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ASSESSMENT AND COMPARISON OF MARKERS OF INFLAMMATION AND SYSTEMIC IMMUNE INFLAMMATION INDEX IN PATIENTS OF BIPOLAR DISORDERCURRENTLYINMANIAANDCONTROLSAT SMS MEDICAL COLLEGE, JAIPUR

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ABSTRACT

Background: Increasing evidence suggests that immune-inflammatory mechanisms play a significant role in the pathophysiology of bipolar disorder, particularly during acute mood episodes. Simple hematological inflammatory markers and the systemic immune-inflammationindex(SII)haveemergedasaccessibletoolstoassesssystemicinflammation, but data focusing specifically on bipolar disorder during mania remain limited, especially from Indian settings.

Aim: To assess and compare markers of systemic inflammation and the systemic immune-inflammationindexinpatientswithbipolardisordercurrentlyinamanicepisodeandhealthy controls.

Materials and Methods: This hospital-based observational comparative study was conducted at the Psychiatric Centre, SMS Medical College, Jaipur, over eight months. Patientsaged18–60yearsdiagnosedwithbipolardisorder,currentepisodemaniaasper DSM-5-TR criteria, were included along with age- and sex-matched healthy controls.
Inflammatory markers assessed included neutrophil-to-lymphocyte ratio (NLR), platelet-to- lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), mean platelet volume (MPV), erythrocyte sedimentation rate (ESR), and systemic immune-inflammation index

(SII).Comparisonsbetweengroupswereperformedusingappropriatestatisticaltests,witha p-value <0.05 considered statistically significant.

Results: Atotal of 158 participants were analyzed, comprising 84 patients with bipolar disorder in a manic episode and 74 healthy controls. Patients with mania demonstrated significantly higher frequencies of lymphopenia, raised NLR (41.7% vs 8.1%), raised MLR (16.7%vs0%),elevatedSII(51.2%vs31.1%),andraisedESR(45.2%vs16.2%)compared with controls (p<0.05 for all). No statistically significant difference was observed in PLR or MPV between the two groups.

Conclusion: Patients with bipolar disorder during mania exhibit a significantly heightened systemic inflammatory state compared with healthy individuals. Simple hematological inflammatorymarkersandSIImayserveasuseful,low-costindicatorsofimmuneactivation inbipolarmaniaandwarrantfurtherinvestigationfortheirclinicalandprognostic relevance.
Keywords: Bipolardisorder;Mania;Inflammation;Neutrophil-to-lymphocyteratio;Systemic immune-inflammation index; Erythrocyte sedimentation rate

Introduction

Severementalillnessessuchasmajordepressivedisorder,schizophrenia,andbipolardisorder constitute a major public health burden worldwide and are leading contributors to disability and premature mortality [1]. Bipolar disorder is a chronic, episodic mood disorder characterized by recurrent episodes of mania, hypomania, and depression, resulting in significantimpairmentinsocial,occupational,andinterpersonalfunctioning[2].Accordingto theGlobalBurdenofDiseaseStudy2019,bipolardisorderranksamongtheleadingcauses of years lived with disability, particularly affecting young adults during their most productive years [1]. Despite advances in psychopharmacological treatments, a substantial proportion of patientswithbipolardisordercontinuetoexperienceresidualsymptoms,frequentrelapses,and functional impairment, underscoring the need for a better understanding of its underlying biological mechanisms [3].

Traditionally, bipolar disorder has been conceptualized primarily as a disorder of neurotransmitter dysregulation involving dopaminergic, serotonergic, and glutamatergic systems. However, growing evidence suggests that this neurochemical model alone is insufficient to explain the complex clinical presentation and heterogeneity of the disorder. In recent years, immune system activation and low-grade systemic inflammation have emerged as important contributors to the pathophysiology of psychiatric disorders [4]. The concept of neuroinflammation highlights the bidirectional interaction between the peripheral immune systemandthecentralnervoussystem,influencingneuronalsignaling,synapticplasticity, and behavior [5].

