

# Neutrophil to Lymphocyte Ratio in Patients with Major Depressive Disorder

Ahmed MNU<sup>1</sup>, Farooq AA<sup>2</sup>, Shams SF<sup>3</sup>, Siddique MAB<sup>4</sup>, Mojumder MRK<sup>5</sup>

DOI: <https://doi.org/10.3329/jafmc.v19i1.70288>

## Abstract

**Introduction:** Depression is common mood disorder that is linked to systemic inflammation. The neutrophil-lymphocyte ratio (NLR) is a non-specific inflammatory marker that is inexpensive and easy to measure. Low-grade inflammation occurs in a subgroup of patients with Major Depressive disorder (MDD).

**Objective:** To examine the role of inflammation in the etiology of depression based on the NLR in MDD patients who are under not receiving pharmacological therapy.

**Methods:** This observational study was carried out in the Department of Psychiatry of Jahurul Islam Medical College Hospital (JIMCH), Bajitpur, Kishoregonj between November 2012 and April 2013. Subjects between the age group of 18 and 65 were included in the study that involved 61 subjects with diagnosed MDD, who received no pharmacological therapy of depression within the past 01 month. The control group included 67 healthy subjects having no psychiatric diseases. A sociodemographic information form and a Beck Depression Scale were administered. Blood sample were taken for biochemical analysis and complete blood parameters were evaluated in the hematology laboratory of JIMCH. All data were expressed as mean±SD. For statistical analysis, Chi-square test ( $\chi^2$ ) was used to compare categorical variables, frequencies, and ratios. An independent sample 't' test was used to compare normally distributed variables between two groups.

**Results:** In the present study, we found significant differences in the NLR, neutrophil count, lymphocyte percentage and leukocyte values of the patient group when compared with control group ( $P < 0.05$ ).

**Conclusion:** The study reveals that NLR tends to be higher in patients with MDD, and a high NLR value supports the view that inflammation is a critical factor in the etiology of MDD.

**Key words:** Major depressive disorder, Neutrophil-lymphocyte ratio, Inflammation, Cytokines.

## Introduction

According to World Risk Report 2015, Bangladesh is Depression is a common, complex disease and it is associated with prominent disability, social burden and reduced quality of life.<sup>1</sup> It is estimated about 450 million people worldwide suffer from mental illness and one in four people meets criteria of mental illness at some point in their life. Among the mental disorders, depression is a disease of global burden affecting 350 million people worldwide.<sup>2</sup> It is characterized by a range of symptoms including a depressed mood or a loss of interest in daily activities for more than two weeks.<sup>3</sup> It also disrupts the ordinary flow of daily life and can manifest across all ages including the young and old.<sup>4</sup> The white blood cell (WBC) count, a non-specific inflammatory marker, is usually measured as part of the complete blood count (CBC) panel. Moreover, a few reports suggest that depression and stress are accompanied by disturbances in total white blood cell counts (i.e., leukocytosis) and leukocyte subset [i.e., neutrophilia, monocytosis, as well as decreased lymphocytes (lymphopenia) counts<sup>5,6</sup>], hypertension, diabetes mellitus and atherosclerotic cardiovascular disease.<sup>7,8</sup>

Previous studies have demonstrated the role of inflammation in the pathogenesis of depression; for example, inflammation in patients with somatic diseases increases the risk of developing depression. Patients with depressive illness have elevated levels of peripheral and central proinflammatory cytokines, and proinflammatory agents have been shown to facilitate the progression of depressive symptoms.<sup>9</sup> Importantly the activation of neutrophils can cause oxidative stress by releasing reactive oxygen species, which may contribute to the pathogenesis of depression.<sup>10</sup>

Several studies have found that depression is associated with higher levels of proinflammatory cytokines and acute phase proteins such as C-reactive protein (CRP), interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha) that may play a role in the etiopathogenesis of depression.<sup>11-13</sup> Studies investigating the possible relationship between MDD and the immune

