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Original Research Article

Assessment and Comparison of Markers of Inflammation and the Systemic Immune–Inflammation Index in Patients with Major Depressive Disorder and Healthy Controls at SMS Medical College, Jaipur: An Observational Case–Control Study

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Abstract

Background: Major depressive disorder (MDD) is increasingly recognized as a disorder with neuroimmune components, where low-grade systemic inflammation may influence neurotransmission, neuroendocrine function, and neuroplasticity. Cell count–derived indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune-inflammation index (SII) are inexpensive and clinically scalable surrogate markers of systemic inflammatory status. Evidence regarding these markers in major depressive disorder has been inconsistent; meta-analytic studies suggest that NLR is often elevated in depression, whereas findings for PLR and MLR remain variable and inconclusive.

Methods: An observational case control study was done at the Psychiatric centre, SMS medical college, Jaipur, Rajasthan, India, during the period October 2024 and August 2025. Adults aged 18-60 years who had MDD according to DSM-5-TR were recruited consecutively (screened n=72; analyzed n=65). Healthy controls after screening by Mini-interview of International Neuropsychiatry Interview (MINI, version 7.0.2) (screened n=85; analyzed n=65). Participants who had systemic illnesses, were pregnant, or taking anti-inflammatory, immunomodulatory and antibiotic medications were excluded. Absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), ESR, NLR, PLR, MLR and SII were determined from peripheral blood. Group comparisons were conducted using appropriate parametric/non-parametric metrics testing procedures (α=0.05)

Results: A total of 130 participants were included in the analysis (65 MDD; 65 controls). Mean age in MDD (31.79±9.72) was higher as compared to controls (22.19±6.65; p=0.02). There was no difference in sex distribution (female 44 vs 43 p=0.99). MDD subjects had numerically higher ANC (5077±1856 vs 4503±2655), AMC (416±211 vs 333±309), NLR (2.54±1.64 vs 1.93±0.57) and ESR (21.51±19.10 vs 9.20±6.45). However, none of the inflammatory indices showed statistically significant between-group differences.

Conclusion: In this sample collected at a hospital, various peripheral indicators of inflammation were trending towards an increase in MDD, but results were not statistically significant, possible reasons include limited statistical power, age mismatch between groups, and single-time-point sampling.

Keywords: Major Depressive Disorder; Inflammation; NLR; PLR; MLR; Systemic Immune - Inflammation Index; ESR; Biomarkers; Case - Control.

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Introduction

Major depressive disorder (MDD) is one of the leading causes of disability worldwide - characterized by pervasive low mood, anhedonia, cognitive changes, disturbances of sleep and appetite, and impaired psychosocial functioning. Although historically there has been a focus on monoaminergic, neuroendocrine and psycho-social models of mechanism, there has recently been accumulating evidence in support of a complementary system, whereby immune and inflammatory dysregulation is involved in the production, maintenance and clinical heterogeneity of depressive illness [1-3]. In this model, "low-grade" systemic inflammation - inflammation which

is subclinical yet biologically meaningful - may work as a transdiagnostic process [1,2], which intersects with stress biology, metabolic risk and neurocircuits dysfunction. Peripheral inflammatory messages can affect the central nervous system in a number of ways. The cytokines, and other associated mediators, that circulate in blood can reach the brain through leaky areas of the blood-brain barrier, by active transport, or through vagal afferent routes, and can activate microglia and change synaptic function and neuroplasticity [2,3]. These immune signals can lead to the modification of neurotransmitter production and reuptake (including serotonin and dopamine receptors), disruption of glutamatergic signaling, and influence hypothalamic-pituitary-adrenal (HPA) axis activity, in ways that plausibly connect inflammation to central depressive symptoms by depicting issues with mood, stimulus sensitivity, fatigue, anhedonia, and psychomotor changes along with hyper-sensitivity to threat [2,4]. This type of mechanism can help explain why some subsets of depressed patients show a higher level of brain and/or systemic inflammatory markers and seem to respond differently to antidepressant treatment and/or adjunctive anti-inflammatory therapies [4-6].

