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C-Reactive protein and Neutrophil leucocyte ratio in Depressive disorder: a hospital based cross sectional study

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Abstract

Aim of the study. To evaluate High sensitive C-reactive Protein (Hs CRP) and neutrophil lymphocyte ratio (NLR) in patients with Depression and to compare HsCRP and NLR in Major Depressive disorder (MDD) and Recurrent depressive disorder (RDD)

Material and Methods. This was a hospital-based case control study conducted in year 2019 for 3 months duration. Ninety eight patients with Depressive disorder and 50 healthy controls were included. HAM-D, HsCRP and NLR was assessed for all subjects.

Results. HsCRP and NLR was more in patients with Depression than in controls and this was statistically significant. HsCRP and NLR was more in RDD compared to MDD. Both HsCRP, NLR were positively correlated with age, duration of illness, number of depressive episodes and HAMD scores. The odds of suicidal ideas in depressive patients was more with increase in HsCRP and NLR.

Discussion. To the best of our knowledge, this is the first study to compare inflammatory parameters in MDD and RDD. In our study, CRP and NLR were more in RDD compared to MDD. This could be explained by immune dysregulation and chronic inflammation in RDD. Resistance to antidepressant therapy, and relapse of depression causes an activation of inflammatory response. In the present study, we observed an association between suicidal ideas and CRP, NLR.

Conclusions. Inflammation plays a significant role in depression as indicated by elevated HsCRP and NLR. These parameters help to assess suicidal risk. A futuristic study can be taken up to assess the effect of antidepressants on their levels.

depression; high sensitive C-reactive protein; neutrophil lymphocyte ratio

INTRODUCTION:

Depression is a common illness worldwide, with more than 300 million people affected. It is also a leading cause of disability worldwide and a major contributor to the overall global burden of disease [1]. The high burden of the disease is because of its recurrent course [2]. When there is unclear aetiology for the disorder the search

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for it continues till, we are able to conclude on it. Among the biological and psychological theories explaining the causes of depression, the hypothesis involving an active inflammatory process taking place in a human organism is becoming increasingly important [3].

Blood parameters like Complete blood count (CBC), C-reactive protein (CRP), and cytokines are used to measure inflammation. During the phase of acute inflammation, cytokine originated from the pathological site upregulates the synthesis of CRP by hepatocytes[4]. Researchers have found High sensitivity CRP (Hs CRP) to be a useful indicator in assessing low grade microvascular inflammation like Coronary heart disease and neuroinflammation in psychiatric conditions [5,6]. In addition, stress and depression may result in an increased number of leukocytes and neutrophils, as well as decreased lymphocytes [7]. Recently, the neutrophil–lymphocyte ratio (NLR) has been found to be a good indicator of inflammatory status, [8]and this ratio has been investigated in a number of neuropsychiatric diseases [9,10].

Although it is unclear the extent to which inflammation contributes to depression onset and relapse [11], it is becoming increasingly clear that inflammation may increase the complexity and severity of illness presentation, as well as treatment response, at least among a subpopulation of individuals with MDD [12]. Although longitudinal studies have shown that elevated serum cytokine levels often precede, and therefore potentially cause depressive symptoms, [13,14] the direction of causality is still being studied and the possibility that depression worsens the course of inflammatory illnesses cannot be ruled out, at least in a subset of patients [15].

There are many studies on association of inflammation and depression with contrasting outcomes and this encouraged us to carry out the present study to examine the role of inflammation in depression using CRP and NLR. We also tried to analyse whether there is any association between the severity and recurrence of depression with inflammation.

METHODOLOGY

This was a hospital-based cross-sectional case control study, conducted in the outpatient department of psychiatry of a tertiary medical college hospital in the year 2019 for duration of 3 months. Ninety-eight consecutive patients in the age group of 18-65 years who were diagnosed with Depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders-*5 (DSM-5)* were included in the study. Among 98 patients 64 had Major depressive disorder (MDD) and 34 had Recurrent depressive disorder (RDD). For an episode to be considered recurrent, there must be an interval of at least 2 consecutive months between separate episodes in which criteria are not met for a major depressive episode. Age and gender matched 50 healthy subjects who were hospital employees or relatives of the patients and did not have any psychiatric, chronic physical illness and acute infections were taken as controls. Subjects who had seizure disorders, mental retardation, other psychiatric disorders, hypertension, hypercholesterolemia, acute or chronic physical illnesses, pregnancy, smoking, alcohol use, and history of any drug use or medication use during the last month, were excluded from the study. Written informed consent was taken from the cases and controls. Psychiatrist administered a semi structured proforma to collect socio demographic details, height, body weight and Hamilton rating scale for depression (HAM-D) scale, an item on suicide, (Question 3) in HAM D scale was used to assess the suicidal ideas. Complete Blood Count, NLR and CRP were measured and recorded for each subject. The study was approved by the Institutional ethics committee (IEC/TOMCHRC/114/2019-20).

