ORIGINAL ARTICLE

Association between Severity of Depression and CRP Level: A Cross-sectional Study

Julia Keisham[1], Vidya Sanapala[2], Niveditha Vasireddy[3], Ramya Spandana Tata[4], Srikrishna Nukala[5], Srinivas Singisetti[6], Abhilash Garapati[7]

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Abstract

Aim and background: Depression is a worldwide mental health issue. Depression is believed to result from multifaceted social, psychological, and biological interactions. Many recent studies have found elevated levels of pro-inflammatory cytokines in patients with depression and speculated on their involvement in the pathophysiology of depression. The autonomic nervous system (ANS) activity and hypothalamic (HPA) axis are linked to depression symptoms and C-reactive protein (CRP) production. So, this study aimed to study the severity of depression (SOD) and its correlation to serum CRP levels and identify the relationship between suicidal ideations and CRP levels.

Materials and methods: This is a cross-sectional study, hospital-based on patients diagnosed with depression who attended the outpatient department, fulfilled the inclusion criteria, and gave consent. A semi-structured proforma for sociodemographic details and the Montgomery-Asberg Depression Rating Scale to assess the SOD were applied to the patients, after which serum C-reactive protein levels (CRP) were tested based on the particle-enhanced turbidimetric immunoassay (PETIA) technique.

Results and conclusion: In our study, we found a statistically significant (*p*-value of 0.001) positive correlation between the SOD and serum CRP levels. A statistically significant (*p*-value = 0.001) association is found between the presence of suicidal ideations and an increase in CRP levels. In conclusion, with the SOD and the presence of suicidal ideations, higher CRP levels were observed.

Clinical significance: These results indicate that CRP levels can be an essential marker for understanding the disease pathophysiology and may contribute to therapeutic management in the future.

Keywords: C-reactive protein, CRP, Cross-sectional observational, Depression, Inflammatory markers, Severity of depression, Suicidal ideation.

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Introduction

Depression is a common mental health problem globally. According to WHO estimates, 3.8% of the global population experiences depression at some point.[1] It usually presents as a low mood or loss of pleasure or interest in activities lasting for long periods. Depression can affect almost all aspects of life, including personal and social relationships, work or studies, self-care, and health. As per NHMS statistics for 2015–16, 1 out of every 20 people over 18 have suffered from depression in India.[2] If present trends continue, the burden of depressive disorder is expected to rise to 5.7% of the overall illness burden by 2023, making it the second most significant cause of disability adjusted life years (DALYs), after only ischemic heart disease (IHD).[3]

Depression occurs due to varied interactions between social, psychological, and biological factors. Recent studies have shown that increased levels of pro-inflammatory cytokines are seen in patients with depression and speculate their involvement in the pathophysiology of depression. Inflammatory cytokines have profound effects on the neuroendocrine system (particularly on the hypothalamic-pituitary-adrenal [HPA] axis) and the CNS, where they can cause a variety of symptoms of illness, such as fever, decreased appetite, withdrawn behavior, and sleep disturbances.[4] The stimulation of the inflammatory response is linked to depression.[5,6] The "monocyte T-cell theory" of mood disorders, such as unipolar and bipolar depression views immune response system activation as the driving force behind mood disorders. Some research suggest the existence of a possible "psycho-neuroimmune affiliation" with both negative mood (depression, anger, and anxiety) and decreased subjective well-being.[7,8] The autonomic nervous system (ANS) activity and HPA axis have been linked to depression symptoms and CRP production.[9,10] C-reactive protein is an inflammatory marker generated mainly by hepatocytes. It is regulated by the pro-inflammatory cytokine interleukin 6 (IL-6).[11] Clinical observations and epidemiological research have revealed that innate immune responses may be implicated in suicidal behavior. According to Osimo et al., systematic review and meta-analysis, around a quarter of patients with depression had signs of low-grade inflammation, and more than half had mildly raised CRP levels.[12] Many previous studies concluded that elevated CRP levels were substantially linked with depression.[13–15]

Taking these findings further, some researchers have studied the severity of depression (SOD) and its association with serum

[1–7]Department of Psychiatry, GITAM Institute of Medical Sciences and Research, Visakhapatnam, Andhra Pradesh, India

Corresponding Author: Vidya Sanapala, Department of Psychiatry, GITAM Institute of Medical Sciences and Research, Visakhapatnam, Andhra Pradesh, India, Phone: +91 9703592412, e-mail: vsanapal@gitam.edu

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CRP levels.[16,17] However, there is a dearth of such studies diving into the association of depression severity or suicidality with serum CRP levels, especially in India. Hence, this present study aims to estimate the relationship between serum CRP levels and the SOD and suicidal ideations to help understand the disease pathophysiology better, which may contribute to therapeutic management in the future.

