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KEY WORDS: Depression, Lymphocyte, Neutrophil, Inflammatory.

NEUTROPHIL / LYMPHOCYTE RATIO IN PATIENTS WITH DEPRESSION AND ITS CORRELATION WITH THE SEVERITY OF DEPRESSION

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ABSTRACT

Objective: The aim of the study is to investigate the relation of Neutrophil / Lymphocyte Ratio (NLR) with severity of depression.
Methods: The study population consisted of 296 patients with depressive disorder. Patients were evaluated with the Hamilton Rating Scale for Depression (HAM- D_{24}). and classified into three groups. Patients were also evaluated for complete blood counts.
Results: Patients with higher HAM- D_{24} score had significantly higher NLR levels compared to patients with lower HAM- D_{24} score (1.48±.05 vs 1.59±.06 vs 1.74±.09 p<0.001). In logistic regression analyses, NLR was an independent predictor for severity of depression. A NLR of 1.59 or higher predicted moderate and severe depression
Conclusion: Higher HAM- D_{24} scores are associated with higher NLR levels in depressive patients.

Introduction

The prevalence of depressive disorders have increased all over the world including India in the recent years. The World Health Organization estimates that the depression will be the second leading cause of morbidity worldwide in 2020.[1,2] Depression has been associated with changes in the central nervous system, immune response, and vascular reactivity and all of these factors are important in the generation of a systemic inflammatory response.[3] Previous studies reveals that depression is associated with elevated inflammatory markers including C-reactive protein (CRP), interleukin-6, and interleukin-1.[4,5,6] A recent study showed that elevated level of CRP is associated with increased risk of depression and psychological distress.[7]

Inflammation is associated with many of chronic disease such as malignancy, diabetes mellitus, hypertension, connective tissue disease, chronic renal disease, cardiovascular (CV) disease and psychiatric disorders.[8-15] White blood cell count and its subtypes are of the predictors of chronic inflammation. Neutrophils and leukocytes have an important role in inflammatory process. The neutrophil to lymphocyte ratio (NLR), which can be derived from the white blood cell count is widely available, inexpensive, reproducible test and has been investigated as a new biomarker for systemic inflammatory response.[16,17,18] NLR has been found to be an important inflammatory marker in previous studies.[18,19] The association of neutrophil to leukocyte in patients of depression with other co morbidities has been found in some studies.[20,21] The aim of this study is to investigate the relation of NLR with severity of depression in Indian population

METHODS

Study population

Patients were selected from psychiatry outpatient of SMS medical college and hospital,Jaipur for evaluation of depressive disorders from March 2016 to June 2017. The study included 296 consecutive drug naďve patients with diagnosed depression according to the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM V). All patients were evaluated for previous medical history. Patients who have systemic disease and using of medical treatment which affect the white blood cell counts, such as hematopoietic system disorders, history of malignancy and/or treatment with chemotherapy, evidence of any concomitant inflammatory disease, acute infection, and chronic inflammatory status, within past 6 months, history of using the glucocorticoid therapy within past 3 months, heart failure, history of chronic renal or hepatic disease and cerebrovascular disease were excluded from this study. The study was approved by the ethics committee and all participants given written informed consent before participating.

Assessment of depression

Patients were evaluated for depressive symptoms by using Hamilton Rating Scale for Depression (24-items) (HAM-D_{24}), it contains a total of 24 items. HAM-D_{24} score <8 points is defined as non-depression and HAM-D_{24} score ≥8 points is defined as depression. HAM-D_{24} score of 8–19 points is defined as mild depression, HAM-D_{24} score of 20–34 points is defined as moderate depression, HAM-D_{24} score of ≥35 points is defined as severe depression.[22,23]. The measurements of HAM-D_{24} were conducted by trained psychiatrist.

Demographic and Laboratory findings

Demographic data were obtained from the medical records. Peripheral blood was sampled taken from patients in a fasting state. Venous blood samples were sent to Clinical Laboratory of Psychiatric Centre, SMS Medical College, Jaipur, India for Complete blood counts which included total white blood cells, neutrophils, and lymphocytes. NLR was calculated as the ratio of neutrophil count to lymphocyte count.

Statistical analysis

The statistical analysis was conducted using SPSS version 23.0 for Windows. Continuous variables were expressed as mean while categorical data were presented as percentages. Categorical variables were expressed as proportions and the differences in categorical variables were analyzed using chi-square test while One way ANOVA were used to compare parametric and nonparametric continuous variables, respectively. Pearson correlation analysis was conducted to determine the correlation between HAM-D_{24} score and each clinical and laboratory factor. Logistic regression analysis was performed to determine the independent predictors of mild and moderate and severe depression. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off level of NLR to predict the mild and moderate versus severe depression. Statistical significance was established at $p < 0.05$.

RESULTS

The study population was consisted of 296 consecutive patients who were diagnosed with depression. All patients were divided into three groups according to scores of HAM-D_{24} such as mild, moderate, and severe depression. Clinical data and Baseline characteristics of study population are shown in Table 1. Patient characteristics are similar between groups.