A large meta-analysis comparing schizophrenia, bipolar disorder, and major depression reported significant alterations in circulating pro-inflammatory cytokine networks, including interleukin-6andtumornecrosisfactor-alpha[6].Similarfindingshavebeenobservedinmajor depressive disorder, where elevated cytokine levels support the presence of systemic inflammatoryactivation[7].Inadditiontocytokines,acute-phasereactantssuchasC-reactive protein have been implicated in psychiatric disorders. Elevated C-reactive protein levels have beendemonstratedinpopulation-basedstudiesofadultswithdepressivesymptoms,suggesting a link between inflammation and mood pathology [8].

The broader role of inflammation in depression has been further supported by translational and clinical research highlighting immune dysregulation as a potential therapeutic target [9]. Importantly, inflammation may not only accompany established psychiatric illness but may also precede its onset. Longitudinal population-based studies have shown that elevated serum

interleukin-6 and C-reactive protein levels during childhood are associated with an increased risk of developing depression and psychosis in young adulthood [10]. Prenatal exposure to maternal immune activation has similarly been associated with an increased risk of schizophreniaspectrumdisorders,suggestingthatearlyimmuneinsultsmaycontributetolater psychiatric vulnerability [11].

Bipolar disorder has increasingly been recognized as a condition associated with immune- inflammatory abnormalities. Reviews focusing on the immunology of bipolar disorder have reported altered cytokine profiles and evidence of persistent low-grade inflammation across different phases of the illness [12]. Further clinical reviews emphasize that inflammatory activationappearstobeparticularlypronouncedduringacutemoodepisodes,includingmania and major depression [13]. Moreover, bipolar disorder frequently coexists with medical comorbidities such as obesity, metabolic syndrome, and cardiovascular disease, all of which are themselves characterized by chronic inflammatory states [14].

Anti-inflammatory mechanisms have been proposed as novel therapeutic targets, and systematic reviews indicate that adjunctive anti-inflammatory agents may offer symptomatic benefit in bipolar depression [15]. These findings suggest that identifying inflammatory subtypes of bipolar disorder may help guide personalized treatment strategies. Theneutrophil-to-lymphocyteratiowasfirstproposedasarapidandsimplemarkerofsystemic inflammatory and stress responses [16]. Building on this concept, the platelet-to-lymphocyte ratio has also been explored as an indicator of inflammatory and prothrombotic activity [17]. Inpsychiatricresearch,thesehematologicalindiceshaveshownpromiseaspotential biomarkers. Elevated neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios have been reportedinpatientswithbipolardisordercomparedwithhealthycontrols,suggestingincreased inflammatoryburden[18].Subsequentstudieshaveconfirmedsignificantlyhigherneutrophil- to-lymphocyteratiosinbipolardisorder,supportingitspotentialroleasaperipheral inflammatory marker [19]. Meta-analytic evidence further supports the presence of elevated neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios across mood disorders [20]. Inflammatoryalterationsappeartobeparticularlyprominentduringmanicepisodes.Increased neutrophil-to-lymphocyte ratio and decreased mean platelet volume have been reported in patients with acute mania, indicating enhanced inflammatory activity and platelet activation [21]. Studies examining different mood states of bipolar disorder have shown that these hematological markers may remain altered across manic, depressive, and euthymic phases, suggestingbothstate-andtrait-relatedinflammatorychanges[22].Additionally,neutrophil-to- lymphocyte ratio has been proposed as a potential marker for distinguishing bipolar-type depression from unipolar depression [23].

More recently, the systemic immune-inflammation index, calculated using platelet count, neutrophil count, and lymphocyte count, has been introduced as a comprehensive marker integratinginnateimmunity,adaptiveimmunity,andthrombocyticactivity.Initiallydeveloped as a prognostic indicator in oncology [24], this index has subsequently been applied to psychiatric populations. Studies evaluating systemic immune-inflammation index in bipolar disorderandschizophreniahavereportedsignificantlyelevatedvaluescomparedwithhealthy controls, indicating heightened inflammatory burden [25]. Accuratediagnosisremainsessentialformeaningfulinterpretationofinflammatoryfindingsin bipolardisorder.TheDiagnosticandStatisticalManualofMentalDisorders,FifthEdition, Text Revision provides standardized diagnostic criteria for bipolar disorder and its mood episodes, ensuring diagnostic consistency across clinical and research settings [26].