MEASUREMENTS:

Hamilton depression rating scale (HAM-D):

HAM –D has 21 items and is an observer rated screening tool. Ratings are made on the basis of clinical interview. Scores 7 and below is considered as normal, 8 – 13 as mild depression, 14 – 18 as moderate depression, 19 – 22 as severe depression and 23 and above as very severe depression [16].

ANALYSIS OF CBC AND CRP:

2.5 ml blood was obtained from medial cubital vein by venepuncture avoiding haemolysis in sterile BD Vacutainer tube (BD Franklin Lakes NJ USA) with 5.4mg of K2 Ethylene Diaminetetraacetic acid (EDTA) for CBC. At the same time about 2 ml of blood was collected in clot activated vacutainer for CRP measurement and was centrifuged at about 3500 RPM. Complete blood count, was determined using Sysmex XP – 100: A1489 haematology analyser (Sysmex, India). In order to measure NLR reliably and to minimize the potential influence of anticoagulant [EDTA], blood samples were analysed within 60 minutes after venepuncture. All the blood samples were analysed at the same laboratory. Quantitative analysis of HsCRP was done with 5 μL of fresh serum sample using Nephelometry of Agape company which works on the principle of Latex enhanced turbidimetric immunoassay. The actual concentration was then determined by interpolation from a calibration curve prepared from calibrators of known concentrations. We used the Agape kits with a lower detection limit of 0.5 mg/L.

Statistical analysis

The data was analysed using SPSS for Windows version 16.0 software (SPSS.INC Chicago, IL, USA). Data were tested for normal distribution using Kolmogorov-Smirnov test. Results obtained were analysed using descriptive and inferential statistical methods. Chi square test was used for categorical data and student t test, ANOVA was used for continuous data. Pearson's correlation was used to know the association of CRP, NLR with age of the patient, duration of illness, number of depressive episodes and HAM-D scores. Logistic regression was used to assess the association between suicidal ideas and CRP, NLR.

RESULTS

There was no statistical difference in the sociodemographic details and body mass index of the cases and the controls. Most of our subjects were females, married from urban area belonging to joint family. (Table-1) Among 98 patients 64 had MDD and 34 had RDD and 50 subjects were in the control group and there was no statistical difference in sociodemographic variables within the groups. (Table 2)

Mean CRP (t=10.12, p<0.001, Cohens d=1.6) and NLR (t=5.62,p<0.0001,Cohens d=0.8) were high in depressive group compared to controls and this difference is statistically significant. (Table 3). The duration of illness (t=9.66, p=0.001), CRP level (t=7.59,p=0.0001, Cohens d=1.7) and NLR (t=3.2, p=0.008, Cohens d=0.65) were more in RDD compared to MDD and it was statistically significant (Table-4).

Pearson correlation showed that CRP was positively correlated with age of the patient (R=0.314, p=0.001), duration of illness (R=0.361, p=0.059), number of depressive episodes (R=0.122,p=0.491) and HAM-D (R=0.664, p=0.0001).

NLR was positively correlated with age (R=0.114,p=0.518), duration of illness (R=0.19,p=0.854) and number of episodes (R=0.043,p=0.675) and HAM-D (R=0.54, p=0.001). There was a positive correlation between CRP and NLR (R=0.014, p=0.93).

The odds of suicidal ideas in depressive patients was more with increase in CRP values (OR=1.15, p<0.05, 95%CI= 0.957-1.399), and increase in NLRvalues (OR=1.379, p<0.05,95% CI=0.952-1.997).

