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Association Between Inflammatory Biomarkers, Sleep Quality, and Depression Severity in Patients with Major Depressive Disorder: A Cross-Sectional Study

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Abstract

Background: Major depressive disorder (MDD) is a common psychiatric disorder associated with significant morbidity and impaired quality of life. Increasing evidence suggests that systemic inflammation and sleep disturbance may contribute to the pathophysiology and severity of depression. Hematological inflammatory biomarkers such as neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have emerged as inexpensive indicators of systemic inflammation.

Aim: To evaluate the association between inflammatory biomarkers, sleep quality, and depression severity among patients with major depressive disorder.

Materials and Methods: This cross-sectional study was conducted among 120 patients diagnosed with MDD attending the Psychiatry Department of a tertiary care hospital. Depression severity was assessed using the Hamilton Depression Rating Scale (HAM-D), while sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI). Complete blood count parameters were used to calculate NLR, PLR, and SII. Correlation analysis and multiple linear regression analysis were performed to identify associations and independent predictors of depression severity.

Results: The mean age of participants was 34.8 ± 10.2 years, with females constituting 56.7% of the study population. NLR, PLR, SII, and PSQI scores showed

significant positive correlations with depression severity ($p < 0.05$). Patients with severe depression demonstrated significantly higher inflammatory biomarker levels and poorer sleep quality compared to those with mild and moderate depression. Multiple linear regression analysis identified NLR, PSQI score, smoking status, and comorbid anxiety as significant independent predictors of depression severity.

Conclusion: Elevated inflammatory biomarkers and poor sleep quality were significantly associated with greater depression severity in patients with major depressive disorder. Hematological inflammatory markers and sleep quality assessment may serve as simple and cost-effective tools for evaluating disease severity in MDD.

Keywords: Major depressive disorder; Depression severity; Neutrophil–lymphocyte ratio; Platelet–lymphocyte ratio; Systemic immune-inflammation index; Sleep quality; Pittsburgh Sleep Quality Index.

Introduction

Major depressive disorder (MDD) is a common and debilitating psychiatric illness characterized by persistent low mood, loss of interest or pleasure, cognitive dysfunction, impaired social functioning, and reduced quality of life. It is among the leading contributors to global disability and imposes substantial psychological, social, and economic burdens on affected individuals and healthcare systems worldwide. Despite extensive research, the biological mechanisms underlying depression remain incompletely understood, and increasing attention has been directed toward the role of systemic inflammation in the pathophysiology of depressive disorders [1–4]. Over the past decade, a growing body of evidence has suggested that immune-inflammatory dysregulation contributes significantly to the development and progression of depression. Several studies have demonstrated elevated levels of pro-inflammatory cytokines, altered leukocyte profiles, and activation of inflammatory signaling pathways among patients with MDD compared to healthy individuals [3,8–12]. Chronic low-grade inflammation is believed to influence neurotransmitter metabolism, hypothalamic–pituitary–adrenal axis activity, neuroplasticity, and neuronal survival, thereby contributing to depressive symptomatology and illness severity [9–12]. Recently, hematological inflammatory biomarkers derived from routine complete blood count investigations have emerged as inexpensive, accessible, and clinically practical indicators of systemic inflammation. Among these, the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have gained increasing attention in psychiatric research [1, 2]. Similarly, PLR and SII are considered reliable markers of inflammatory burden and immune dysregulation and have shown potential associations with psychiatric morbidity and disease severity [8,10,12]. Sleep disturbance is another major clinical feature of MDD and is frequently reported among patients with depression. Symptoms such as insomnia, poor sleep quality, prolonged sleep latency, fragmented sleep, early morning awakening, and excessive daytime sleepiness are highly prevalent among individuals with depressive disorders [5,6]. Sleep abnormalities not only worsen emotional and cognitive functioning but also negatively affect treatment outcomes and increase the risk of relapse. Emerging evidence suggests a complex bidirectional relationship between sleep dysfunction and inflammation, wherein poor sleep quality may promote inflammatory activation, while inflammatory mediators may further disrupt sleep regulation and circadian rhythms [6,7,11,12]. Although several previous studies have independently examined inflammatory biomarkers and sleep disturbances in