Multiple meta-analyses concluding on elevated circulating inflammatory biomarkers, particularly IL-6, TNF- α and CRP in MDD with heterogeneous effect sizes were published and depend on clinical phenotype, obesity/metabolic status, smoking, medication exposure and medical comorbidity. [1,5,6] While cytokine assays can be informative, they are not always practical in routine clinical practice based on cost, variability and infrastructure requirements. Consequently, there has been a new focus on hematological indices that come from standard complete blood counts. Ratios like neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) reflect immune balance and systemic inflammatory status of the host. The systemic immune--inflammation index (SII; typically calculated as neutrophils × platelets / lymphocytes, integrates these three cellular components into a single composite marker [7]. A recent analysis of data from several studies found that there were significantly higher values of NLR in depression versus healthy control groups, while findings from studies in PLR and MLR were less consistent [7]. Emerging work also suggests that SII may be associated with depressive severity and subtype, though results are inconsistent with respect to the setting and sample composition [8,9].

Despite the rising interest, the evidence is still heterogeneous and there is little data available from Indian tertiary care psychiatric settings that employed contemporaneous healthy controls screened by structured interview. Against this background, the present study was aimed to assess and compare the values of NLR, PLR, MLR, SII, and ESR between patients with MDD and healthy controls attending Psychiatric centre, SMS Medical College, Jaipur, Rajasthan, India.

Aim and Objectives

Aim: To assess and compare markers of inflammation and the systemic immune–inflammation index in patients with major depressive disorder and a healthy comparison group.

Objectives

1. To assess NLR, PLR, MLR, SII, and ESR in adults with MDD diagnosed as per DSM-5-TR.
2. To compare these inflammatory indices between MDD patients and healthy controls screened using MINI, version 7.0.2.

Material and Methods

Materials and Methods: This observational, hospital-based case–control study was conducted at the Psychiatric Centre, Department of Psychiatry, SMS Medical College, Jaipur, Rajasthan, India, from October 2024 to August 2025. The study population comprised adults presenting to the psychiatric outpatient and inpatient services of the institute during the study period. Patients aged 18–60 years who met DSM-5-TR criteria for Major Depressive Disorder (MDD) were recruited consecutively as cases. A total of 72 patients were screened, of whom seven were excluded based on the predefined exclusion criteria, resulting in 65 participants included in the final analysis. Healthy individuals aged 18–60 years without current or past psychiatric illness were recruited as controls and screened using the Mini International Neuropsychiatric Interview (MINI, version 7.0.2; English version aligned with DSM-5). Eighty-five individuals were screened, and twenty were excluded, yielding 65 controls for analysis. A participant flow diagram is presented in Figure 1.

Inclusion criteria for cases were DSM-5-TR diagnosis of MDD, age between 18 and 60 years, either sex, or provision of written informed consent by the participant or caregiver. Controls included individuals with no current or past psychiatric illness on screening, aged 18–60 years, of either sex, or willing to provide written informed consent. Participants in both groups were excluded if they were taking medications known to affect inflammatory indices (such as NSAIDs, corticosteroids, immunosuppressants, systemic antibiotics, or antimetabolites), had any acute or chronic systemic illness (e.g., COPD, diabetes mellitus), or were pregnant.

The study protocol was approved by the Institutional Ethics Committee of SMS Medical College, Jaipur, Rajasthan, India. Written informed consent was

obtained from all participants prior to enrolment. Confidentiality was ensured, and data were analysed in aggregate form.

Venous blood samples were collected once at enrolment for laboratory analysis. The parameters recorded included absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), and erythrocyte sedimentation rate (ESR, mm/hr). Derived inflammatory indices were calculated as follows: neutrophil-to-lymphocyte ratio (NLR = ANC/ALC), monocyte-to-lymphocyte ratio (MLR = AMC/ALC), platelet-to-lymphocyte ratio (PLR = platelet count/ALC), and systemic immune–inflammation index (SII = [ANC × platelet count]/ALC), as conventionally defined. Sociodemographic variables such as age and sex were also recorded.

Data were summarized as mean ± standard deviation (SD) for continuous variables and as frequencies and proportions for categorical variables. Normality of distribution was assessed prior to analysis. Between-group comparisons were performed using the independent-samples t-test or Mann–Whitney U test, as appropriate, and the chi-square test was used for categorical variables. A two-sided p value of <0.05 was considered statistically significant.