Aims and Objectives

- To study the association between the SOD and CRP levels.
- To study the association between suicidal ideations and CRP levels.

Materials and Methods

The Department of Psychiatry at a tertiary care teaching hospital in a semi-urban area conducted this cross-sectional observational research. This study used consecutive sampling from November 2022 to May 2023, with clearance from the Institutional Ethics Committee.

Sample Size Calculation

The sample size was estimated using the following formula based on the fraction of the population with elevated CRP levels:

$$n = \frac{Z_{\alpha}^2 pq}{L^2}$$

Using the above formula, the minimum sample required was obtained as $n = 115$.

Subjects aged 18–55 who fulfilled ICD-10 criteria for diagnosing depressive disorder with 1st episode depressive disorder or RDD, currently symptomatic episode, were taken into the study. The subjects with other co-morbid psychiatric illnesses, chronic physical illness, substance use, and RDD in remission were not considered for admission into the study. Also, patients with any condition that is known to cause raised CRP levels have been excluded (acute infections of the respiratory tract, malignancies of the breast, lung, and gastrointestinal tract, acute pancreatitis, history of surgery or burn during the previous month, leukemia, tobacco smoking, hormone replacement therapy (HRT), oral contraceptive pill (OCP) use, obesity (BMI ≥30), metabolic syndrome, rheumatoid arthritis, systemic lupus erythematosus (SLE), connective tissue diseases, myocardial infarction in the last 3 months, inflammatory bowel disease (IBD), rheumatic fever.

The subjects who qualified for the study were informed about the study's aims and procedures, and those who satisfied the inclusion criteria and gave consent were recruited into the study. We collected the subjects' sociodemographic details using a semi-structured proforma. A detailed psychiatric interview and the Montgomery-Asberg Depression Rating Scale (MADRS) assessment scale were applied. The MADRS score,[18] which consists of 10 items, assesses the severity levels in adult patients diagnosed with depression. A score below or equal to 8 refers to the absence of depression, whereas scores of 9–17, 18–34, and 35–60 indicate mild, moderate, and severe forms of depression, respectively. Subjects rating 4 and above on item 10 of the MADRS have been considered to have suicidal ideations. Four clinicians were trained to assess the scale to ensure no inter-rater bias. The correlation for the MADRS is 0.71.

Table 1: Sociodemographic characteristics of the sample

Sociodemographic details	*Frequency*
Gender	
Female	64 (55.7%)
Male	51 (44.3%)
Education	
Illiterate	34 (29.6%)
literate	81 (70.4%)
Socioeconomic status	
Lower-middle	36 (31.3%)
Upper-middle	79 (68.7%)
Employment status	
Employed	70 (60.9%)
Unemployed	45 (39.1%)

Table 2: Clinical characteristics of MADRS score and serum CRP levels

	n (%)	*MADRS mean*	*CRP mean*
Mild depression	42 (36.5%)	13.45	0.6
Moderate depression	47 (40.8%)	25.05	4.8
Severe depression	26 (25.2%)	43.41	13.2

Inter-rater reliability of MADRS ranges in studies from 0.89 to 0.97, and intraclass coefficients are between 0.66 and 0.82. Serum C-reactive protein (CRP) levels of the subjects were estimated based on the technique of particle-enhanced turbidimetric immunoassay (PETIA). A standardized CRP measurement technique was used to prevent measurement bias. Based on a previous study, a serum CRP value less than 0.3 mg/dL is taken as normal, 0.3–1.0 is considered normal to mild elevation, 1.0–10.0 denotes moderate elevation, and a serum CRP value greater than 10 is considered marked elevation.[19]

SPSS version 21 and MS Excel 2007 were used for all statistical analyses. To express qualitative characteristics, frequencies and percentages were used. We used mean and standard deviation to describe quantitative variables. We used the Chi-square test to examine the categorical data. The mean difference between the two groups was determined using a student-independent sample *t*-test. ANOVA with *post hoc* analysis was used to find the mean difference between more than two groups and for multiple comparisons. The Karl-Pearson correlation coefficient was utilized to investigate the link between two quantitative variables.

Results

Out of 115 cases enrolled in the study, 64 were females (55.7%) (Table 1), 51 were males (44.3%), and the mean (SD) age of the sample was 42.9 (11.82) years. Most patients were of upper-middle or lower-middle socioeconomic status (70%) and were primarily literate (70.4%).

