ORIGINAL ARTICLE

Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and their association with the severity of depression and as biomarkers for suicidal behaviour among patients diagnosed with depression

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Abstract

Background: Depression has a significant impact on a person's quality of life and is a leading cause of death by suicide. Growing evidence points to a function for the immune and inflammatory systems in the pathophysiology of depression. Studies have shown that Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) are positively associated with depression severity and may be peripheral biomarkers of suicidal behaviour in depressed patients. *Aim and Objectives:* To find out NLR, and PLR values in patients with depression and their association with the severity of depression and to test their validity as biomarkers for suicidality. *Material and Methods:* Our study population consisted of 150 patients with diagnosed depressive disorder. Patients were evaluated with the Hamilton Depression Rating Scale (HAM-D). Patients were classified into 3 groups according to their HAM-D score such as mild, moderate and severe depression. NLR and PLR values were estimated. *Results:* Patients with higher HAM-D score had significantly higher NLR and PLR levels compared to patients with lower HAM-D score. NLR and PLR values were substantially higher for the suicide attempters group than the non-suicide attempters. The optimal cut off value for NLR in predicting the risk for suicide attempt was 1.96 with sensitivity of 75%, and specificity of 74%. *Conclusion:* Our data suggest that NLR and PLR values may be considered as easily accessible and cost-effective strategies to determine suicide risk in depression.

Keywords: Depression, Neutrophil -to-Lymphocyte Ratio, Platelet -to- Lymphocyte Ratio

Introduction

Depression is a common and severe mental illness. Depression is characterized by persistent depressed mood with a loss of interest in activities, for most of the day, nearly every day, for at least two weeks. Several other symptoms like poor concentration, feelings of excessive guilt or low self-worth, hopelessness about the future, thoughts about dying or suicide, disrupted sleep, changes in appetite or weight may also be present [1].

Depression has a significant impact on a person's quality of life and is a leading cause of death by suicide that is often ignored. According to World Health Organization (WHO), an estimated 3.8% of the world's population suffers from depression [2]. A cross-sectional study conducted by Arvind *et al*. [3] in 2019 reported that the prevalence of lifetime and current depressive disorders in India was 5.25% and 2.68%. At its worst, depression can cause suicidal thoughts, and more than 700,000 people die by suicide each year. For those aged 15 to 29, it is the fourth biggest cause of mortality [4]. According to a study, depressive disorders carried

the worst burden accounting for 37.3% of Disability Adjusted Life Years (DALYs) and were 2nd highest cause of Years of healthy life Lost due to Disability (YLD) in 2019 [5].

Growing evidence points to a function for the immune and inflammatory systems in the pathophysiology of depression [6]. Repeated stress exposing peripheral blood markers to enter into the brain contribute to development of neuroinflammation. By hindering the production of monoamine neurotransmitters, disrupting glutamatergic signalling, changing neurogenesis, and altering synaptic plasticity, neuroinflammation can have an impact on depressive symptoms [7].

Neutrophils serve as the primary defence cells of the innate immune system and contribute to phagocytosis and apoptosis by enhancing inflammatory mediators. When activated, neutrophils can migrate to the spleen and stimulate the production of T1 antibodies by activating marginal zone B cells, a proliferation-inducing ligand, and IL-21. Neutrophils have the ability to transport antigens to lymph nodes and directly present them to T cells. They can also stimulate T cells directly by producing Neutrophil Extracellular Traps (NETs), which reduce the activation threshold of T cells. Additionally, neutrophils can act as antigen-presenting cells and present antigen molecules to T cells. They can also transfer antigens to dendritic cells, thereby enhancing the effectiveness of dendritic cells in initiating T cell activation and promoting TH1 and TH17 differentiation [8].

In contrast, lymphocytes serve as the primary effectors of adaptive immunity, facilitating pathogen-specific immune recognition, immune memory production, and regulation of host immune homeostasis [9]. Lymphocytes play a regulatory or protective role in adaptive immunity, and a decrease in lymphocytes indicates poor general condition and physiological stress [10]. The neutrophil-to-lymphocyte ratio is determined by the absolute counts of these cells and represents two distinct yet complementary components of the immune system [8].

The ease of obtaining the Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR), coupled with their relative insensitivity to confounding factors due to their ratio-based nature, renders them superior to other inflammatory variables. According to Postea *et al*. [11], the formation of platelet-monocyte complexes can occur when the platelet-expressed chemokine (C-X3-C Motif) Receptor 1 binds to the monocytes' (C-X3-C Motif) ligand 1. Platelets have comparable secretory vesicles in terms of their contents, which store molecules such as serotonin or 5-Hydroxytryptamine (5-HT), dopamine, glutamate, gamma-aminobutyric acid, and Serotonin Transporters (SRET), brain-derived neurotrophic factor etc. [12]. These shared contents and proteins play a crucial role in the pathophysiology [8].