Results

A total of 130 participants were included in the final analysis which included 65 patients with MDD and 65 healthy controls. The recruiting process is summarized in Figure 1. The MDD group had a higher age than the control group (31.79±9.72 vs 22.19±6.65 years), and the difference was statistically significant (p=0.02). Sex distribution was balanced between groups and females were the majority group in both arms (44/65 in MDD and 43/65 in controls; p=0.99).

Across indices of hematological and derived inflammatory markers, the MDD group showed numerically increased markers of innate immunological activation and the inflammatory burden. In particular, ANC, AMC, NLR, and ESR were higher in MDD subjects than controls. On the contrary, ALC and PLR were lower in MDD and SII was slightly lower overall, showing that the composite index was not increased even though neutrophil-related measures were higher in this dataset.

Despite these directional trends there was no statistically significant differences, at α=0.05, between groups for any inflammatory marker in the final study analysis. The lack of significance was in the context of significant within-group variability - especially for ESR and SII - with a significant imbalance of age at the two groups that may have added to residual confounding and diminished the interpretability of unadjusted comparisons.

Table 1: Demographic characteristics of participants

Characteristic	MDD (n=65)	Controls (n=65)	p value
Age, years (mean ± SD)	31.79 ± 9.72	22.19 ± 6.65	0.02
Female, n	44	43	0.99
Male, n	21	22	0.99

Participants with MDD were much older than controls, indicating that the study did not adjust for age and this is a potential source of confounding because the inflammatory indices may rise with age. In contrast, sex distribution was similar which reduces sex related bias for comparisons of groups. Given the age difference, it is important to interpret the inflammatory indices cautiously, and future work should prioritize either matching or adjustment in order to isolate immune differences due to depression.

Table 2: Inflammatory markers and derived indices in MDD vs controls (mean ± SD)

Parameter	MDD (n=65)	Controls (n=65)
ANC (cells/µL)	5077.387 ± 1856.482	4502.72 ± 2655.22
ALC (cells/µL)	1998.328 ± 591.1479	2325.25 ± 1957.26
AMC (cells/µL)	416.0175 ± 211.1922	332.85 ± 309.35
NLR	2.540817 ± 1.638959	1.93 ± 0.574
MLR	0.20 ± 0.107	0.143 ± 0.056
PLR	87.93321 ± 44.77932	107.198 ± 53.884
SII	446470.8 ± 346685.5	482687.2 ± 278623.9
ESR (mm/hr)	21.51 ± 19.10095	9.2008 ± 6.448

Mean correlation of ANC, AMC, NLR, MLR and ESR in MDD and controls were higher in line with a tendency towards an increased innate immune activation and systemic inflammatory tone. However, ALC and PLR were reduced in the MDD group, and SII was not elevated, indicating that composite indices may act differently depending on the balance of neutrophils, lymphocytes and platelets. Substantial dispersion - particularly for SII and ESR - probably reduced power to detect differences.

Table 3: Effect sizes (standardized mean differences) for inflammatory indices

Marker	Direction (MDD vs control)	Cohen's d (approx.)
ANC	Higher	0.25
ALC	Lower	−0.23
AMC	Higher	0.31
NLR	Higher	0.50
MLR	Higher	0.67
PLR	Lower	−0.39
SII	Lower	−0.12
ESR	Higher	0.86

Standardized differences were indicative of small-to-moderate elevations for NLR and MLR and a relatively larger elevation for ESR, and a decrease for ALC and PLR. Importantly, these effect sizes have to be interpreted against the conclusion of non-significance from the study and marked variance for several of the markers. The pattern is compatible with biological plausible changes in MDD due to inflammation but appears that larger age matched groups will be required to replicate these patterns.