The present study aimed to determine presence of low grade systemic inflammation among patient of bipolar disorder currently in mania fulfilling diagnostic criteria as per DSM 5 TR with help of 6 inflammatory marker (NLR, PLR, MLR, MPV, SII, ESR) and comparisons were made with control group.

METHODS

Thiswasahospital-basedobservationalcomparativestudyconductedtoevaluateinflammatory markers and the systemic immune inflammation index in patients admitted with bipolar disorder currently in mania and in a healthy comparison group. The study was carried out at the Psychiatric Centre, SMS Medical College, Jaipur, a tertiary care teaching hospital, over a period of approximately eight months, from September 2024 to April 2025. The study populationcomprisedtwogroups:cases,whichincludedpatientsadmittedwithadiagnosisof bipolar disorder, currently in a manic episode fulfilling diagnostic criteria as per DSM-5-TR, and a healthy comparison group consisting of apparently healthy individuals with no current or past history of psychiatric illness. Patients in the case group were diagnosed with bipolar disorder,currentepisode mania,according totheDiagnostic andStatistical ManualofMental Disorders,FifthEdition,TextRevision(DSM-5-TR)criteria,anddiagnosiswasestablishedby a qualified psychiatrist after detailed clinical evaluation.

The sample size was initially calculated based on previously reported differences in platelet- to-lymphocyteratio(PLR)betweenpatientswithbipolardisorderandhealthycontrols,which yielded a minimum requirement of 65 participants per group at a 95% confidence level and 80% study power. However, during the study period, a larger number of eligible participants fulfilling the inclusion and exclusion criteria consented to participate. Therefore, all consecutivelyrecruitedandeligiblesubjectswereincludedinthefinalanalysis.Consequently, the final sample comprised 84 patients with bipolar disorder in current manic episode and 74 healthy controls, and analyses were performed on this final sample.

Inclusioncriteriaforthebipolardisordergroupwerepatientsdiagnosedwithbipolardisorder, currentepisodemania,fulfillingDSM-5-TRcriteria;agebetween18and60years;patientsof either gender; and patient or legally authorized caregiver willing to provide written informed consent. Inclusion criteria for the healthy comparison group were individuals aged 18 to 60 years, either gender, with no current or past history of any psychiatric illness, and willingness toprovidewritteninformedconsent.Exclusioncriteriaforbothgroupsincludedcurrentuseof medicationsknowntoaffectinflammatoryparameterssuchasnon-steroidalanti-inflammatory drugs, corticosteroids, immunosuppressive agents, systemic antibiotics, and antimetabolites; presence of any acute or chronic systemic medical illness such as diabetes mellitus, chronic obstructive pulmonary disease, and autoimmune or inflammatory disorders; and pregnant or lactating females. After obtaining informed consent, socio-demographic and clinical details were recorded using a structured proforma, and for patients, relevant clinical information including diagnosis and current episode status was documented. Venous blood samples were collected under aseptic conditions from all participants, and inflammatory parameters including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), mean platelet volume (MPV), and erythrocyte sedimentation rate (ESR) were assessed using standard laboratory techniques. The systemic immune inflammation index (SII) was calculated using the formula: SII = platelet count × neutrophil / lymphocyte count.

Data were entered into Microsoft Excel

and analyzed using appropriate statistical software. Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Comparison of inflammatory markers between the bipolar disordergroupandthehealthycomparisongroupwasperformedusingappropriateparametric or non-parametric tests depending on data distribution, and a p-value < 0.05 was considered statisticallysignificant.Thestudywasconductedafterobtainingapproval fromtheInstitutional Ethics Committee, SMS Medical College, Jaipur, and written informed consent was obtained from all participants or their caregivers prior to enrollment. Confidentiality of patient information was strictly maintained throughout the study.

RESULTS

A total of 158 participants were included in the final analysis, comprising 84 patients with bipolar disorder in current manic episode (study group) and 74 age- and sex-matched healthy controls. All participants underwent clinical assessment and laboratory evaluation, including complete blood count parameters and derived inflammatory indices.