As evident from Table 2, The sample's mean MADRS score of depression was 25.4 (SD 13.02). In this sample of 115 patients, 44 (22.6%) had suicidal ideas. The mean CRP value for this sample was 3.6, and it was noted that 67 patients (58.3%) had a normal to mild elevation of CRP, 32 (27.8%) had moderate elevation, and 16 (13.9%) had marked elevation. The mean serum CRP of the sample was 3.6 (SD 4.82).

Table 3: Association of severity of depression with serum CRP levels

	CRP level			
	Normal–mild	*Moderate*	*Marked*	*Total*
Severity of depression				
Mild				
No. of pts	39	3	0	42
%	92.8%	7.1%	0%	
Moderate				
No. of pts	19	25	3	47
%	40.4%	53.1%	6.3%	
Severe				
No. of pts	9	4	13	26
%	34.6%	15.3%	50%	
Total				
No. of pts	67	32	16	115
p-value		0.001		

Table 4: Association of suicidal ideations with serum CRP levels

	CRP level			
	Normal–mild	*Moderate*	*Marked*	*Total*
Suicidality				
Ab				
No. of pts	48	21	2	71
%	67.6%	29.5%	2.8%	
Pr				
No. of pts	19	11	14	44
%	43.1%	25.0%	31.8%	
Total				
No. of pts	67	32	16	115
p-value		0.001		

Table 5: Means of CRP levels and MADRS scores in relation to suicidality

Suicidality	*N*	*Mean*	*Std. deviation*	*p-value*
CRP levels				
Present	44	6.168	6.1559	0.001
Absent	71	2.008	2.8247	
MADRS score				
Present	44	35.43	12.147	0.001
Absent	71	19.25	9.157	

MADRS score, CRP levels, LSD

As given in Table 3, none of the patients with mild depression had marked elevation of CRP. Most patients with moderate depression had a moderate elevation of CRP level followed by mild elevation. In patients with severe depression, most of them had marked elevation of serum CRP levels. These findings had statistical significance with a *p*-value of 0.001.

As depicted in Table 4, among patients with suicidal ideations, 14 (31.8%) have marked elevations in CRP. These findings were statistically significant with a *p*-value of 0.001 (Table 5).

This scatter plot shows a positive correlation between rising MADRS scores and elevation in serum CRP levels. Pearson correlation coefficient (two-tailed) was calculated for CRP Levels and MADRS scores and it is statistically significant with a *p*-value of <0.001 (Tables 6 and 7).

Discussion

Increased levels of pro-inflammatory cytokines have been linked to the development of major depression.[20] Multiple and recurring episodes of depression have been linked to high CRP levels. As a result, we sought to investigate this association.

Our study sample is primarily literate (70.4%) and employed (60.9%), with almost equal gender distribution, contrary to a similar study done by Soni Singh et al. at Kings George Medical University Lucknow. They had more male preponderance (55%) and fewer literate and employed subjects.[20] This difference might have been due to the semi-urban location of our study sample, causing a difference in the demographic statistics between the samples. Also, being educated and employed could have contributed to a better knowledge and awareness of depression, which probably led to psychiatric consultations.

The mean age of the sample is 42.9 years, similar to Soni et al. (34.7 years),[20] which might be due to more awareness of mental illness in middle-aged people compared with older adults who usually accept depressive features as a part of normal aging.[21]

We found the SOD and serum CRP levels had a statistically significant correlation with severe depression having marked elevations, similar to the findings of Soni Singh et al.[20] They studied the association between mild and severe depression with CRP but not moderate depression and found a significantly marked elevation of CRP in severe depression. As in their study, we also found that the mild depressive group only had a normal to mild elevation; however, the mean CRP in that group was slightly greater than that in our study, probably due to the difference in the methodology.

Jitendra et al. also studied the SOD and their association with CRP and Il-6. Similar to this study, they discovered a significant positive correlation between severe depression and increased CRP levels, but no such association was found between mild and moderate depression. However, this study found moderate elevation of CRP levels even in the moderate depressive group. This difference in observation could be because of the different rating scales used for classifying the SOD. According to Jitendra et al., there is a causal relationship between changes in CRP levels and the severity of depressive episodes.[22] A systematic review conducted by Laura Orsolini et al. included 56 studies, out of which 24 studies found a positive correlation between elevated CRP levels and depression as in this study.[13]