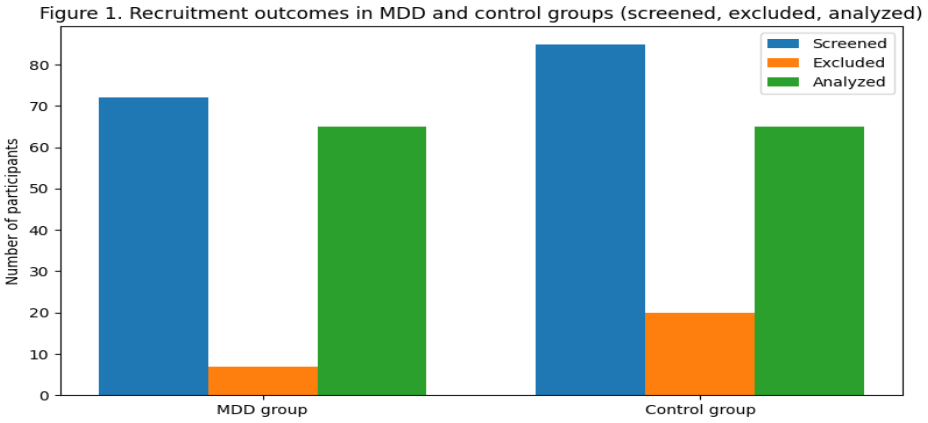

Figure 1: Recruitment outcomes in MDD and control groups (screened, excluded, analyzed)

This bar chart summarizes recruitment and final analytic inclusion of participants into each of the study arms. The MDD group included 72 people screened, 7 who were excluded for applying eligibility criteria, and 65 in the final analysis. The control group was 85 screened, with a higher count of people excluded (n=20) after the MINI screening and exclusion criteria, yielding the same number of individuals for final analysis (n=65). Equal analysed sample sizes increased comparability, while different proportions of exclusion represent more stringent screening in controls.

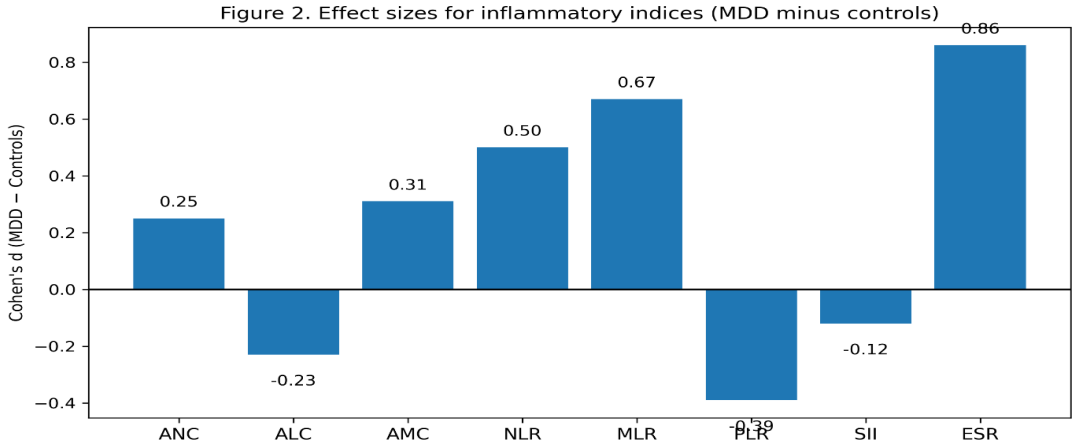

Figure 2: Standardized mean differences (Cohen's d) for inflammatory markers in MDD compared with controls

This figure shows standardized mean differences (Cohen's d) across inflammatory markers between MDD and control subjects (allowing these variables to be compared across the compositions of scale-free). The positive value values indicate higher levels in MDD and the negative values indicate lower levels. The highest elevation was observed for ESR, followed by MLR and NLR and suggests a

possible trend of increased inflammatory burden and innate immune predominance in MDD. PLR, ALC and SII become lower indicating heterogeneity in composite indices and cell-line balance.

Discussion

This case-control study assessed peripheral inflammatory parameters and indices in adults with MDD with healthy controls in a tertiary care psychiatric setting in Jaipur. The principal finding was that several markers (ANC, AMC, NLR, ESR) were higher numerically among patients with MDD; however, during the final analysis, none of the differences between groups were found to be statistically significant. These findings are consistent with the broader literature suggesting the presence of inflammation-related signals in major depressive disorder, while also emphasizing that effect sizes are often small and context-dependent, particularly in the presence of substantial confounding and variability.