SociodemographicCharacteristics

The age distribution differed significantly between the two groups. In the study group, the largestproportionofparticipantsbelongedtothe21–30yearsagegroup(34.5%),followedby 31–40 years (25.0%) and 41–50 years (23.8%). Notably, a higher proportion of participants aged ≤20 years was observed in the study group (14.3%) compared with controls (2.7%). In contrast, the control group had a relatively higher proportion of participants aged >50 years (10.8% vs 2.4%).

Gender distribution was comparable between groups, with males constituting 64.3% of the study group and 68.9% of the control group; the difference was not statistically significant.

Table1.Baselinecharacteristicsofstudyparticipants(agegroupandgender)

Variable	Category	Control(n=74)n(%)	Study(n=84)n (%)	p value
Agegroup(years)	≤20	2 (2.7)	12 (14.3)	**0.017**
	21–30	30 (40.5)	29 (34.5)	
	31–40	13 (17.6)	21 (25.0)	
	41–50	21 (28.4)	20 (23.8)	
	>50	8 (10.8)	2 (2.4)	
Gender	Male	51 (68.9)	54 (64.3)	**0.655**
	Female	23 (31.1)	30 (35.7)	

SubstanceUse Pattern

A significant difference in substance use pattern was observed between groups. Absence of substanceusewasreportedby56.0%ofthestudygroupand60.8%ofcontrols.Smokingalone was more frequent among controls (24.3%) than the study group (13.1%), while tobacco use alone was comparable (16.7% vs 14.9%). Importantly, multiple substance use was observed exclusively in the study group (14.3%), whereas none of the controls reported multiple substance use.

Table2.Substanceuse pattern

Substanceuse	**Control(n=74)n(%)**	**Study(n=84)n (%)**	**p value**
Nil(nosubstanceuse)	45 (60.8)	47 (56.0)	**0.0036**
Smoking only	18 (24.3)	11 (13.1)	
Tobaccoonly	11 (14.9)	14 (16.7)	
Multiplesubstances	0 (0.0)	12 (14.3)	

Hematological Parameters

Totalleukocytecount(TLC)waswithinthenormalrange(4,000–11,000/mm³)inthemajority ofparticipantsinbothgroups.ElevatedTLC(>11,000/mm³)wasobservedin9.5%ofthestudy group and 1.4% of controls; however, this difference did not reach statistical significance.

Absolute neutrophil count (ANC) distribution showed a statistically significant difference betweengroups.Neutropenia(<1,500/mm³)waspresentin14.3%ofthestudygroupcompared with 1.4% of controls. Neutrophilia (>8,000/mm³) was also more frequent in the study group (9.5%) than in controls (4.0%).

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A marked and highly significant difference was noted in absolute lymphocyte count (ALC) categories.Thevastmajorityofpatientsinthestudygroup(95.2%)hadALC<1,000cells/µL, whereasonly12.2%ofcontrolsfellintothiscategory.Conversely,normalALC(1,000–4,000 cells/µL) was observed in 87.8% of controls compared with only 4.8% of the study group.

Platelet count distribution did not differ significantly between groups. Similarly, absolute monocyte count (AMC) showed no significant difference, with raised AMC (>800 cells/µL) observed in 2.4% of the study group and 1.4% of controls

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Table3.Hemogramcategories(TLC,ANC,ALC,Platelets,AMC)

Parameter	**Category**	**Controln(%)**	**Studyn (%)**	**p value**
TLC (/mm³)	4,000–11,000	73 (98.6)	76 (90.5)	**0.062**
	>11,000	1 (1.4)	8 (9.5)	
ANC (/mm³)	<1,500 (Neutropenia)	1 (1.4)	12 (14.3)	**0.0036**
	1,500–8,000 (Normal)	70 (94.6)	64 (76.2)	
	>8,000 (Neutrophilia)	3 (4.0)	8 (9.5)	
ALC(cells/µL)	<1000	9 (12.2)	80 (95.2)	**<0.0001**
	1000–4000	65 (87.8)	4 (4.8)	
Platelets(/µL)	<150,000	23 (31.1)	30 (35.7)	**0.675**
	150,000–450,000	49 (66.2)	53 (63.1)	
	>450,000	2 (2.7)	1 (1.2)	
AMC(cells/µL)	≤800 (Normal)	73 (98.6)	82 (97.6)	**1.000**
	>800 (Raised)	1 (1.4)	2 (2.4)	