Table 1. Baseline and clinical characteristics of the study groups

	Mild (N=68)	Moderate (N=68)	Severe (N=160)	p
Age (years)	35.838±7.33	35.11±5.47	35.01±5.94	0.649

Gender (male-%)	54(80)	50(74)	124(78)	0.702
Height (cm)	162.7±11.14	163.1±10.54	161.2±10.85	0.391
Weight (kg)	65.5±9.57	68.9±9.55	68.3±9.70	0.085
Married (N-%)	33(49)	35(52)	77(49)	0.895

Table 2. Comparison of the complete blood count parameters in the study groups

	Mild (N=68)	**Moderate (N=68)**	**Severe (N=160)**	**p**
Leukocytes (1/mm3)	7611±126	7658±140	7651±137	0.081
Neutrophils (1/mm3)	3834±129	4131±125	4480±167	<0.001
Lymphocytes (1/mm3)	2584±35	2597±69	2575±97	0.160
Platelets (103/mm3)	275±53	286±40	284±40	0.260
MPV (mL)	8.80±.08	8.79±.09	8.80±.09	0.980
Hemoglobin (g/dL)	12.1±.57	12.1±.64	12.2±.58	0.169
Hematocrit (%)	36.1±2.4	36.5±2.5	36.3±2.6	0.708
Red blood cells (103/mm3)	4.46±.28	4.48±.31	4.43±.34	0.604
RDW	13.7±.94	13.8±1.0	13.8±1.0	0.941
NLR	1.48±.05	1.59±.06	1.74±.09	<0.001

NLR: neutrophil to lymphocyte ratio, RDW: red cell distribution width, MPV: mean platelet volume

Complete blood count measurements of study population are expressed in Table 2. We compared severity of depression and NLR between groups. Patients who have higher HAM- D_{24} scores had significantly higher NLR levels compared to patients with lower HAM- D_{24} scores. Correlation analysis finds that severity of depression is associated with NLR ($r=0.333$, $p<0.001$) in patients with depressive disorders.

The patients were divided into three groups according to scores of HAM-D_{24} such as mild and moderate and severe depression. Mild, moderate and severe depression had significant difference in NLR levels (1.48±.05 vs 1.59±.06 vs 1.74±.09 $p<0.001$). In univariate and multivariate logistic regression analyses, NLR was an independent predictor for severity of depression NLR (odds ratio: 3.02, 95% confidence interval: 1.47–4.66, $p<0.001$. ROC analysis was performed to determine the cut-off value of NLR to predict the moderate and severe depression. A NLR of 1.59 or higher predicted moderate and severe depression with a sensitivity of 63.3% and specificity of 62.1%.

DISCUSSION

The present study revealed that higher HAM-D_{24} scores were associated with higher NLR values in patients with depressive disorders. Severity of depression was also correlated with NLR in such patients. Moreover NLR more than 1.59 was an independent predictor of moderate and severe depression. To the best of our knowledge, this is the first study in literature to evaluate the association between NLR and severity of depression in Indian population.

Depression is a common, complex disorder and it is associated with prominent disability, social burden and reduced quality of life.[25] Immune system is altered during the process of development of clinical depression. Although acute stress stimulates immune functions, chronic stress suppresses immune system.[26] Inflammatory cytokines are important biomarkers in the course of depression including diagnosis, treatment selection and long-term follow-up.[26,27] Although inflammatory cytokines are useful biomarkers, but their cost and limited attainability is the issue.

White blood cell count is a cheap and easily available commonly used inflammatory marker. Neutrophils are the most abundant type of the white blood cells. Neutrophils and leukocytes play an important role in the course of development of inflammatory diseases. They play important roles in the inflammatory response. Neutrophils are the first and important cells responding to inflammation especially caused by bacterial infection, cancer and environmental exposure. NLR which can be derived from the white blood cell count is an inexpensive, routinely used, reproducible test and has shown as a marker of systemic inflammatory response. Neutrophil leads to secretion of several inflammatory cytokines. Inflammation triggered by these molecules can induce an oxidative stress and further inflammation due to cell dysfunction in various organs.[28,29]. Increased NLR is also interconnected with oxidative stress and increased cytokine productions, and these findings were found in depressive disorder.[30]

NLR is a new parameter which gives us information not only about the systemic inflammation but also the stress response of the patient. While mainly high neutrophil counts reflect to inflammation, low lymphocyte counts reflect poor general health and physiological stress.[30] Our findings demonstrates that NLR is associated with severity of depression. According to our study results, this ratio may be a state marker of presence and severity of depressive disorder.

Our study has important clinical implications. We have shown the association between NLR and severity of depression. We demonstrated that NLR levels may be related with the severity of depression in the patients that definitely have no other conditions that may activate inflammatory response. NLR seems to be a simple, easily available and cost effective method for evaluation of the severity of depression in depressive disorder and it may be used in outpatient clinic setting. Close follow up can be performed for these patients who have higher NLR levels.

LIMITATION

Our study was designed as a cross-sectional study. As the prognostic value of the NLR in such patients needs to be addressed so further cohort studies are required to explore the relation between the course of depression and NLR levels in patients after anti depressant treatment. Since we did not determine the subtype of depression, we could not assess the relationship between NLR and these sub groups, further studies may determine this association. Lack of a healthy control group as comparators was an important limitation of our study. It would have been better if we displayed the effect of psychological stress on NLR levels. Therefore, further large scale, prospective studies are needed to explore extensive information about the impact of NLR on severity and subtypes of depression.

CONCLUSION

Higher HAM-D_{24} scores were associated with higher NLR levels in patients with depressive disorder and severity of depression was also correlated with NLR in these patients. Moreover NLR more than 1.59 was an independent predictor of moderate to severe depression. A simple cheap investigation of white blood cell count may also give an idea about the severity of depression and can be included in psychiatric evaluation of these patients.

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