The evidence of immune-inflammatory contribution to depression is well supported, as meta-analyses demonstrate increases in the expression of IL-6, TNF-α and CRP and mechanistic models of cytokine action on neurotransmitter breakdown and neurocircuit activity [10-12]. These observations provided the motivation for increasing interest in haematological indices that can be obtained from routine blood counts. A meta-analysis and meta-regression in 2022 showed that ESR was significantly increased in depressed persons relative to healthy controls; however, the studies that examined PLR and MLR were inconsistent in their results, indicating heterogeneity of samples, the time of measurement, and clinical characteristics. In the present dataset, NLR was higher in MDD (2.54±1.64 vs 1.93±0.57) and the standardised difference was moderate, despite the high variance and absence of statistical significance. This departure from some of the previous positive results may be related to sample size, to clinical characteristics (e.g., severity, duration, comorbidity), or to uncontrolled differences in lifestyle (e.g., smoking, obesity, sleep disruption).

With respect to SII, there are emerging studies showing possible relationships with depressive subtype and severity and possible elevations of the SII especially in more severe presentations. For example, one large sample study found associations between SII and categories of depression severity. In contrast, the present study did not show SII increased in MDD patients, despite elevated levels of neutrophil-related measures. This could be because a balance was achieved by platelet and lymphocyte patterns that counteracted changes in neutrophils or the clinical state in which a sample was taken that did not have an equally elevated composite inflammatory burden. Additionally, high SD of SIIs in both of these groups implies fairly large biological dispersions and/or measurement variability that can obscure group differences.

A major methodological issue is the large age gap between groups (MDD older than controls). Age is followed by immune remodelling and increased inflammatory activity; thus, residual confounding is possible even if statistical tests are applied. Inflammatory biomarkers in depression are also affected by body mass index, metabolic syndrome, infections, the status of menstruation and medication exposure. Although the present study included, by design, a sample that excluded those with systemic illness and anti-inflammatory/immunomodulating medication use, strengthening internal validity, future work inclusion of that could be done by tighter matching and multivariable adjustment. Longitudinal sampling is also important: inflammatory indices may vary across depressive episodes and with treatment response, and single-time-point measurements may miss dynamic immune changes.

Clinically the present findings retain their relevance. Even without statistical significance, the observed trends of directionality are consistent with biological plausibility as well as the literature that supports depressive phenotypes that are associated with inflammation [13,14]. The study adds local data from a North Indian tertiary-care centre, structured control screening using MINI, version 7.0.2 and estimates of effect size which can be used in sample-size calculations going forward. These results indicate that indices related to inflammation may not be useful markers detectable solely on unselected samples of an outpatient population for these reasons, but that they can be important contributors to multi-marker risk stratification - particularly if combined with measures of symptoms, metabolism and change over time.

Limitations

(1) Single centre and small sample size which may limit generalisability and statistical power

(2) Only one baseline blood sample was taken; post-treatment measures were unavailable.

(3) Age mismatch between groups may have confounded between inflammatory comparisons.

(4) Subgroup analyses by age/sex or clinical severity were not conducted.

Research implications

Prospective, multicentre studies involving controls matched by age and BMI, having repeated measures on the treatment group and predefined stratification of the phenotypes (i.e. melancholic vs. atypical, severe vs. moderate, psychotic features) are

warranted to clarify which inflammatory indices are clinically meaningful in MDD.

Conclusion

In this observational case-control study from SMS Medical College, Jaipur, inflammatory markers based on peripheral blood counts demonstrated trend-level elevations in MDD (especially ANC, AMC, NLR and ESR) compared with healthy controls although no parameter was statistically significant in the final analysis. These findings highlight the heterogeneity and sensitivity to confounding (largely due to age) and biological variability in inflammation-linked biomarkers of depression. While low-grade systemic inflammation is a reasonable transdiagnostic mechanism of disease in MDD, larger, age-matched, multicentre longitudinal studies are required to establish whether indices such as NLR, PLR, MLR, and SII are reliable for identifying patients who may benefit from adjunctive anti-inflammatory interventions.

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