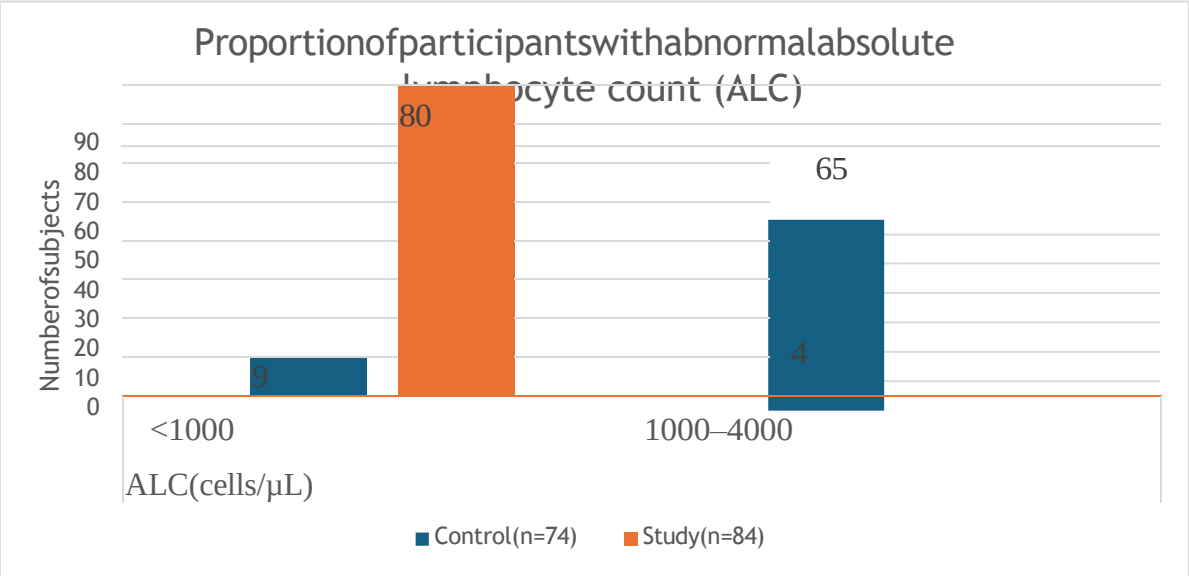

Figure1:Comparisonofabsolutelymphocytecountcategoriesbetweenstudyandcontrol groups

InflammatoryIndices

A significantly higher proportion of patients in the study group had raised neutrophil– lymphocyte ratio (NLR ≥3) compared with controls (41.7% vs 8.1%). Raised monocyte–lymphocyteratio(MLR≥0.3)wasobservedin16.7%ofthestudygroup,whereasnoneofthe controls had elevated MLR, and this difference was statistically significant.

Nosignificantdifferencewasobservedforplatelet–lymphocyteratio(PLR≥150)betweenthestudyandcontrolgroups(10.8%vs16.7%).

Meanplateletvolume(MPV)valuesabove11fL weremorefrequentinthestudygroup(64.3%)thanincontrols(50.0%),thoughthisdifference did not achieve statistical significance (p = 0.099).

Systemic immune-inflammation index (SII ≥500,000) was significantly elevated in the study group (51.2%) compared with controls (31.1%). Raised ESR (>20 mm/hr) was present in 45.2%ofthestudygroupcomparedwith16.2%ofcontrols,indicatingastatisticallysignificant difference (p = 0.00018).