depression, limited research has comprehensively investigated the combined relationship between hematological inflammatory markers, sleep quality, and depression severity within a single clinical framework [1–7]. Understanding these interrelationships may help identify low-cost, readily available biomarkers that can assist in the assessment of disease severity and improve clinical monitoring in patients with depression. Therefore, the present study aimed to evaluate the association between inflammatory biomarkers, sleep quality, and depression severity among patients with major depressive disorder.

Materials and Methods

Study Design and Setting

This cross-sectional observational study was conducted in the Department of Psychiatry of a tertiary care teaching hospital between January 2025 and December 2025.

Study Population

Adult patients diagnosed with major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, attending the Psychiatry Outpatient Department during the study period, were screened for eligibility.

Sample Size

A total of 120 patients were included in the study using consecutive sampling.

Inclusion Criteria

1. Patients aged 18–65 years.
2. Patients diagnosed with major depressive disorder according to DSM-5 criteria.
3. Patients willing to provide written informed consent.
4. Patients able to complete study questionnaires and interviews.

Exclusion Criteria

1. Patients with bipolar disorder, schizophrenia, or other psychotic disorders.
2. Patients with acute or chronic inflammatory diseases.
3. Patients with autoimmune disorders.
4. Patients with active infections within the previous four weeks.
5. Patients with malignancy.
6. Patients receiving immunosuppressive therapy.
7. Pregnant or lactating women.
8. Patients with severe cognitive impairment preventing questionnaire completion.

Data Collection

After obtaining informed consent, demographic and clinical information including age, gender, body mass index (BMI), smoking status, duration of illness, antidepressant use, and presence of comorbid anxiety disorders were recorded using a structured proforma.

Assessment of Depression Severity

Depression severity was assessed using the Hamilton Depression Rating Scale (HAM-D).

Assessment of Sleep Quality

Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), a validated self-administered questionnaire assessing sleep quality over the preceding month.

Laboratory Assessment

Venous blood samples were collected from all participants under standard aseptic precautions. Complete blood count parameters were measured using an automated hematology analyzer.

The following inflammatory biomarkers were calculated:

NLR = Absolute Neutrophil Count / Absolute Lymphocyte Count

PLR = Platelet Count / Absolute Lymphocyte Count

SII = (Platelet Count × Absolute Neutrophil Count) / Absolute Lymphocyte Count

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics for Windows, Version 21 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. Comparisons between depression severity groups were performed using one-way analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. Pearson correlation analysis and multiple linear regression analysis were performed to identify independent predictors of depression severity. A p-value <0.05 was considered statistically significant.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee (IEC No: IEC/2024/ASCOMS/I/65). Written informed consent was obtained from all participants before enrollment.

Results

A total of 120 patients with major depressive disorder were included in the study, with females constituting 56.7% of the study population. The mean HAM-D score was 19.6 ± 5.7, while the mean PSQI score was 10.8 ± 3.9.

Table 1: Sociodemographic and Clinical Characteristics of Study Participants (N = 120)

Variable	Frequency (n)	Percentage (%)
18–25 years	28	23.3
26–35 years	42	35.0
36–45 years	31	25.8
>45 years	19	15.8
Male	52	43.3
Female	68	56.7
Smoker	38	31.7
Non-smoker	82	68.3
Antidepressant use	74	61.7
Comorbid anxiety	46	38.3
Continuous Variables		
Variable	Mean ± SD	
Age (years)	34.8 ± 10.2	
BMI (kg/m²)	25.7 ± 4.3	
Duration of illness (years)	3.6 ± 2.1	