Table 1. Socio-demographic details of depressive patients and Controls

Variables		Depressive disorder N=98	Controls N=50	Statistical analysis
Age		37.918±10.6	37.68±13.49	t=3.465 p=0.065
Gender	male	40(41)	21(42)	x2=0.19 p=0.89
	female	58(59)	29(58)	

Marital status	**married**	84(85)	39(78)	x2=1.4 p=0.23
	unmarried	14(15)	11(22)	
place	**urban**	56(57)	27(54)	x2=0.133 p=0.716
	rural	42(43)	23(46)	
family	**nuclear**	60(61)	34(68)	x2=0.656 p=0.418
	joint	38(39)	16(32)	
Occupation	**employed**	36(37)	20(40)	x2=3.41 p=0.33
	farmer	30(31)	11(22)	
	Un-employed	11(11)	3(6)	
	homemaker	21(22)	16(32)	
Socioeconomic status	**upper**	16(16)	9(18)	x2=0.227 p=0.89
	middle	55(56)	26(52)	
	lower	27(28)	15(30)	
BMI		22.86±2.79	22.9±2.58	t=0.08 p=0.93

*p<0.05 – significant

Figures in parenthesis are in percentages

Table 2. Socio-demographic details of MDD,RDD and Controls

Variables		**MDD N=64**	**RDD N=34**	**Controls N=50**	**Statistical analysis**
Age		35.12±9.56	40.17±10.61	37.68±13.49	F=2.31 P=0.1008
Gender	**male**	30(46.9)	10(29.4)	21(42)	x2=2.814 p=0.245
	female	34(53.1)	24(70.6)	29(58)	
Marital status	**married**	54(84.4)	30(88.2)	39(78)	x2=1.639 p=0.441
	unmarried	10(15.6)	4(11.8)	11(22)	
place	**urban**	38(59.4)	18(52.9)	27(54)	x2=1.639 p=0.441
	rural	26(40.6)	16(47.1)	23(46)	
family	**nuclear**	42(65.6)	18(52.9)	34(68)	x2=2.19 p=0.33
	joint	22(34.4)	16(47.1)	16(32)	
Occupation	**employed**	21(32.8)	15(44.1)	20(40)	x2=6.16 p=0.405
	farmer	23(35.9)	7(20.6)	11(22)	
	Un-employed	7(10.9)	4(8.8)	3(6)	
	homemaker	13(20.3)	8(23.3)	16(32)	
Socioeconomic status	**upper**	10(15.6)	6(17.6)	9(18)	x2=0.64 p=0.95
	middle	35(54.68)	20(58.9)	26(52)	
	lower	19(29.6)	8(23.5)	15(30)	
BMI		23.22±2.46	22.4±3.12	22.9±2.58	F=1.055 p=0.3508

*p<0.05 is significant

Table 3. Clinical and Biochemical variables of depressive patients and Controls

Variables	Depressive disorder N=98	Controls N=50	Statistical analysis
HAM-D	22.92.18	6	t=49.42 p<0.0001*
Hb	11.36	11.5	t=0.36 p=0.71
Neutrophils	4402.15	4096	t=1.16 p=0.24
lymphocytes	2195.01	2236	t=5.62 p<0.001*
NLR	2.295	1.81	t=5.62 p<0.0001*
CRP	2.365	1.2	t=10.12 p<0.001*

*p<0.05 is significant

Table 4. Clinical and biochemical variable between MDD and RDD

Variables	MDD N=64	RDD N=34	Statistical analysis
HAM-D	23.09	22.58	t=1.104 p=0.27
BMI	23.22±2.46	22.4±3.12	t=1.142 p=0.156
Age of onset	31.6713.8	31.41	t=0.09 p=0.922
Duration of illness	1.25	11.76	t=9.66 p=0.001*
Number of episodes	First episode	2.94	-
Hb	11.5	11.1	t=1.44 p=0.15
Neutrophils	4445.7	4358.6	t=0.249 p=0.80
Lymphocytes	2225.03	2165	t=0.395 p=0.694
Monocytes	351.15	318.6	t=1.225 p=0.224
eosinophils	246.3	311.64	t=1.567 p=0.120
platelets	250656.25	241588.23	t=0.498 p=0.62
RBC	4.82	4.44	t=1.59 p=0.36

WBC	7282.18	6864.7	t=1.19 p=0.235
NLR	2.09	2.32	t=3.2 p=0.0018*
MLR	0.208	0.19	t=0.488 p=0.627
PLR	127.68	118.39	t=0.906 p=0.367
CRP	1.93	2.8	t=7.59 p=0.0001*

*p is <0.05 and is significant

DISCUSSION

In our study, we found that the Hs CRP and NLR levels were high in patients with depression compared to control group. In our study, CRP and NLR were more in RDD compared to MDD. There was a positive correlation between inflammatory markers, HAM D scores, duration of illness and number of episodes. Present study concurs with the previous studies where there is increased CRP [17,18,19] and NLR in depressive groups [20,21,22].

