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Association between Sleep Quality and Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio in Patients with Bipolar Disorder

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Abstract

Background: Many patients with bipolar disorder (BD) experience sleep problems. Sleep abnormalities are associated with immune dysfunction, which may be reflected by hematological indices.

Purpose: This study aimed to investigate the association between sleep quality and the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) in patients with BD.

Methods: This cross-sectional study was performed at Imam Hossein Hospital, Tehran, Iran, from March to September 2023. Hospitalized patients newly diagnosed with BD were interviewed to complete questionnaires. Sleep quality and manic and depressive symptoms of the participants were assessed using the Pittsburg Sleep Quality Index (PSQI), the Young Mania Rating Scale (YMRS), and the Hamilton Depression Rating Scale (HDRS), respectively. Furthermore, blood samples were taken from each patient to investigate hematological indices. Continuous and categorical variables were compared between groups using an independent-sample t test and chi-square/Fisher's exact tests, respectively. The Poisson regression model was also used to investigate predictors of the PSQI score.

Results: Of 305 patients included in the study, 78.7% and 21.3% were experiencing manic and depressive episodes, and 90.20% had poor sleep quality. The prevalence of poor sleep quality was significantly higher in depressed patients than in manic patients (100% vs. 87.5%; $P = 0.003$). Depressed patients had significantly higher platelet counts (mean difference [MD], 34.09 [95% CI, 9.35-58.83]; $P = 0.007$) and PLR (MD, 38.14 [95%CI, 10.25-66.02]; $P = 0.008$) and lower lymphocyte counts (MD, 266.04 [95% CI, [14.41-517.67]; $P = 0.038$) compared with manic patients. The Poisson regression model with adjustment revealed that men (risk ratio [RR], 1.113; $P = 0.025$), those with lower educational levels (RR, 1.164; $P = 0.001$), and those with higher HDRS scores (RR, 1.370; $P < 0.001$) had significantly deteriorated sleep quality.

Conclusion: Most bipolar patients have poor sleep quality, particularly those with depressive episodes. Depressed patients had significantly higher platelet counts and PLR. Also, depressed patients with male sex, lower educational levels, and more severe depressive symptoms had poorer sleep quality.

Keywords: Bipolar Disorder, Blood Cell Count, Depression, Mania, Sleep Quality

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Introduction

Bipolar disorder (BD) is a multifactorial disorder characterized by mood fluctuations (1). The global prevalence

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↑What is "already known" in this topic:
Many patients with bipolar disorder experience sleep problems. Sleep disturbances adversely affect disease course, overall treatment outcome, and subjective quality of life. Sleep abnormalities are associated with immune dysfunction, which may be reflected by hematological indices such as the neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio (PLR).

→What this article adds:
Most bipolar patients have poor sleep quality, particularly those with depressive episodes. Depressed patients had significantly higher platelet counts and PLR. Also, depressed patients with male sex, lower educational levels, and more severe depressive symptoms had poorer sleep quality.

of BD is estimated to be more than 1% and rising (2). It can cause cognitive and functional impairments, resulting in reduced quality of life and increased mortality, mostly by suicide. In addition, bipolar patients mainly suffer from cognition and functioning problems, as well as physical diseases, such as cardiovascular disorders and diabetes mellitus (1). According to recent studies, inflammation plays a crucial role in the pathophysiology of BD. Different immunological and inflammatory alterations may be observed in patients with BD, including increased levels of inflammatory cytokines and activated lymphocyte cells (3). Chronic inflammation may lead to structural brain abnormalities and cognitive deficits in bipolar patients (4).

Recurrent episodes of mania (or hypomania) and depression in bipolar patients are associated with a substantial burden of morbidity and mortality (5). Bipolar patients have often disturbances in mood, energy, activity, cognition, behavior, sleep, and interpersonal functioning (6). Many of them suffer from sleep disturbances, presented differently at various episodes of their disease. Sleep disturbances adversely affect disease course, overall treatment outcome, and subjective quality of life. Moreover, poor sleep quality may increase the risk of suicidal ideation and attempts in these patients (7). Sleep disturbances directly impair cognitive functioning in bipolar patients (8).

Sleep abnormalities are strongly associated with alterations in the immune system. The interaction between poor sleep quality and increased levels of proinflammatory cytokines leads to a vicious cycle (9). Several proinflammatory cytokines (eg, IL-2, IL-6, TNF, and MCP1) are raised in bipolar patients. However, the high expenses make researchers and health care professionals reluctant to measure cytokine levels (10).