Table 1 shows the baseline demographic and clinical profile of the 120 study participants. The majority of patients belonged to the 26–35 years age group (42 patients, 35.0%), followed by the 36–45 years group (31 patients, 25.8%). Female participants were more common, accounting for 68 patients (56.7%), while males constituted 52 patients (43.3%). Smoking was reported in 38 patients (31.7%), and antidepressant use was observed in 74 patients (61.7%). Comorbid anxiety was present in 46 patients (38.3%). The mean age of the

participants was 34.8 ± 10.2 years, mean BMI was 25.7 ± 4.3 kg/m², and mean duration of illness was 3.6 ± 2.1 years.

Table 2: Inflammatory Biomarkers, Sleep Quality, and Depression Severity Scores

Variable	Mean ± SD	Minimum	Maximum
NLR	3.42 ± 1.18	1.2	6.8
PLR	142.6 ± 38.5	78	256
SII	712.4 ± 218.3	320	1320
PSQI Score	10.8 ± 3.9	3	19
HAM-D Score	19.6 ± 5.7	8	31

Table 2 presents the mean inflammatory biomarker levels, sleep quality scores, and depression severity scores among the study participants. The mean NLR was 3.42 ± 1.18, while the mean PLR and SII were 142.6 ± 38.5 and 712.4 ± 218.3, respectively, indicating increased inflammatory activity among patients with depression. The mean PSQI score was 10.8 ± 3.9, suggesting generally poor sleep quality in the study population. The mean HAM-D score was 19.6 ± 5.7, indicating overall moderate depression severity.

Table 3: Distribution of Depression Severity According to HAM-D Scores

Severity Category	Frequency (n)	Percentage (%)
Mild Depression	32	26.7
Moderate Depression	58	48.3
Severe Depression	30	25.0

Table 3 demonstrates the distribution of patients according to HAM-D severity categories. Moderate depression was the most common category, observed in 58 patients (48.3%). Mild depression was present in 32 patients (26.7%), while severe depression was observed in 30 patients (25.0%). These findings indicate that nearly half of the participants had moderate depressive symptoms.

Table 4: Correlation of Biomarkers and Sleep Quality with Depression Severity

Variable	Correlation Coefficient (r)	p-value
NLR	0.48	<0.001
PLR	0.31	0.002
SII	0.44	<0.001
PSQI Score	0.59	<0.001
BMI	0.19	0.041
Duration of Illness	0.28	0.006

Table 4 shows the correlation between inflammatory biomarkers, sleep quality, and depression severity. NLR demonstrated a moderate positive correlation with HAM-D score ($r = 0.48$, $p < 0.001$), indicating that higher NLR values were associated with greater depression severity. PLR also showed a significant positive correlation ($r = 0.31$, $p = 0.002$), while SII demonstrated a moderate positive correlation with depression severity ($r = 0.44$, $p < 0.001$). Among all variables, PSQI score showed the strongest correlation with HAM-D score ($r = 0.59$, $p <$

0.001), suggesting that poorer sleep quality was strongly associated with increased depressive symptom severity. BMI (r = 0.19, p = 0.041) and duration of illness (r = 0.28, p = 0.006) also demonstrated weak but statistically significant positive correlations with depression severity.

Table 5: Comparison of Biomarker Levels Across Depression Severity Groups

Variable	Mild Depression	Moderate Depression	Severe Depression	p-value
NLR	2.41 ± 0.82	3.37 ± 0.96	4.82 ± 1.21	<0.001
PLR	118.5 ± 22.1	141.3 ± 31.8	176.4 ± 40.5	<0.001
SII	521.2 ± 110.4	702.6 ± 168.5	981.3 ± 242.8	<0.001
PSQI Score	7.2 ± 2.4	10.6 ± 3.1	14.3 ± 3.8	<0.001

Table 5 compares inflammatory biomarker levels and sleep quality scores across mild, moderate, and severe depression groups. Mean NLR values progressively increased from 2.41 ± 0.82 in mild depression to 3.37 ± 0.96 in moderate depression and 4.82 ± 1.21 in severe depression (p < 0.001).

