exclusion and inclusion criteria BPAD patients Sample for CBC was collected at department of psychiatry and sent to our hospital laboratory, healthy control's blood sample collected at department of blood transfusion in our hospital and sent to our hospital laboratory and our study was cross sectional.

(Ugur C. et al(April 2015) [15]conducted study at Department of Psychiatry, Abant Izzet Baysal University School of Medicine, Bolu, Turkey, their study was retrospective , 103 patients with BPAD and 126 healthy control subjects were analyzed for complete blood count.[15]

(Suleyman D. et al Aug 2015) [16] conducted at Department of Psychiatry, Dicle University, Diyarbakir, and Department of Biochemistry, Turkey. A total of 41 patients diagnosed with Major Depressive Disorder, who didn't recieve antidepressant therapy within the past 1 month, were included in the study, which took place between January and March 2015. The control group consisted of 47 healthy subjects with no psychiatric disorders.[16]

(Ozdin S, et al June 2017)[13] conducted study (comparative) of the neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in schizophrenia and bipolar disorder patients at the Ondokuz Mayıs University Medical Faculty Psychiatry Department, Turkey. In their study 157 healthy donors were included as a control group and 165 bipolar affective disorder with mania were included. White blood cell (WBC), neutrophil, lymphocyte, platelet and monocyte numbers were noted retrospectively from complete blood counts at time of admission.[13]

(Kose, Çinar Rugula, et al 2016) [14] conducted study at Turkey, they reviewed electronic medical records of patients with BPAD diagnosed between January 2004 and December 2014 for measuring differences between mania and euthymia. They identified and confirmed BD type I diagnoses via our inpatient and outpatient clinical records Patients admitted to the psychiatry clinic with manic episodes were identified. Complete blood counts were recorded during the admissions and one year later (euthymic states) for the same patients. A total of 133 patients met the inclusion criteria. Patients having data from both the manic episode and the euthymic state (approximately 1 year later) were selected.[14]

(Jeenger J et al 2018) [19] conducted study in GMCH Udaipur Rajasthan, India in Dec. 2018, Consecutive drug-naive patients with First episode of depression and Recurrent depression disorder (n = 85) and 50 Healthy Controls were studied. Serum concentrations of CRP, brain-derived nerve growth factor (BDNF), and IL-2 were measured. [19]

2.) PLR AND NLR VALUES :

Results of our study shows that mean value of neutrophils% in BPAD patients is 63.38±8.31 that is significantly higher ($p<0.05$) than control subjects 60.59±3.90, mean NLR value of BPAD patients (2.68±1.21) was also significantly higher($p<0.05$) in BPAD compare to control(2.20±0.39) and mean MPV values was also significantly higher in BPAD patients (10.89±1.94) compare to control (9.61±1.64).Mean values of lymphocytes in BPAD was low, mean platelets values was high and mean PLR was also high but p value was >0.05 that was not significant. After comparison between BPAD with depression and BPAD with manic episode of BPAD found that mean value of neutrophil (64.41±8.91) in BPAD with mania was significantly higher ($p<0.05$) with compare to BPAD with depression(56.97±6.08) , mean values of lymphocytes was lower in BPAD with mania then BPAD with depression but p value was not significant and no significant difference is found in NLR,PLR and MPV values. (Ugur C. et al April 2015) [15] results of this study revealed that patients with bipolar disorder have statistically significant elevated NLR than healthy compares. According to this finding, elevated levels of NLR may be involved in inflammatory pathophysiology of bipolar disorder.[15]

(Suleyman D. et al Aug 2015) [16] Significant differences were identified in the NLR, neutrophil count, lymphocyte percentage, and leukocyte values of the patient group when compared with the control group ($P<0.05$). The findings of the study reveal that NLR tends to be higher in patients with MDD, and a high NLR value supports the view that inflammation is a critical factor in the etiology of MDD.[16]

Ozdin S, et al (June 2017) [13] NLR, PLR and MLR values and platelet numbers in that study were higher and lymphocyte numbers were lower in bipolar disorder patients compared to the controls.[13]

Kose, Çinar Rugula, et al(2016)[14] NLR, PLR were recorded. Result shows that during mania, NLR and PLR were higher than euthymia. The euthymia NLR was negatively correlated with lithium use (rho = -0.272, $p = 0.002$) and positively correlated with valproate use (rho = 0.202, $p = 0.022$). Also, euthymia PLR was negatively correlated with lithium use (rho = -0.246, $p = 0.005$) and positively associated with valproate use (rho = 0.221, $p = 0.012$).[14]

Jeenger J et al (2018)[19] The FED (first episode of depression) and RDD (recurrent depressive disorder) groups had statistically significant lower serum concentration of BDNF and higher IL-2 compared to the HC group, whereas no statistically significant difference was observed with regard to CRP level. No statistically significant differences were observed with regard to the severity of depression and serum concentrations of CRP, BDNF, and IL-2 in the FED and RDD groups. No significant correlation was found between severity of depression and serum concentration of CRP, BDNF, and IL-2 in both the groups. Serum CRP concentration was significantly higher in patients with ≥2 stressful life events. No significant difference was observed between number of stressful life events and BDNF and IL-2 in patients with depression.[19]

It seemed so logical in 2019 that inflammation could only produce psychiatric illness when a person had a exposure for inflammation, such as an infection or a cancer. We were not aware of that psychological stress activates inflammation and that activation would be found to predict the later development of psychopathology. [17] Far from being specific to any psychiatric illness, inflammation may be a common denominator and likely a risk factor for every manner of psychiatric disturbance and illness, from schizophrenia to obsessive compulsive disorder, from mania to depression. [18]

CONCLUSION

We found that neutrophils, NLR, MPV values were higher in BPAD patients and BPAD with mania patients also have higher neutrophils count than BPAD with depression and other parameters mean values also high in BPAD and in BPAD with mania patients that conclude that immune system activation have been suggested to be involved in the pathogenesis of BPAD disorder and among BPAD patients during manic episode inflammatory response is differ from depressive episode in BPAD.