The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) are cost-effective parameters, obtained easily from a complete blood count test (11). Thus, hematological indices, like the NLR and PLR, are candidates to indicate the severity of symptoms in bipolar patients. Based on the literature, available data about the association between sleep quality and the PLR and NLR in patients with BD is restricted. This study aimed to investigate the association between sleep quality and the NLR and PLR in patients with different episodes of BD.

Methods

Study Design and Patients

This cross-sectional study was conducted at Imam Hossein Hospital, Tehran, Iran, from March to September 2023. The study population was patients hospitalized in the psychiatric ward with a new diagnosis of BD. The inclusion criteria were as follows: Diagnosis of bipolar disorder by 2 psychiatrists based on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (6), age between 18 and 75 years, willingness to participate in the study, and literacy to read and write. Patients with the following features were excluded from the study: pregnancy or recent childbirth; smoking, alcohol, or drug consumption; simultaneously suffering from other psychiatric disorders; suffering from rheumatological, autoimmune, or infectious diseases; consumption of antibiotics or immunosuppressive medication; abnormal counts of white blood cells, neutrophils, lymphocytes, and platelets in laboratory findings.

Data Collection

Based on a study by Montezano et al (12) and considering $\alpha = 5\%$, $s = 5.1$, $d = 0.6$, and a dropout rate of 10%, the sample size was estimated to be 305. In this study, sampling was based on the consecutive sampling method. After signing written informed consent, eligible patients were interviewed to complete a set of questionnaires as follows: a checklist of baseline characteristics—including age, sex, marital status, occupational status, and educational status; the Young Mania Rating Scale (YMRS); the Hamilton Depression Rating Scale (HDRS); and the Pittsburg Sleep Quality Index (PSQI). Moreover, a psychiatrist guided the patients in case of any ambiguity or difficulty regarding the statements. Also, blood samples were taken from each patient by a trained nurse. Subsequently, samples (citrated plasma) were rapidly transferred at 20ºC to the laboratory of Imam Hossein Hospital to investigate hematological indices.

Instruments of the Study

Young Mania Rating Scale

The YMRS assesses manic symptoms in the preceding 48 hours. It has 11 statements scored based on the Likert scale. The scores of all statements are summed together, ranging between 0 and 60. An overall score ≥17 is considered a manic episode (13). A study by Mohammadi et al reported the reliability of the Persian version of the YMRS with a Cronbach's alpha coefficient of 0.72. The validity of the aforementioned scale was assessed by Exploratory Factor Analysis (Comparative Fit Index, 0.91) (14).

Hamilton Depression Rating Scale

The HDRS assesses the depressive symptoms of the patients, with 17 statements scored based on the Likert scale. The scores of all statements are summed together, ranging between 0 and 54. An overall score of ≥8 is considered a depressive episode. A study by Ahmadpanah et al reported the reliability of the Persian version of the HDRS with a Cronbach's alpha coefficient of 0.88. The validity of the aforementioned scale was assessed by the correlation between the Montgomery–Asberg Depression Rating Scale and the HDRS ($r = 0.92$; $P < 0.001$) (15).

Pittsburg Sleep Quality Index

The PSQI is a questionnaire comprising 19 questions that assesses sleep quality in the preceding month, with 7 components as follows: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medication, and daily dysfunction. Each component is scored on a range between 0 (without problem) and 3 (severe problem). The scores of the 7 components are summed together, and an overall PSQI score of ≥6 indicates poor sleep quality (16). A study by Farrahi et al reported the reliability of the Persian version of the

PSQI with a Cronbach's alpha coefficient of 0.77. The validity of the aforementioned scale was assessed by the correlation between the General Health Questionnaire-12 and the PSQI (r = 0.54; $P < 0.001$) (17).

Statistical Analysis

Data were processed using Statistical Package for the Social Sciences (SPSS) software Version 16.0. Variables were described as frequency, percentage, mean, standard deviation, mean difference, and 95% CIs. Continuous variables were compared between groups using an independent-sample t test. Categorical variables were compared between groups using the chi-square and Fisher's exact tests. The Poisson regression model was also used to investigate predictors of the PSQI score—the associations were illustrated by Wald χ^2. In the best model, parameters were adjusted for age, sex, marital status, educational status, occupation, HDRS, YMRS, neutrophil count, lymphocyte count, NLR, and PLR. In this study, $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of the Patients

The mean age of 305 patients in this study was 43.11 ± 13.72 years (range, 19-72 years), and 70.5% were women. Furthermore, 78.7% and 21.3% of them were experiencing either manic or depressive episodes of BD, respectively. Table 1 demonstrates the baseline characteristics of the patients in detail.