1. Lt Col Mohammad Nesar Uddin Ahmed, MBBS, MPhil, Instructor of Surgery, Armed Forces Medical College, Dhaka Cantonment (E-mail: nesarj9@gmail.com)  
 2. Dr Abdullah Al Farooq, MBBS, FCPS, Professor and Head, Department of Psychiatry, Jahurul Islam Medical College & Hospital, Bajitpur, Kishoregonj  
 3. Dr Syed Faheem Shams, MBBS, MD, Associate Professor and Head, Department of Psychiatry, Uttara Adhunik Medical College & Hospital, Uttara, Dhaka  
 4. Lt Col Md Abu Baker Siddique, MBBS, DA, Graded Specialist in Anaesthesiology, BANMED-2/1, MINUSCA, Central African Republic (CAR) 5. Dr Md. Rezaul Karim Mojumder, MBBS, MS, Medical Officer, Kurmitola General Hospital, Dhaka.

system have been increasing in recent years, and it has been shown that MDD, together with suppressing the immune system, may cause alterations in the inflammatory process. Neutrophil and leukocyte subsets play an important role in inflammatory processes, to decrease and normalize high pretherapeutic serum proinflammatory cytokine levels.<sup>14</sup> It has been shown that the rate of NLR gets higher, as a response to systematic inflammation in stress and depression. Recently, the NLR has been found to be a good indicator of inflammatory status<sup>15</sup> and this ratio has been investigated in a number of diseases.<sup>16</sup> A number of studies have shown that NLR is likely to be higher in both schizophrenia and Alzheimer's disease patients when compared with healthy subjects.<sup>17,18</sup> Furthermore, several studies have also shown that NLR is associated with a variety of depression states, such as post-stroke depression<sup>19</sup> adolescent depression<sup>20</sup> and severe depression.<sup>21</sup>

The purpose of the present study is to explore the role of inflammation in the etiology of depression using NLR in MDD patients who are undergoing no medical treatment and to identify the role of inflammation in the etiology of depression.

## Materials and Methods

This observational study was carried out in the Department of Psychiatry of JIMCH, Bajitpur, Kishoregonj from November 2012 and April 2013. This study population consisted of healthy volunteers as control and MDD individuals who presented at the Out Patient Department (OPD) of Department of Psychiatry of JIMCH, Bajitpur, Kishoregonj. Subjects between the ages of 18 and 65 years were included in the study that involved 61 subjects with diagnosed MDD according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition who had undergone no pharmacological therapy within the previous month, while the control group included 67 healthy subjects having no psychiatric disease. The Sociodemographic characteristics of the patients and controls were similar and age, sex, body mass index (BMI), level of education, socioeconomic status and occupation were adjusted to prevent any effect on the hemogram variables.

The exclusion criteria were as follows: psychiatric diseases having comorbidity according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, inflammatory or autoimmune diseases, severe systemic diseases, a leukocyte value suggesting infection, active infections, hypertension, diabetes mellitus, epilepsy, myocardial infarction, heart failure and other cardiac disease, hepatic failure, renal failure, alcohol or other substance addiction, severe head injury, mental retardation, pregnancy, obesity (BMI>30 kg/m<sup>2</sup>), drug use for any reason, smoking habit.

All the selected patients were informed detail about the aim and procedure of the study and were encouraged for their voluntary participation. An informed written consent was taken from all participants. Detail personal, medical, family, socioeconomic, occupational and drug history were taken as well. Thorough physical examination of each patient were done and documented. Beck Depression Scale (BDS) was administered. Blood was taken for biochemical analyses. After 12 hours of fasting, blood samples of study subjects were taken from antecubital vein and stored in hemogram tubes (08 am), after which complete blood parameters were evaluated in the hematology laboratory of JIMCH. The study protocol was approved by the institutional local Ethical Review Committee (ERC).

All data were expressed as mean±SD. For statistical analysis, Chi-square test ( $\chi^2$ ) was used to compare categorical variables, frequencies, and ratios. An independent sample 't' test was used to compare normally distributed variables between two groups. Statistical analyses were performed by using Statistical Package for the Social Sciences (SPSS v16.0). In the interpretation of results, p value of <0.05 was considered as statistically significant.