With the presence of suicidal ideations, we noticed higher levels of CRP. When O'Donovan et al. explored variations in inflammatory markers in individuals with MDD with and without high levels of suicidal ideation, they discovered that patients with strong suicidal ideations had higher levels of inflammatory markers than healthy controls.[23] Our findings are consistent with those of Ekinci O and Ekinci A, who found a link between lipid profile, and low-grade inflammation and suicidal behavior in patients with MDD, indicating that CRP may be an essential phenotypic marker of attempted suicide in individuals with low-grade inflammation.[24] Park RJ and Kim YH investigated suicidal behavior in the general population and its relationship with CRP levels. They believed that greater levels of CRP were linked to suicide acts in the general population, indicating a distinct mechanism unrelated to depression.[25] Our study, though

Table 6: *Post hoc* analysis of severity of depression

Severity of depression (SOD) group (I)	*Severity of depression (SOD) group (J)*	*Mean difference (I–J)*	*Std. Error*	*Sig.*	*95% Confidence interval*	
					Lower bound	*Upper bound*
Mild	Moderate	−11.59	1.275	0.001	−14.12	−9.07
	Severe	−29.96	1.427	0.001	−32.79	−27.13
Moderate	Mild	11.59	1.275	0.001	9.07	14.12
	Severe	−18.37	1.414	0.001	−21.17	−15.57
Severe	Mild	29.96	1.427	0.001	27.13	32.79
	Moderate	18.37	1.414	0.001	15.57	21.17

Table 7: *Post hoc* analysis of serum CRP levels

Serum CRP (SCRP) Group (I)	*Serum CRP (SCRP) group (J)*	*Mean difference (I–J)*	*Std. Error*	*p-value*	*95% Confidence interval*	
					Lower bound	*Upper bound*
Marked	Mild	13.29	0.47	<0.001	12.35	14.22
	Moderate	9.20	0.52	<0.001	8.16	10.22
Mild	Marked	−13.29	0.47	<0.001	−14.22	−12.35
	Moderate	−4.09	0.36	<0.001	−4.82	−3.37
Moderate	Marked	−9.19	0.52	<0.001	−10.22	−8.16
	Mild	4.09	0.36	<0.001	3.37	4.82

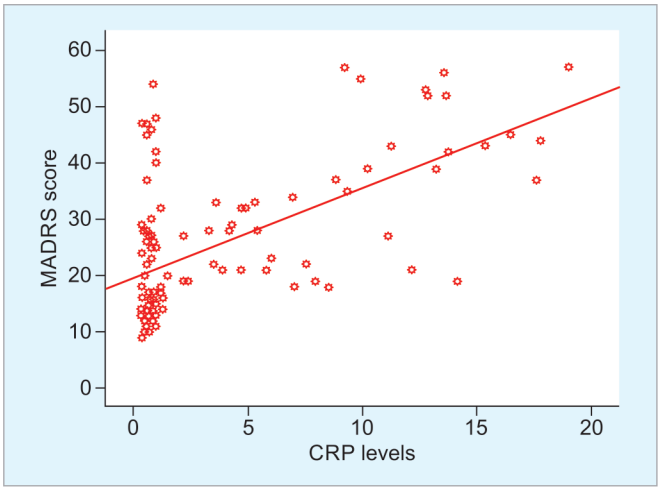

Fig. 1: A Scatter plot denoting the relationship between serum CRP levels and MADRS score

different from theirs as we studied CRP levels only in depressed patients and not in the general population, found similar results, wherein those with suicidal ideations had a higher elevation of CRP.

Köhler-Forsberg et al. investigated the relationship between CRP levels and overall MADRS symptom severity and discovered that higher CRP levels were substantially linked with increased overall MADRS symptom severity.[26] These findings are similar as shown in Figure 1.

Limitations

- The research was a one-time cross-sectional examination with no follow-up. So, prospective studies are required to clarify the causality.
- As our study sample is small, it might be difficult to generalize to the general population.
- Our sampling has yet to be stratified, which again limits the generalizability of our findings.

Conclusion

In conclusion, greater CRP levels were shown to correlate with the degree of depression. Amongst those depressed patients with suicidal ideations, significantly elevated CRP levels were found compared with those without.

Further studies in this literature can lead to us coming up with better management protocols for depression to consider anti-inflammatory drugs as augmenting agents along with antidepressant treatment, especially in cases of resistant depression and in cases of suicidality.

Orcid

Julia Keisham https://orcid.org/0009-0001-2458-0236
Vidya Sanapala https://orcid.org/0009-0001-7793-9396
Niveditha Vasireddy https://orcid.org/0000-0001-6785-1174
Ramya Spandana Tata https://orcid.org/0000-0002-8953-0926
Srikrishna Nukala https://orcid.org/0000-0001-7368-9759
Srinivas Singisetti https://orcid.org/0009-0008-9795-261X

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