Sleep Quality of the Patients

The mean PSQI score of the patients was 9.17 ± 2.63, indicating an overall poor sleep quality. In other words, 90.20% of participants had poor sleep quality. The prevalence of poor sleep quality was significantly higher in depressed patients than in manic patients (100% vs. 87.5%; $P = 0.003$). Most components of the PSQI significantly differed between depressed and manic patients: subjective sleep quality ($P = 0.014$), sleep duration ($P = 0.003$), sleep disturbances ($P = 0.014$), sleep medication ($P < 0.001$), and daily dysfunction ($P < 0.001$). Table 2 depicts overall sleep quality and its components in the patients.

Hematological Indices of the Patients

Table 3 presents the hematological indices of the patients. Depressed patients had significantly higher platelet counts (MD, 34.09 [95% CI, 9.35-58.83]; $P = 0.007$) and P/L ratio (MD, 38.14 [95% CI, 10.25-66.02]; $P = 0.008$) compared with manic patients. Moreover, manic patients had significantly higher lymphocyte counts compared with depressed patients (MD, 266.04; [95% CI, 14.41-517.67]; $P = 0.038$). Other hematological indices did not differ significantly between groups.

Poisson Regression Model

The model fitness indices were within the acceptable range (Pearson Chi-square value, 146.400; df, 293; value/df, 0.500). The omnibus test's result was also significant (likelihood ratio chi-square, 93.081; df, 11; $P < 0.001$). The Poisson regression model with adjustment revealed that men (risk ratio [RR], 1.113; $P = 0.025$), those with lower educational levels (RR, 1.164; $P = 0.001$), and those with higher HDRS scores (RR, 1.370; $P < 0.001$) had significantly deteriorated sleep quality (Table 4).

Discussion

Our study investigated the association between sleep quality and NLR and PLR among hospitalized patients with BD. Our study had 3 major findings. Depressed patients had worse sleep quality compared with manic patients. Some hematological indices, such as the NLR, the PLR, and lymphocyte count, were significantly different between the 2 groups of patients (depressed vs. manic). Furthermore, male sex, lower educational levels, and higher Hamilton scores were predictors of worse sleep quality.

Table 1. Baseline Characteristics of the Patients (n = 305)

Variables	Manic Patients (n = 240)	Depressed Patients (n = 65)	Total (n=305)	*P* Value
Age (years)	43.72±12.79	37.66±15.62	43.11±13.72	0.005
Sex				0.140
Male	66(27.5)	24(36.9)	90(29.5)	
Female	174(72.5)	41(63.1)	215(70.5)	
Marital status				0.084
Single	130(54.2)	26(40.0)	156(51.1)	
Married	86(35.8)	33(50.8)	119(39.1)	
Divorced	24(10.0)	6(9.2)	30(9.8)	
Occupational status				0.771
Employed	52(21.7)	13(20.0)	65(21.3)	
Unemployed	188(78.3)	52(80.0)	240(78.7)	
Educational status				0.349
Primary school	86(35.8)	21(32.3)	107(35.1)	
Secondary school	100(41.7)	32(49.2)	132(43.3)	
University	54(22.5)	12(21.4)	66(21.6)	
Symptoms of manic and depressive episodes based on questionnaires				<0.001
Young mania rating score	23.45±6.51	10.16±5.85	20.62±8.38	
Hamilton depression rating score*	6.14±3.44	10.23±2.88	7.01±3.72	

Values are reported as frequency (%) or mean± standard deviation.
*All depressed patients had mild presentations.

Table 2. Sleep Quality of the Patients Based on the Pittsburg Sleep Quality Index