## Results

In this study, both the control and experimental patients were comparable, in respect of age, sex, BMI, education, socioeconomic status and occupation as their differences were statistically non-significant (Table-I). The complete blood count parameters in the patient and control groups were compared statistically and it was found that neutrophil counts, percentages of lymphocyte, leukocyte values and NLR of the patient group differed significantly in comparison to the control group (Table-II).

In the patient group, the age, BMI and complete blood parameters were compared statistically between two sexes. The red blood cell (RBC), hemoglobin and hematocrit (Hct) values were significantly higher in male patients in comparison to the female patients. On the other hand, other variables did not differ significantly between the sexes (Table-III).

**Table-I:** Sociodemographic characteristics of study subjects in both groups (n=128)

Variables	Patient (n=61)	Control (n=67)	p value	
Age (years)	32.6±9.8 (18-65)	33.4±9.1 (18-65)	0.409	
Sex	Male	16 (25.9%)	18 (26.5%)	0.820
	Female	45 (74.1%)	49 (73.5%)	
BMI (kg/m <sup>2</sup> )	22.8±4.2	23.9±1.6	0.180	
Education	≤ 5 years	15 (24.6%)	16 (23.9%)	0.130
	6-8 years	21 (34.43%)	23 (34.33%)	
	9-11 years	14 (23%)	18 (26.9%)	
	>11 years	11 (18.03%)	10 (14.93%)	
Socioeconomic status (score)	1.59±0.78 (1-4)	1.78±0.83 (1-4)	0.298	
Occupation (score)	2.07±1.06 (1-4)	2.40±1.06 (1-4)	0.242	

Data were expressed as mean±SD. Figures in parentheses indicate ranges. Statistical analysis was done with independent sample 't' test and Chi-square test.

**Table-II:** Complete blood count parameters in the patient and control groups

Variables	Patient (n=61)	Control (n=67)	P value
Neutrophil (%)	62.5±8.7	60.0±6.7	0.124
Neutrophil count (x10 <sup>3</sup> )	5.1±1.2	4.2±1.1	0.006*
Lymphocyte (%)	29.0±7.5	33.1±5.9	0.028*
Lymphocyte count (x10 <sup>3</sup> )	2.37±0.7	2.41±0.6	0.246
Leukocyte count (x10 <sup>3</sup> )	7.1±1.6	6.0±1.2	0.007*
Neutrophil/Lymphocyte ratio	2.35±1.0	1.95±0.5	0.011*
RBC count (10 <sup>6</sup> /ml)	4.7±0.4	4.9±0.3	0.201
Hemoglobin (gm/dl)	13.5±1.4	14.2±1.3	0.101
Hct (%)	40.9±4.2	41.7±3.2	0.199
Platelet count (10 <sup>9</sup> /L)	234.6±52.7	248.6±42.7	0.157

Data were expressed as mean±SD. Figures in parentheses indicate ranges. Statistical analysis was done with independent sample 't' test and Chi-square test.

**Table-III:** Age, BMI and Complete blood count parameters in the patient groups of the male and female subjects

Variables	Male (n=15)	Female (n=46)	P value
Age	30.5±7.8	29.6±8.8	0.380
BMI	23.1±2.2	23.8±3.6	0.101
Neutrophil (%)	57.4±9.7	61.5±8.0	0.187
Neutrophil count (x10 <sup>3</sup> )	4.5±1.4	4.9±1.3	0.170
Lymphocyte (%)	30.1±8.5	28.0±7.5	0.490
Lymphocyte count (x10 <sup>3</sup> )	2.41±0.7	2.31±0.7	0.490
Leukocyte count (x10 <sup>3</sup> )	7.3±1.8	7.8±1.6	0.490
Neutrophil/Lymphocyte ratio	2.01±1.2	2.3±1.1	0.442
RBC count (10 <sup>6</sup> /ml)	5.0±0.2	4.2±0.4	0.002*
Hemoglobin (gm/dl)	14.9±0.9	13.2±1.4	0.004*
Hct (%)	44.9±3.2	40.9±2.2	0.002*
Platelet count (10 <sup>9</sup> /L)	225.6±33.7	240.6±55.7	0.170

Data were expressed as mean±SD. Figures in parentheses indicate ranges. Statistical analysis was done with independent sample 't' test and Chi-square test.