Similarly, mean PLR values increased from 118.5 ± 22.1 in mild depression to 176.4 ± 40.5 in severe depression. SII values also showed a marked increase across severity groups, ranging from 521.2 ± 110.4 in mild depression to 981.3 ± 242.8 in severe depression. PSQI scores increased progressively with depression severity, with mean scores of 7.2 ± 2.4 in mild depression, 10.6 ± 3.1 in moderate depression, and 14.3 ± 3.8 in severe depression. All comparisons were statistically significant (p < 0.001), indicating worsening inflammation and sleep quality with increasing depression severity.

Table 6: Multiple Linear Regression Analysis Predicting Depression Severity

Predictor Variable	β Coefficient	Standard Error	p-value
NLR	2.84	0.67	<0.001
PSQI Score	1.16	0.22	<0.001
BMI	0.28	0.16	0.082
Smoking Status	1.92	0.74	0.014
Comorbid Anxiety	2.31	0.71	0.002

Table 6 presents the independent predictors of depression severity after adjusting for confounding variables. NLR emerged as a significant independent predictor of higher HAM-D scores (β = 2.84, p < 0.001). PSQI score also showed a strong independent association with depression severity (β = 1.16, p < 0.001), suggesting that poor sleep quality significantly contributes to worsening depressive symptoms. Smoking status (β = 1.92, p = 0.014) and comorbid anxiety (β = 2.31, p = 0.002) were also significantly associated with higher depression severity. Although BMI demonstrated a positive association with HAM-D score (β = 0.28), it did not remain statistically significant after adjustment for other variables (p = 0.082).

Discussion

The present study evaluated the association between inflammatory biomarkers, sleep quality, and depression severity among patients with major depressive disorder (MDD). The findings demonstrated that elevated inflammatory biomarkers, including neutrophil–

lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), were significantly associated with greater depression severity. In addition, poor sleep quality measured using the Pittsburgh Sleep Quality Index (PSQI) showed a strong positive correlation with depressive symptom severity. These findings support the growing evidence suggesting that systemic inflammation and sleep dysfunction play important roles in the pathophysiology of depression. In the present study, NLR demonstrated a significant positive association with HAM-D scores, indicating that higher inflammatory activity was associated with greater severity of depressive symptoms. Similar findings have been reported in previous studies evaluating inflammatory biomarkers in psychiatric disorders [13–18]. Chronic low-grade inflammatory activation may influence neurotransmitter metabolism, neuroendocrine pathways, and neuroplasticity, thereby contributing to depressive symptomatology [13,14]. Elevated inflammatory mediators may also alter serotonin metabolism and hypothalamic–pituitary–adrenal axis function, which are important biological mechanisms implicated in depression [14,16]. PLR and SII were also significantly elevated among patients with severe depression compared to those with mild and moderate disease severity. These findings suggest that combined hematological inflammatory indices may reflect the systemic inflammatory burden associated with depressive disorders. Previous studies and meta-analyses have similarly demonstrated increased inflammatory activity and elevated inflammatory biomarkers among patients with depression [14–18]. The progressive increase in NLR, PLR, and SII values across depression severity groups observed in the present study further strengthens the evidence supporting immune-inflammatory dysregulation in MDD. Sleep disturbance emerged as another important finding in the present study. Patients with severe depression demonstrated significantly higher PSQI scores compared to those with mild and moderate depression, indicating poorer sleep quality with increasing depression severity. Sleep abnormalities such as insomnia, fragmented sleep, prolonged sleep latency, and reduced sleep efficiency are common manifestations of depression and significantly affect emotional regulation and daily functioning [19]. The strong positive correlation between PSQI score and HAM-D score observed in this study suggests that worsening sleep quality is closely associated with greater depressive symptom severity. The bidirectional relationship between sleep dysfunction and inflammation may partly explain the observed association between poor sleep quality and severe depression. Previous studies have shown that inflammatory activation can disrupt sleep regulation and circadian rhythm pathways, while chronic sleep disturbance itself may increase systemic inflammatory responses [13,19,20]. Elevated inflammatory cytokines have been associated with impaired sleep continuity, daytime fatigue, and worsening mood symptoms, suggesting that inflammation and sleep dysfunction may act synergistically in the progression of depressive disorders [20]. The present study also identified smoking status and comorbid anxiety as significant independent predictors of depression severity. Smoking has previously been associated with increased inflammatory activity and altered immune responses, which may exacerbate depressive symptoms and worsen disease severity [16]. Similarly, comorbid anxiety disorders commonly coexist with depression and are known to negatively affect sleep quality, emotional functioning, and overall quality of life. These factors may therefore contribute to higher HAM-D scores among affected individuals. The findings of this study have important clinical implications.