STRENGTH AND LIMITATIONS

The strength of our study was the good sample size and matched patient group and control group. Limitations are that the Subtypes of lymphocytes were not investigated, Other indicators of immune system function, such as cytokines, were not evaluated; therefore, it is not possible to determine whether increased NLR values represent an independent marker of alterations in the immune system in patients with BPAD, Lack of an analysis of cytokines in combination with NLR, In our study severity level were not assessed and Another limitation is the absence of knowledge about the lifestyle, dietary habits-restrictions.

FINANCIAL DISCLOSURE

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

There is no conflict of interest to be declared by any of the authors.

ACKNOWLEDGEMENT

This study was a part of the MD thesis work of the first author and I am very thankful for support and help of co-authors.

REFERENCES :

1. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, Yücel M, Gama CS, Dodd S, Dean B, Magalhaes PVS, Amminger P, McGorry P, Malhi GS. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. NeurosciBiobehavRev. 2011;35:804–817. https://doi.org/10.1016/j.neubiorev.2010.10.001. [PubMed]
2. Dean B. Understanding the role of inflammatory-related pathways in the pathophysiology and treatment of psychiatric disorders: evidence from human peripheral studies and CNS studies. IntJNeuropsychopharmacol. 2011;14:997–1012. https://doi.org/10.1017/S1461145710001410. [PubMed]
3. (Gendelman HE (December 2002). "Neural immunity: Friend or foe?". Journal of Neurovirology. 8 (6): 474–9. doi:10.1080/13550280290168631. PMID 12476342)
4. (European Psychiatry Volume 29, Issue 8, Supplement, November 2014, Pages 551-552)
5. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. NeurosciBiobehav Rev 2010; 35(1): 2-16.
6. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: a review of the interactions between inflammation and mood disorders. Prog Neuropsycho pharmacol Biol Psychiatry 2014; 53: 23-34.
7. Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, et al. Can bipolar disorder be viewed as a multisystem inflammatory disease? J Affect Disord 2012; 141(1): 1-10.
8. Cole SW, Mendoza SP, Capitanio JP. Social stress desensitizes lymphocytes to regulation by endogenous glucocorticoids: insights from in vivo cell trafficking dynamics in rhesus macaques. Psychosom Med 2009; 71(6): 591-597
9. Barbosa IG, Nogueira CR, Rocha NP, Queiroz AL, Vago JP, Tavares LP, et al. Altered intracellular signaling cascades in peripheral blood mononuclear cells from BD patients. J Psychiatr Res 2013; 47(12): 1949-1954.
10. Hochman E, Weizman A, Valevski A, Fischel T, Krivoy A. Association between bipolar

episodes and fluid and electrolyte homeostasis: a retrospective longitudinal study. Bipolar Disord 2014; 16(8): 781-789.
11. Sperner-Unterweger B. Immunological etiology of major psychiatric disorders: evidence and therapeutic implications. Drugs 2005;65(11):1493-520.
12. Madhusudan A, Vogel P, Knuesel I. Impact of prenatal immune system disturbances on brain development. J NeuroimmunePharmacol 2013;8(1):79-86.
13. SelçukÖzdin , GökhanSarisoy&ÖmerBöke (Jun 2017);A comparison of the neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in schizophrenia and bipolar disorder patients - a retrospective file review; Nord J psychiatry . 2017Jun 23:1- 4.PMID:28644753.
14. KöseÇinarRugüla, GörgülüYaseminaSönmez Mehmet BülentaKahyaciKiliçEvnurb (April 2016).Haematological and biochemical differences between mania and euthymia. Eur. J. Psychiat.(online).2016, vol.30, n.3, pp163-171. ISSN 0213-6163
15. UğurÇakır, Taha Can Tuman& Osman Yıldırım, (April 2015). increased neutrophil/lymphoctye ratio in patients with bipolar disorder. PsychiatriaDanubina, 2015; Vol. 27, No. 2, pp 180-184
16. Süleyman D,1 Abdullah Atli,1 Mahmut Bulut,1 AslıhanOkan İbiloğlu,1 Mehmet Güneş,1 Mehmet Cemal Kaya,1 Özlem Demirpençe,2 and Aytekin Sır(Aug 2015);Neutrophil–lymphocyte ratio in patients with major depressive disorder undergoing no pharmacological therapy. Neuropsychiatr Dis Treat. 2015; 11: 2253–2258
17. Wirtz PH1, von Känel R. Psychological stress, inflammation, and coronary heart disease. Curr Cardiol Rep. 2017;19:111.
18. Miller AH1, Haroon E1, Felger JC1. Therapeutic implications of brain-immune interactions: treatment in translation. Neuropsychopharmacol. 2017;42:334-359.
19. Jeenger J et al; Department of Psychiatry, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India http://www.indianjpsychiatry.org on Tuesday, December 25, 2018, IP: 106.207.188.42]