Previous studies have looked into possible biological predictors and markers for suicide and other suicidal behaviour, particularly in the context of mood disorders [13]. Dysfunctions of the serotonin system and the Hypothalamic-Pituitary-Adrenal (HPA) axis have been claimed to be strongly related with suicide among people with mood disorders, despite the fact that research into this topic has not yet produced any definitive results [14].

In recent years, an increasing number of studies have investigated NLR, and PLR in psychiatric disorders and found them to be higher than in healthy controls [10]. However, still there is limited understanding of the links between NLR,

and PLR values and their relation to the severity of depression and suicidality in the Indian setting. In this background, the current study was undertaken to find NLR, and PLR in patients with depression and their correlation with the severity of depression and suicidal behaviour among patients diagnosed with depression.

Material and Methods

After obtaining approval from Institutional Ethics Committee (IEC-SUIMS/28/2022-23), all patients within 18-65 years age group presenting to Outpatient Department of Psychiatry, Subbaiah Institute of Medical Sciences, Shivamogga with history suggestive of depression based on ICD 10 Criteria were included [16]. One-hundred-fifty consenting patients with depression, during the study period of two years, were enrolled. Exclusion criteria was patients with potential confounding factors such as tobacco use and patients with BMI > 30 kg/m^2, acute or chronic inflammation or auto-immune disease, critically ill patients or patients with severe end-stage diseases, patients on current treatment with anti-inflammatory or immuno-suppressive medications, patients with significant abnormalities in laboratory test results. Socio-demographic details and clinical data including history of suicide attempts in the past 15 days were collected using semi structured proforma. Severity of depression was assessed using Hamilton Depression Rating Scale (HAM-D) and patients were classified in to mild, moderate or severe depression based on their scores [17]. NLR and PLR ratios were estimated. The correlation between NLR and PLR values to severity of depression was assessed. According to their history, patients with recent suicide attempts were identified. Their NLR and PLR values were correlated to see whether they were statistically significant to predict suicidal behaviour.

Statistical analysis

Statistical analyses were performed using SPSS 20.0 statistical package for Windows. Continuous data were expressed as Mean ± Standard Deviation (SD) while categorical data were presented as percentages. To test the statistical significance of the difference in the mean of continuous variable between two groups, independent sample 't' test for normally distributed data or Mann-Whitney U test for skewed data were used. To compare the statistical significance of the difference in the mean of continuous variable more than two groups, one way Anova or Kruskal-Wallis test were used. To test the statistical significance of the proportion of categorical variables between the groups, Chi-square tests was used. Normal distribution was assessed by the Kolmogorov Smirnov test. Receiver Operating Characteristic (ROC) curve analysis was performed to determine the cut-off level of NLR and PLR to predict the suicide attempt. Value of $p < 0.05$ was considered statistically significant.

Results

Our study population consisted of 150 consecutive patients who were diagnosed with depression. Mean age of the study group was 43.54 ± 13.39 years, with 91 females (60.7%) and 59 males (39.3%). Patients were divided into three groups according to scores of HAM-D such as mild, moderate or severe depression (HAM-D scores: 8-16, 17-23, ⩾ 24, respectively).

Severity of depression was mild in 56%, moderate in 48% and severe in 18% of patients according to the HAM-D scores. No significant difference in the distribution of age among the HAM-D Score

group of patients. A mean NLR ratio of 1.74 ± 0.77 and mean PLR ratio of 70.8 ± 34.6 were observed in our study (Table 1).

Table 1: Severity of depression with NLR and PLR ratio

HAM-D Score	Blood Count	
	NLR	PLR
	Mean ± SD	
Mild (84)	1.43 ± 0.33	54.1 ± 17.0
Moderate (48)	1.87 ± 0.44	81.3 ± 30.2
Severe (18)	2.86 ± 1.51	120.7 ± 46.3
p	<0.001	<0.001

Eight patients (5.3%) had history of current suicide attempt with mean age of 40.50 ± 17.96 years. Statistically significant association was found between severity of depression and suicide attempt (Table 2). No association was found between NLR or PLR with gender (p = 0.548 and p = 0.925 respectively). NLR and PLR values were found to be more statistically significant in the presence of stressors (p = <0.001, p = 0.008 respectively).

Table 2: Suicide attempt with NLR and PLR ratio

Suicide Attempt	Blood Count	
	NLR	PLR
	Mean ± SD	
Yes (8)	2.71±1.58	124.4±58.3
No (142)	1.69±0.67	67.8±30.4
p	0.001	<0.001

Statistically significant association was found between NLR and depression severity (p < 0.001) as well as PLR and depression severity (p < 0.001). NLR and PLR values were substantially higher for the suicide attempters group than the non-suicide attempters (p = 0.001 and p < 0.001 respectively) (Table 2). According to the ROC curve analysis (Figure 1), the optimal cut-off value for NLR in predicting suicide attempt was 1.96 (area under the curve = 0.839, sensitivity = 75%, and specificity = 74%) and the optimal cut-off value for PLR in predicting suicide attempt was 88 (area under the curve = 8.73, sensitivity = 75%, and specificity = 76%).