## Discussion

In this study, we found elevated NLR values in patients with depressive disorders when compared with healthy individuals. Moreover, leukocyte and neutrophil counts were also elevated, while lymphocyte percentages were decreased in the group of patient in comparison to the healthy subjects.

Immunological changes are known to be found in depressive illness patient. Immune response plays an important role in the cause of MDD<sup>22</sup> and increased inflammatory changes have been found in depressive illness patients.<sup>23</sup> Immune system is altered during the process of clinical depression. Although acute stress stimulates immune functions, chronic stress represses immune system.<sup>24</sup> Alterations in the levels of inflammatory cytokines including tumor necrosis factor alpha (TNF-α) and interleukins (IL-1, IL-6) are central to the pathophysiology of depression.<sup>25</sup> Inflammatory cytokines are

important biomarkers in the course of any disease including diagnosis, treatment selection and long term follow-up.<sup>24,25</sup> A decreased lymphocyte response to mitogen stimulation and disorders in neutrophil activity have been observed in depression.<sup>26</sup> It has been observed that, in MDD, the number, serum concentration and proliferation of lymphocytes, B-cells and T-cells decrease. In addition, cellular immunity is suppressed, whereas total leukocyte and neutrophil count increase.<sup>6</sup> In another studies supporting these findings, lymphocyte proliferation was found to be suppressed, and leukocyte and neutrophil were seen to be increased in travelers, while cellular immune functions decreased in subjects undergoing severe and those exposed to trauma.<sup>27</sup> In some studies T-lymphocyte and neutrophil phagocytes count have been shown to be decreased in depressive illness patients when receiving no drugs; some T-cell subtypes and activities were increased; although the capacity for lymphocyte production did not change with significant difference when compared with the control group.<sup>28</sup> It has been suggested that an increased severity of depression was associated with immunological alterations, while lymphocyte response is decreased as the severity of depression increases.<sup>29</sup>

In the patient group, the RBC, Htc, hemoglobin values were higher in males than in females, although these levels may be expected to be higher in men than in women. In this study, the RBC, Htc, and hemoglobin values in the male and female patients were within normal ranges, and they were in accordance with the usual differences observed between the two sexes.

## Conclusion

This study reveals that, NLR which is obtained from hemograms tends to be higher in patients with MDD and supports the view that inflammation, a complex process involving several cells and molecules which may play role in the pathophysiology of MDD.

## Acknowledgement

The authors of this study are immensely grateful to the Department of Psychiatry as well as authority of JIMCH, Bajitpur, Kishoregonj for their wholehearted cooperation during sample collection and also thankful to the study subjects for their active and enthusiastic participation.

## References

1. Kessler RC, Berglund P, Demler O et al. The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289(23):3095-105.
2. WHO, 2012. Depression: A Global Crisis. World Mental Health Day, 10 October 2012. World Federation for Mental Health, Occoquan, Va, USA.
3. Rottenberg J. Mood and emotion in major depression. Current Directions in Psychological Science. 2005; 14(3):167-70.

