

Association of C-Reactive Protein (CRP) with Bipolar Disorder & Gender

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ABSTRACT

Background: Bipolar disorder (BD) is a mental disorder with mood swings that fluctuate between mania, hypomania, and depression. C-reactive protein (CRP) levels in bipolar patients have been studied across the globe, but the results are variable. A very limited research has been conducted in this area in Pakistan. Therefore, the goal of the current investigation was to evaluate CRP in bipolar illness. Moreover any link between CRP and gender was also investigated.

Materials and methods: In this cross-sectional study, 112 subjects (82 bipolar patients and 30 controls) were included. The patients were randomly selected from Punjab Institute of Mental Health (PIMH) and Sheikh Zayed Hospital, Lahore. After the consent of the subjects, venous blood samples were collected. CRP levels were semi-quantitatively estimated by agglutination method. The data obtained was analyzed through SPSS.

Results: The difference in the mean CRP level among bipolar and control groups was statistically significant ($p = 0.001$). Moreover, males had higher CRP levels than females but the difference was non-significant ($p=0.134$). Comparison of CRP levels among various stages of BD and control showed a significant difference between the groups ($p=0.009$).

Increased CRP levels give an idea about the inflammation and severity of the disease. CRP levels could be of help in the diagnosis and prognosis of BD.

Conclusions: The present study suggests a significant association of CRP with bipolar disorder. No significant relation of CRP and gender was depicted.

Keywords: Bipolar Disorder, C-reactive protein, Gender

INTRODUCTION

Bipolar disorder (alternatively recognized as a disorder with mania and depression) is a neurological disease due to which there is an alteration in the affected subject's mood, ability to work and self esteem. It is a mental illness that leaves a person permanently disabled. In BD, the mood alters between mania, hypomania, and depression. Bipolar emotional episodes can destroy relationships, influence work capacity of a person and can be a cause of distractibility and self destruction⁽¹⁾. According to the data of World Health Organization (WHO), BD has the twelfth-greatest global morbidity and mortality rate. Additionally, it has been noted that self-inflicted injuries accounted for 2.5 out of every 1000 deaths and severe public health issues, such as psychiatric illnesses, cause almost 1 million deaths each year⁽²⁾. South Asian studies reported a lower frequency of psychiatric illness in adolescence and a sharp increase in adulthood⁽³⁾. Bipolar patients have a higher suicidal tendency with 4-14% death rate and 23-26% suicidal attempt rate. It has been estimated that almost 25-50% of the bipolar patients seek to attempt suicide sometime throughout their lifetime and 8-19% do commit suicide⁽⁴⁾.

Based on symptoms the symptoms of BD, the disease is classified into manic and depressive episodes. Manic episodes are defined as an unusually high or elevated mood and the patient remain in this phase for at least one week. Other symptoms include high level of irritability, easy distraction, and psychosis, which may include delusions or hallucinations. Depression is characterized by persistent sadness, tears, hopelessness, or emptiness for the bulk of each day, lack of interest in everyday activities, changes in weight, and excessive crying⁽⁵⁾.

A number of risk factors are linked to BD, including age, gender genetic predisposition, history of suicide attempts and stressful life events⁽⁶⁾. Biological alterations in cytokine profiles, highly sensitive C-reactive proteins (hsCRP), immunoglobulins, and complement proteins are linked to mood episodes in bipolar disorder.

A pentameric protein called C-reactive protein (CRP) is synthesized in the liver and released into the bloodstream. It is a key player in the inflammatory process. Monitoring CRP levels in the blood offers a trustworthy indicator of inflammation brought on by viral diseases and other inflammatory triggers⁽⁷⁾. CRP levels that are higher have been linked to inflammatory cardiovascular problems, persistent infections, and other inflammatory illnesses.

CRP levels are also triggered by elevated levels of inflammation markers like TNF- α , IL-6 and IL-1⁽⁸⁾. Value of CRP, an acute phase protein, can rise to 10,000-fold in response to injury and infection. Its usage as a biochemical marker has drawn a lot of attention because it provides a direct and quantitative measurement of the entire acute phase reaction⁽⁹⁾. Levels of CRP may serve as a diagnostic of mood state in BD⁽¹⁰⁾, and high CRP levels in depressed patients may also serve as a precursor to the initiation of manic symptoms⁽¹¹⁾.

Suicidality and BD had been linked to CRP levels⁽¹²⁾. In a German population, the CRP concentration has been correlated with various genetics variants among bipolar patients. The goal of that study was to confirm earlier findings that showed altered CRP levels in BD and to determine if expression of peripheral proteins and variations at genetic level of CRP are related. It was found that, after accounting for body mass index (BMI), age, polarity in BD, and leukocyte count, there were no changes in C-reactive protein levels related to the genotypes. A substantial difference was found in the CRP protein expression when rs1205 SNP was taken into account. Manic individuals' CRP protein expression was substantially higher than that of euthymic and depressive patients⁽¹³⁾. Berardis et, al. indicated that patients with mania and depression have elevated CRP values while total cholesterol was decreased in all bipolar patients than in controls⁽¹⁴⁾.