Sleep Quality Components	Manic Patients (n = 240)	Depressed Patients (n = 65)	Total (n = 305)	*P* Value
Subjective sleep quality				0.014
Very good /Fairly good	103(42.9)	17(26.2)	120(39.3)	
Fairly bad/ Very bad	137(57.1)	48(73.8)	185(60.7)	
Sleep latency				0.220
<15 minutes	24(10.0)	6(9.2)	30(9.8)	
15-29 minutes	133(55.4)	28(43.1)	161(52.8)	
30-59 minutes	29(12.1)	13(20.0)	42(13.8)	
≥60 minutes	54(22.5)	18(27.7)	72(23.6)	
Sleep duration				0.003
≥7 hours	121 (50.4)	47(72.3)	168(55.1)	
6-7 hours	42(17.5)	11(16.9)	53(17.4)	
5-6 hours	35(14.6)	1(1.5)	36(11.8)	
<5 hours	42(17.5)	6(9.2)	48(15.7)	
Sleep efficiency				0.646
≥85%	0(0)	0(0)	0(0)	
75-84%	18(7.5)	6(9.2)	24(7.9)	
65-74%	0(0)	0(0)	0(0)	
<65%	222(92.5)	59(90.8)	281(92.1)	
Sleep disturbances				0.014
No	72(30.0)	12(18.5)	84(27.5)	
Low	162(67.5)	47(72.3)	209(68.5)	
Moderate	6(2.5)	6(9.2)	12(3.9)	
Severe	0(0)	0(0)	0(0)	
Sleep medication				<0.001
Not during the previous month	211(87.9)	52(80.0)	263(86.2)	
Less than once a week	29(12.1)	7(10.8)	36(11.8)	
Once or twice a week	0(0)	6(9.2)	6(2.0)	
Three or more times a week	0(0)	0(0)	0(0)	
Daily dysfunction				<0.001
No	54(22.5)	0(0)	54(17.7)	
Low	127(52.9)	34(52.3)	161(52.8)	
Moderate	53(22.1)	19(29.2)	72(23.6)	
Severe	6(2.5)	12(18.5)	18(5.9)	
PSQI global score	8.94±2.75	10.01±1.91	9.17±2.63	<0.001

Values are reported as frequency (%) or mean± standard deviation.

According to our findings, 90.20% of patients with BD had poor sleep quality. Esan et al found that 48.7% of euthymic bipolar patients had poor sleep quality (18). The disparity in the prevalence of poor sleep quality observed in the 2 studies can be attributed to differences in the target populations. It is foreseeable that patients experiencing manic and depressive episodes will have deteriorated sleep quality compared with those experiencing euthymic episodes. Also, we did not find any studies that compared sleep quality between manic and depressive episodes.

Rising evidence indicates that inflammation plays a significant role in the pathophysiology of BD. The severity of inflammation is reflected in the symptoms of BD, including cognition, sleep, mood, energy, and motivation (19). Researchers are focusing on discovering novel inflammatory markers that are cost-effective, reproducible, and easily detectable from complete blood count parameters (10). The NLR and PLR are less affected by confounders (eg, exercise and catecholamine release) than white blood cell count and differential or other established inflammatory markers. Furthermore, previous publications demonstrate a strong correlation between these ratios and common inflammatory markers, oxidative stress, and pro-inflammatory cytokines (10).

The NLR is a suitable parameter reflecting the severity of stress and systemic inflammation. The NLR represents the balance between innate (neutrophils) and adaptive (lymphocytes) immune responses. Neutrophils are the first line of the immune response, exhibiting phagocytosis and apoptosis through the secretion of inflammatory mediators. Lymphocytes are inflammatory mediators with a regulatory or protective function. Lymphopenia may indicate a state of poor general health and physiologic stress. Thus, the NLR is useful for detecting the severity of inflammatory response and subsequent cytokine cascade associated with BD. Proinflammatory cytokines (eg, IL-2, IL-6, TNF, MCP1, and P-selectin), which are elevated in bipolar patients, mediate alterations in neurotransmission, especially synthesis and metabolism of 5-hyrdoxytryptophan, an essential metabolite in the biosynthesis of serotonin (10, 20).

Serotonin plays a crucial role in anxiety, anger, sleep, and cognition. It has been investigated as one of the main pathophysiological mechanisms of BD. The role of serotonin in different episodes of BD is not simple; it cannot be concluded that patients with lower serotonin levels are in depressed mood and higher in a manic phase (21).

Platelet count and PLR may predict the inflammatory response in psychiatric disorders. Platelets are inflammatory markers involved in neutrophil and macrophage recruitment and endothelial permeability. Platelet activation is mediated by cytokines, serotonin, glutamate, and dopamine (10). There is a bidirectional relationship between platelets and serotonin. Platelets have serotonin in their granules, serotonin receptors, and transporters on the cell membrane. On the other hand, the activation and aggregation of platelets is induced by serotonin, which participates in the pathophysiology of BD (20, 22).

Table 3. Hematological Indices of the Patients

Indices	Manic Patients (n = 240)	Depressed Patients (n = 65)	Total (n = 305)	*P* Value
WBC count (cells/mm^3)	7067.5±2031.5	7084.6±2673.7	7071.1±2179.3	0.962
Neutrophil count (cells/mm^3)	3799.2±1407.1	4078.2±2373.6	3858.7±1660.1	0.368
Lymphocyte count (cells/mm^3)	2517.4±941.1	2251.3±807.4	2460.7±919.5	0.038
NLR	1.64±0.66	2.09±1.77	1.75±1.02	0.057
RBC count (×10^{12} cells/mm^3)	4.54±0.52	4.62±0.58	4.56±0.53	0.280
Hemoglobin (mg/dL)	12.75±1.34	12.91±1.33	12.78±1.34	0.388
PLT count (×10^3 cells/mm^3)	228.8±77.2	262.9±126.4	236.0±90.8	0.007
PLR	100.45±45.61	138.59±110.18	108.58±66.60	0.008

NLR: Neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PLT: platelet, WBC: white blood cells
Indices are reported as mean± standard deviation.