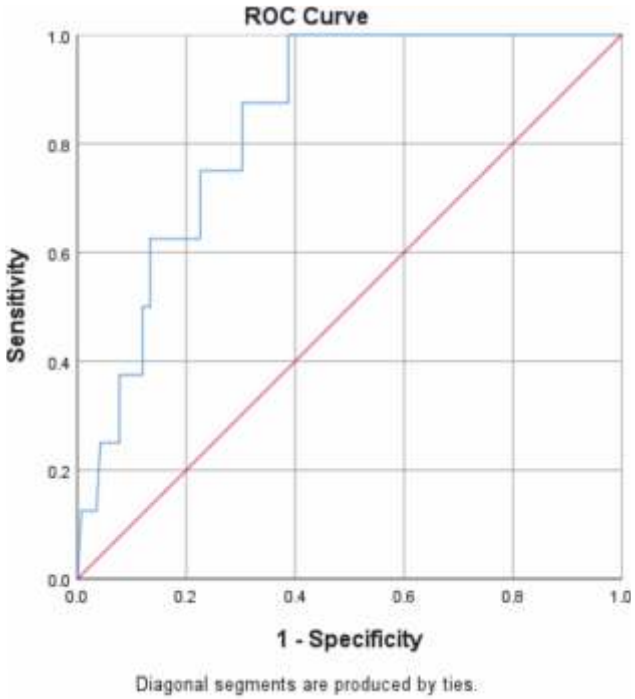

Figure 1: ROC Curve of NLR

Discussion

In this study, we found that higher HAM-D scores were associated with higher NLR values in patients with depressive disorders, which was consistent with the meta-analysis conducted by Mazza *et al*. [10] which showed that NLR were significantly higher in patients with depression than those in controls.

Increased NLR is associated with oxidative stress and increased cytokine production, and these findings have been observed in depressive disorders [18]. Neutrophils and platelets have a lifespan of 24 hours and 10 days in humans, respectively. On the other hand, it has been reported that patients with a clinical diagnosis of depression develop chronic low-grade inflammation and that PLR increases according to the severity of depression. NLR and PLR may thus reflect acute and chronic inflammation, respectively [19].

Velasco *et al*. [20] found that the mean NLR was 2.12, which was higher than the mean NLR observed in our own study, where it was 1.74. Conversely, Lee *et al*. [21] reported a mean NLR of 1.65, which was lower than our study's findings. Furthermore, our study found no significant differences in NLR and PLR based on gender and age. These results were in line with the findings of Ekinci *et al*. [15], Lee *et al*. [21] and Velasco *et al*. [20].

NLR was higher in suicide attempters. These results are in line with previous findings by Ekinci *et al*. [15] and Velasco *et al*. [20] that NLR may be a marker of suicidal vulnerability in depression. PLR has previously been correlated with severity of depression [22]. The mean PLR was 70.8 ± 34.6. A study performed by Lee *et al*. [21] in 2018 reported the mean PLR as 132.4, which was higher than our study. In the present study, it was found that the PLR was significantly increased and correlated with symptom severity and higher PLR values were found in those with history of suicide attempts indicating the importance of the PLR value as a biomarker which is consistent with the findings of Meng *et al*. [23]. Thus, the present study shows that inflammation may play a central role in depression.

To date, this is one of the few studies suggesting a NLR and PLR cut-off value associated with suicide attempts. Our data suggested that NLR and PLR were significantly associated with suicide attempts in patients with depression with an optimal cut-off value of 1.96 (sensitivity 75% and specificity 74%) for NLR and an optimal cut-off value of 88 (sensitivity 75% and specificity 76%) for PLR.

Strengths and limitation of the study

The sample size of our study was relatively small. This was a cross-sectional study and could not establish a direct causal relationship between increased NLR and suicidal risk in depressed patients. Other limitations may include potential confounding factors such as the number of previous depressive episodes, psychiatric antidepressant treatment including dose and duration of treatment, or the lack of a healthy control group.

Conclusion

In conclusion, it can be inferred that elevated HAM-D scores exhibit a positive correlation with increased levels of NLR and PLR in individuals diagnosed with depressive disorder. Furthermore, the severity of depression was also found to be linked with NLR and PLR values in these patients.

Our data suggests that using NLR may be a valuable, reproducible, easily accessible, and cost-effective strategy in clinical practice for detecting suicide vulnerability in patients with depression. To date, there is no strong biomarker associated with suicidality. However, prospective studies are needed to establish causal relationships.

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