Table4.Inflammatoryratios(NLR,PLR,MLR)

Marker	Category	Controln(%)	Studyn (%)	p value
NLR	<3 (Normal)	68 (91.9)	49 (58.3)	**<0.00001**
	≥3 (Raised)	6 (8.1)	35 (41.7)	
PLR	<150 (Normal)	70 (83.3)	66 (89.2)	**0.406**
	≥150 (Raised)	14 (16.7)	8 (10.8)	

MLR	<0.3 (Normal)	74 (100)	70 (83.3)	**0.00068**
	≥0.3 (Raised)	0 (0)	14 (16.7)	
MPV	≤11 fL (Normal)	37 (50.0)	30 (35.7)	**0.099**
	>11 fL (Raised)	37 (50.0)	54 (64.3)	
SII	<500,000 (Normal)	51 (68.9)	41 (48.8)	**0.0166**
	≥500,000 (Raised)	23 (31.1)	43 (51.2)	
ESR	≤20 mm/hr (Normal)	62 (83.8)	46 (54.8)	**0.00018**
	>20mm/hr(Raised)	12 (16.2)	38 (45.2)	

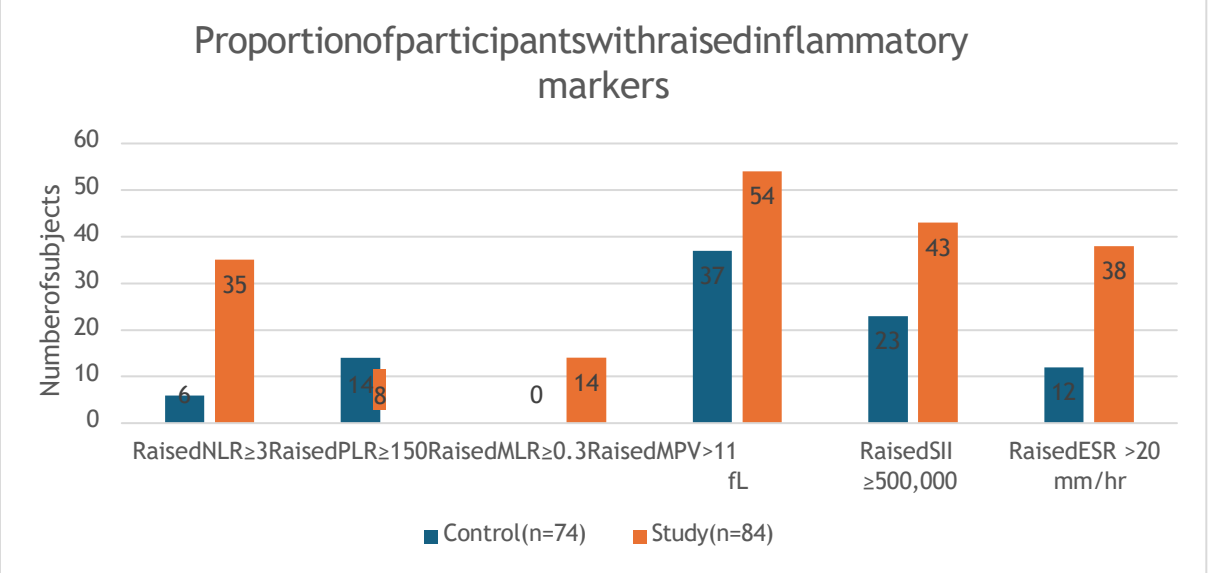

Figure2.Proportionofparticipantswith“raised”inflammatorymarkersinstudyvscontrol.

Insummary,Patientswithbipolardisorderin currentmanicepisodedemonstratedsignific antly higher frequencies of neutropenia, lymphopenia, raised NLR, raised MLR, raised SII, and raised ESR compared with healthy controls, suggesting an enhanced systemic inflammatory state in mania.

DISCUSSION

The present study demonstrates that patients with bipolar disorder in a current manic episode exhibitasignificantlyheightenedsystemicin flammatorystatecomparedwithhealthycont rols, as evidenced by higher frequencies of lymphopenia, raised neutrophil-to-lymphocyte ratio (NLR),raisedmonocyte-to-lymphocyteratio(MLR),elevatedsystemici mmune-inflammation index(SII),andincreasederythrocytesedim entationrate(ESR).Thesefindingsprovidef urther support for the growing body of evidence implicating immune-inflammatory mechanisms in the pathophysiology of bipolar disorder. The markedly higher proportion of patients with raised NLR in the manic group (41.7% vs 8.1%incontrols)isconsistentwithpreviouss tudiesidentifyingNLRasasensitiveperipher