4. Valiengo LDCL, Stella F, Forlenza OV. Mood disorders in the elderly: Prevalence, functional impact and management challenges. *Neuropsychiatr Dis Treat.* 2016; 12:2105-14.
5. Maes M, Van der Planken M, Stevens WJ et al. Leukocytosis, monocytosis and neutrophilia: Hallmarks of severe depression. *J of Psychiatr Res.* 1992; 26(2):125-34.
6. Tuglu C, Kara SH. Depression, cytokines and immune system. *Psychiatry and Clinical Psychopharmacology.* 2003; 13:142-50.
7. Nakanishi N, Yoshida H, Matsuo Y et al. White blood cell count and the risk of impaired fasting glucose or Type II diabetes in middle aged Japanese men. *Diabetologia.* 2002; 45:42-8.
8. Whitworth JA. Relationship between white blood cell count and incident hypertension. *Am J Hypertens.* 2004; 17(9):861-2.
9. Kohler O, Krogh J, Mors O, Benros ME. Inflammation in depression and the potential for anti-inflammatory treatment. *Curr Neuropharmacol.* 2016; 14(7):732-42.
10. Salim S. Oxidative stress and psychological disorders. *Curr Neuropharmacol.* 2014; 12(2):140-7.
11. Baune BT, Smith E, Reppermund S et al. Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: The prospective Sydney Memory and Aging Study. *Psychoneuroendocrinology.* 2012; 37:1521-30.
12. Danner M, Kasl SV, Abramson JL, Vaccarino V. Association between depression and elevated C-reactive protein. *Psychosomatic Medicine.* 2003; 65(3):347-56.
13. Gimeno D, Kivimaki M, Brunner EJ et al. Association of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychological Medicine.* 2009; 39:413-23.
14. Janssen DGA, Caniato RN, Verster JC, Baune BT. A psycho-neuroimmunological review on cytokines involved in antidepressant treatment response. *Hum Psychopharmacol.* 2010; 25(3):201-15.
15. Gibson PH, Cuthbertson BH, Croal BL et al. Usefulness of neutrophil/lymphocyte ratio as predictor of new onset atrial fibrillation after coronary artery bypass grafting. *Am J Cardiol.* 2010; 105(2):186-91.
16. Azab B, Jaglall N, Atallah JP et al. Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. *Pancreatology.* 2011; 11(4):445-52.
17. Semiz M, Yildirim O, Canan F et al. Elevated neutrophil/lymphocyte ratio in patients with schizophrenia. *Psychiatr Danub.* 2014; 26(3):220-5.
18. Kuyumeu ME, Yesil Y, Ozturk ZA et al. The elevation of neutrophil lymphocyte ratio in Alzheimer's disease. *Dement Geriatr Cogn Disord.* 2012; 34(2):69-74.
19. Chen H, Luan X, Zhao K et al. The association between neutrophil to lymphocyte ratio and post-stroke depression. *Clin Chim Acta.* 2018; 486:298-302.
20. Ozyurt G, Binici NC. Increased neutrophil-lymphocyte ratios in depressive adolescents is correlated with the severity of depression. *Psychiatry Res.* 2018; 268:426-31.
21. Mazza MG, Lucchi S, Tringali AGM et al. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: A meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry.* 2018; 84(Pt A):229-36.
22. Sadock BJ, Sadock VA. Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry. 9th Rev ed. Lippincott, Williams and Wilkins. (Cev.ed: Bozkurt A). Gunes Tip Kitabevleri. Ankara. 3:128-133; 15:536-9.
23. Raison CL, Miller AH. Is depression an inflammatory disorder? *Curr Psychiatry Rep.* 2011; 13(6):467-75.
24. Dinan TG. Inflammatory markers in depression. *Curr Opin Psychiatry.* 2009; 22:32-6.
25. Hasmi AM, Butt Z, Umair M. Is depression an inflammatory condition? A review of available evidence. *J Pak Med Assoc.* 2013; 63(7):899-906.
26. Sertoz OO, Mete HE. Bedensel Hastaliklarda Depression [Depression in somatic illness]. *Klinik Psikiyatri.* 2004; 2(Suppl):63-9.
27. Maes M. Evidence for an immune response in major depression: A review and hypothesis. *Prog Neuropsychopharmacol Biol Psychiatry.* 1995; 19(1):11-38.
28. McAdams C, Leonard BE. Neutrophil and monocyte phagocytosis in depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry.* 1993; 17:971-84.
29. Miller GE, Cohen S, Herbert TB. Pathways linking major depression and immunity in ambulatory female patients. *Psychosom Med.* 1999; 61(6):850-60.