Hematological inflammatory biomarkers such as NLR, PLR, and SII are inexpensive, readily available, and easily obtainable from routine laboratory investigations. Their use in clinical settings may help identify patients at risk of severe depression and assist in monitoring disease progression. Furthermore, assessment of sleep quality using simple validated questionnaires such as PSQI may improve the overall clinical evaluation of patients with depression. The use of low-cost inflammatory markers and sleep assessment tools increases the practical applicability of these findings, particularly in resource-limited healthcare settings. The present study has several strengths. It simultaneously evaluated inflammatory biomarkers, sleep quality, and depression severity within a single clinical framework. Additionally, inexpensive and routinely available hematological parameters were utilized, improving the practical applicability of the findings in routine psychiatric practice. The use of validated assessment tools, including HAM-D and PSQI, further strengthened the reliability of the study findings. However, certain limitations should be acknowledged. First, the cross-sectional design limited the ability to establish causal relationships between inflammatory biomarkers, sleep quality, and depression severity. Second, the study was conducted at a single tertiary care center with a relatively small sample size, which may limit the generalizability of the findings. Third, inflammatory cytokines and advanced biochemical markers were not evaluated. Additionally, potential confounding factors such as physical activity, dietary habits, and socioeconomic status were not comprehensively assessed. Overall, the findings of the present study support the growing evidence linking systemic inflammation and sleep dysfunction with depression severity. Future longitudinal studies with larger sample sizes are warranted to further clarify the causal relationship between inflammatory dysregulation, sleep quality, and depressive symptom severity.

Conclusion

The present study demonstrated a significant association between inflammatory biomarkers, sleep quality, and depression severity among patients with major depressive disorder. Elevated levels of neutrophil–lymphocyte ratio, platelet–lymphocyte ratio, and systemic immune-inflammation index were associated with greater severity of depressive symptoms. Poor sleep quality also showed a strong positive correlation with depression severity. These findings support the role of systemic inflammation and sleep dysfunction in the pathophysiology of depression.

Strengths and Limitations

The present study has several strengths. It simultaneously evaluated inflammatory biomarkers, sleep quality, and depression severity within a single clinical framework. Additionally, inexpensive and routinely available hematological parameters were utilized, improving the practical applicability of the findings in routine psychiatric practice. The use of validated assessment tools, including the Hamilton Depression Rating Scale (HAM-D) and Pittsburgh Sleep Quality Index (PSQI), further strengthened the reliability of the study findings.

However, the present study also had certain limitations. First, the cross-sectional design limited the ability to establish causal relationships between inflammatory biomarkers, sleep quality, and depression severity. Second, the study was conducted at a single tertiary care center with a relatively small sample size, which may limit the generalizability of the findings. Third, inflammatory cytokines and advanced biochemical markers were not evaluated. Additionally, potential confounding factors such as physical activity, dietary

habits, and socioeconomic status were not comprehensively assessed.

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