al markerofinflammationinbipolardisorder.Kaleliogluetal.reportedsignificantlyhigherNLR values in patients with bipolar disorder compared with healthy controls, suggesting increased inflammatory burden even outside acute medical illness (16). Similarly, Çakır et al. demonstratedelevatedNLRinbipolarpatients,supportingitspotentialroleasareadily accessible biomarker (17). A meta-analysis by Mazza et al. further confirmed that NLR is significantlyincreasedacrossmooddisorders,reinforcingtherobustnessofthisassociation (18). The present findings extend these observations by demonstrating a high prevalence of raised NLR specifically during manic episodes.

Inflammatoryactivationappearstobeparticularlyprominentinmania.Maydaetal.observed increased NLR and decreased mean platelet volume (MPV) in patients with acute mania, indicating enhanced inflammatory activity and platelet activation (19).Although MPVvalues in the present study were numerically higher in the manic group, the difference did not reach statistical significance, which may be related to sample size or inter-individual variability. Nevertheless, the overall trend aligns with prior evidence suggesting platelet involvement in inflammatory pathways during acute mood states.

The present study also identified significantly higher MLR values in the manic group, with none of the controls showing elevated MLR. While fewer studies have examined MLR in bipolar disorder, emerging data suggest that monocyte-based ratios may reflect chronic immuneactivation.Dionisieetal.reportedthatinflammatoryratios,includingNLR,mayhelp differentiate bipolar-type depression from unipolar depression, supporting the broader relevanceofleukocyte-basedindicesinmooddisorders(21).Thecurrentfindingssuggestthat MLR may represent an additional marker of immune dysregulation in mania.

SII was significantly elevated in over half of patients with mania compared with one-third of controls. Recent psychiatric studies have reported higher SII values in bipolar disorder and schizophrenia, indicating heightened inflammatory burden (22,23). These findings are in line with the present results and support the utility of SII as an integrated marker combining information from neutrophils, lymphocytes, and platelets. Given that SII was originally developed as a prognostic indicator in oncology (24), its emerging relevance in psychiatry highlights the shared biological pathways linking inflammation and disease severity.

RaisedESRwasalsosignificantlymorecommonamongpatientswithmania.Population-based studies have demonstrated associations between depressive symptoms and elevated inflammatory markers such as CRP (11), and broader reviews emphasize the central role of inflammation in mood disorders (8,9). The present study adds to this literature by demonstrating that conventional inflammatory markers such as ESR remain useful indicators of systemic inflammation in bipolar mania.

The overall pattern of findings supports prior reviews indicating that bipolar disorder is associated with immune-inflammatory abnormalities, with greater activation during acute mood episodes (12,13). The coexistence of medical comorbidities characterized by chronic inflammation, such as metabolic syndrome and cardiovascular disease, may further amplify inflammatoryburdeninthispopulation(14). Moreover,evidencethatanti-inflammatoryagents may provide therapeutic benefit in bipolar depression underscores the clinical relevance of identifying patients with elevated inflammatory markers (25).

Strengthsofthisstudyincludetheinclusionofahealthycontrolgroup,assessmentofmultiple inflammatory markers simultaneously, and evaluation of SII alongside conventional hematologicalindices.Theuseofreadilyavailablelaboratoryparametersenhancestheclinical applicability of the findings. Several

limitations should be acknowledged.The cross-sectional design precludes causal inference. Cytokine levels and other specific immune mediators were not measured, limiting mechanistic interpretation. Potential confounding factors such as diet, bodymassindex,andsubclinicalinfectionswerenotsystematicallyassessed.Finally,thestudy was conducted at a single center with a modest sample size, which may limit generalizability.

Conclusion

In conclusion, patients with bipolar disorder in a current manic episode demonstrate significantlyhighersystemicinflammatory burdencomparedwithhealthycontrols.These findings strengthen the evidence for an immuno-inflammatory component in bipolar disorder andsupportthepotentialutilityofsimplehematologicalindicesandSIIasaccessiblemarkers of inflammation in clinical practice.

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