Table 4. Predictors of Pittsburg Sleep Quality Index Score Based on Poisson Regression Model

Factors/Covariates	RR (95% CI)	*P* Value
Age	0.998 (0.994, 1.002)	0.262
Sex, Male	1.113 (1.013, 1.222)	0.025
Sex, Female	Reference	-
Marital status, Single	0.987 (0.893, 1.090)	0.794
Marital status, Married/divorced	Reference	-
Educational level 1	1.164 (1.064, 1.274)	0.001
Educational level 2	Reference	-
Employed	Reference	-
Unemployed	1.047 (0.941, 1.164)	0.400
Hamilton depression rating scale score	1.370 (1.260, 1.480)	<0.001
Young manic rating scale score	0.998 (0.993, 1.003)	0.390
Neutrophil count	1.000 (1.000, 1.000)	0.654
Lymphocyte count	1.000 (1.000, 1.000)	0.249
NLR	0.994 (0.864, 1.145)	0.937
PLR	1.000 (0.998, 1.001)	0.487

Educational level 1: primary school, Educational level 2: secondary school/university, NLR: Neutrophil to lymphocyte ratio, P/L ratio: platelet to lymphocyte ratio.

Previous studies disagree about the association between hematological indices and episodes of BD. Inconsistent with our findings, most studies reported that hematological indices are higher in manic episodes than in depressive episodes (23). For instance, in a study by Fusar-Poli et al (hypo), manic patients had significantly higher platelet counts, NLR, and PLR than depressed patients (24). Another study reported that the NLR and monocyte-to-lymphocyte ratio were significantly higher in patients with manic episodes compared with patients with depressive episodes (25). Interestingly, Kulacaoglu et al reported that leukocyte count, lymphocyte count, neutrophil count, platelet count, NLR, and PLR did not differ between manic and depressive episodes (26). In our study, depressed patients had higher platelet counts and P/L ratios but lower lymphocyte counts than manic patients. At first glance, our findings appear to contradict the literature. However, as Wu et al reported, changes in inflammatory markers in bipolar patients were state-dependent. Patients in the mild depressive episode had an activated immune system, while those in the moderate and severe depressive episode, as well as patients in the manic episode, had an inhibited immune system (27). Almost all depressed patients were classified as mild in our study. Thus, the higher platelet counts and PLR in depressed patients compared with manic patients can be justified.

Studies on patients with BD that use regression models to determine predictive factors of sleep quality are limited. Based on a study by Melo et al, the relationship between sleep quality and inflammatory ratios like NLR and PLR was not found (28), which is in agreement with our findings. Consistent with our results, Krishnamurthy et al found that the HDRS score, unlike the YMRS score, could predict the sleep time of patients with BD (29).

Our findings should be considered in light of some limitations. The data were analyzed using a regression model to adjust for the effects of confounding variables. However, there may be other potential confounders that we did not consider in the study. We were unable to determine the role of symptom severity in sleep quality because almost all depressed patients had mild presentations. Moreover, the available studies investigating the association between sleep quality and hematological indices were limited, thus, we faced challenges in interpreting the results. In this study, sleep quality was subjectively assessed. It is suggested to objectively measure the sleep quality of bipolar patients using polysomnography in future studies.

Conclusion

Our results revealed that most bipolar patients had poor sleep quality, particularly those with depressive episodes. Depressed patients with male sex, lower educational levels, and more severe depressive symptoms had poorer sleep quality.

Authors' Contributions

Conceptualization, study design, supervision: R.V.H. Data analysis, critical thinking, editing the manuscript: A.K. Editing the manuscript, writing the primary draft: Y.S. Data collection, data analysis, writing the primary draft: H.N.

Ethical Considerations

The study protocol was approved by the Research Ethics Committee of the School of Medical Education, Sha-

hid Beheshti University of Medical Sciences (IR.SBMU.SME.REC.1401.086). The study was performed in accordance with the Helsinki Declaration of 2000. All participants completed written informed consent forms.

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Conflict of Interests

The authors declare that they have no competing interests.

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