Dowlati et al, has observed the increase in inflammatory markers would be in much lower range compared to infection and autoimmune diseases, this has also corroborated with the present study [23].

Most of the evidence that connects MDD to inflammation derives from three factors: 1) patients with inflammatory diseases are more likely to show greater rates of Depression 2) a large number (approximately one-third) of people with major depression show elevated peripheral inflammatory biomarkers, even in the absence of a medical illness, and 3) patients treated with cytokines (i.e. for chronic infective hepatitis) are at increased risk of developing depression. Indeed, inflammatory mediators have been found to alter glutamate and monoamine neurotransmission, glucocorticoid receptor resistance and hippocampal neurogenesis [23,24,25,26]. Moreover, inflammation is able to alter brain signalling patterns, to affect cognition and to contribute to the production of a pattern of symptoms, clustering in a syndrome named 'sickness behaviour' and closely related to depression [8].

In this study there was a positive correlation of CRP with both age of patient and age of onset of depression. Increase in age is associated with microvascular inflammation and atherothrombotic lesions [26]. Hence, patients who present at a later age may have these changes not only in cardiovascular but in neural microvasculature as well. This may be the reason for a higher CRP level in patients with increased age.

In the present study, we observed an association between suicidal ideas and CRP, NLR. A 9 year prospective study by Batty et al has also reported a positive correlation between CRP and suicide [27]. According to a study CRP and IL6 were found to be elevated in patients with high suicidal ideation [28]. Meydeneri et al has reported higher NLR in patients with more suicide attempts [29]. Though, Bergman et al did not find any association between the two.[30] These discrepancies may be attributed to differences in sample size, study design, and controls used in each study. We believe that, HsCRP and NLR could also be utilized as a conjunctive marker to assess suicidal ideation along with HAM D scores. This could help in early intervention towards preventing suicidal attempts. Though more studies are needed to further clarify the association.

In our study, CRP and NLR were more in RDD compared to MDD. There was a positive correlation between inflammatory markers, duration of illness and number of episodes. This could be explained by immune dysregulation and chron-

ic inflammation in RDD [31]. Resistance to antidepressant therapy, and relapse of depression causes an activation of inflammatory response. There are studies which indicate that in treatment resistant MDD cases the level of proinflammatory cytokines are elevated, in turn leading to high CRP [5]. A possible explanation for this is that, during inflammation, microglia, neurons and macrophages activate metabolism of serotonin and tryptophan breakdown thus decreasing response to SSRIs [32]. Patients with RDD have repeated episodes and runs a chronic course which would lead to higher levels of inflammatory markers. Over the due course of relapses increasing age of the patient may also contribute to the higher levels of these markers. Because, higher age itself may be linked with chronic low grade inflammation, which can lead to increase in levels of cytokines and hence CRP, which is also called 'Inflammaging' [33]. In our study the age group of RDD patients were higher than MDD and control group and this can also be one of the reason for higher CRP and NLR in this group.

This was a hospital based cross sectional case control study, wherein we have assessed the role inflammatory biomarkers in depression, which are inexpensive and can be carried out in any primary set up. To the best of our knowledge, this is the first study to compare inflammatory parameters in MDD and RDD. Subjects in our study did not have any kind of infection, acute inflammation, history of smoking, alcohol, drug intake and medications, as these factors are known to cause significant changes in levels of inflammatory biomarkers. Thereby, we have eliminated most of the known confounding factors. Patients were drug free for at least one month and hence there was no effect of drugs on these parameters.

There were certain limitations in our study, this was a hospital-based study and had small number of subjects so could not be generalised to the community. For suicidal ideas we had used an item from HAM-D, a specific scale for suicidal ideation would have been more appropriate. It is a cross sectional study which hinders casual associations between predictors and outcome variables. We did not assess the influence of gender on these parameters.

There is further scope for longitudinal assessment, to know the association of inflammatory biomarkers, depression and coronary heart disease, the effect of antidepressants on inflammatory markers and influence of these biomarkers on developing resistance to these drugs.

To conclude, we substantiate the role of inflammation in Depression, as evidenced by elevated levels of Hs CRP and NLR. Also, it would be prudent to say that, along with HAMD scores, HsCRP and NLR could be used as pragmatic indicators in patients with depression, as an accessory aid to assess the severity of depression and also as a prognostic indicator.

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