Dickerson et al., have reported that elevated CRP levels were related with impaired cognitive functioning in bipolar patients, indicating role of inflammation in cognitive dysfunction⁽¹⁵⁾. Previous investigations on C- reactive protein showed that bipolar individuals using lithium alone had a much lower risk of having increased CRP⁽¹⁶⁾.

To determine any link between CRP and bipolar disorder, numerous researches have been carried out internationally with varied degrees of success. Any such research has not been conducted in Pakistan. Therefore, a study was planned and executed to measure CRP levels and determine whether they were related to BD in the local community. Moreover, relation of CRP with gender was also evaluated.

MATERIALS AND METHODS

It is a cross-sectional study. Bipolar patients between the age range of 20 to 70 years were selected. The patients were registered for the study after confirmation of clinical diagnosis on the basis of

DSM- 5 criteria by certified psychiatrists. The patients were selected from Punjab Institute of Mental Health Lahore (PIMH) and Sheikh Zayed Hospital Lahore (SZH). Clinical history along with demographic variables were recorded in a separate proforma. Patients having diabetes mellitus, cardiovascular illness, any inflammatory illness, high blood pressure, and other mental disorder were excluded from study. Among 112 subjects, 82 were bipolar patients and 30 were normal subjects taken as controls with no history of mental illness, diabetes, cardiovascular disorder or any inflammatory illness. Total 74 (66.07%) males and 38 (33.62%) female subjects participated in this study.

Fasting blood samples were collected. Blood was centrifuged to separate the serum. Serum was stored at -20°C in aliquots till further use. CRP was estimated through semi-quantitative latex agglutination method (NS Bio-Tec).

For data interpretation Statistical Package for the Social Sciences (SPSS) version 25 was utilized (SPSS Inc, Chicago). Mean and standard deviation (SD) of continuous variables were estimated. Independent 2-tailed t-test was applied to compare the mean CRP levels among patients and controls. Difference in CRP levels among males and females were also estimated and compared. The patients were further divided according to the stages of BD (manic, euthymic and depressive) and compared their CRP values using one-way ANOVA. Result was considered significant when $p \leq 0.05$.

RESULTS

Analyzing the demographic variables revealed that 58 patients were male and 24 were female. Among controls 16 were males and 14 were females. 35.3% of cases had a positive family history of BD, 51.2% of cases showed symptoms of altered psychotic behavior, 21.9% of cases depicted suicidal tendency and 63.4% of cases experienced stressful life events before the onset of the illness. Data analysis revealed that the average age of onset of disease of patients was 25.2 years. 39% of patients were involved in smoking while only 13% of controls were addicted to smoking.

Table 1: Demographic Features of the Research Participants

Variables	Demographic Features	
	Control	Cases
Gender	Male	16
	Female	58
Age (Years)	22-67	20-70
Family History of Bipolar Disorder	-	29
Smoking History	Positive	4
	Negative	32
Average age of onset of disease (Years)	-	25.2
Psychotic behavior	-	42
Suicidal behavior	-	18
Stressful event	-	52

Comparison of mean CRP levels of patients and control group using independent t-test (2-tailed), manifest that patients have a significantly elevated CRP level, $p=0.001$ (Table 2).

Table 2: Comparison of CRP levels among Research Participants

Variables	Control group	Bipolar group	T	P-value
N	30	82		
CRP (mg/l)	3.88±1.12	15.18±17.88	-3.448	0.001*

*Significant p-value ≤ 0.05

CRP levels: <6 mg/l =Normal; > 6 mg/l = High

Table 3: Comparison of CRP levels among Males and Females

Variables	Male	Female	t	P-value
N	74	38		
CRP (mg/l)	13.79±17.48	8.97±12.56	1.508	0.134

*Significant p-value ≤ 0.05

CRP levels: <6 mg/l =Normal; > 6 mg/l = High

Mean CRP levels were estimated and compared among male and females subjects using independent t-test. Although males had a

higher mean CRP value but the difference between males and females was non significant, $p\text{-value} = 0.134$ (Table 3).

Male and female patients were further segregated according to the stage of BD into manic, euthymic and depressive group. Difference in the mean CRP levels were analyzed by using ANOVA in these subgroups. It was found that the mean CRP levels were higher among males as compared to females in all the groups. But the difference in the CRP levels were non-significant between both genders in all the sub groups, $p\text{-value} > 0.05$. (Table 4)

Table 4: Comparison of CRP levels in different Stages of BD with respect to gender

Stages of Bipolar	Variables	Male	Female	P-value
Manic	No of cases	39	11	
	CRP (mg/l)	15.28±19.97	13.27±13.93	0.756
Depressive	No of cases	14	11	
	CRP (mg/l)	17.04±14.88	12.05±17.80	0.453
Euthymic	No of cases	5	2	
	CRP (mg/l)	24.40±22.01	5.00±0.00	0.292
Control	No of cases	17	13	
	CRP (mg/l)	4.05±1.05	3.96±1.18	0.814

ANOVA, (*p-value significant at 0.05) (F= Degree of freedom)

Mean CRP levels were also compared among different stages of bipolar disorder without considering gender. Mean CRP levels of manic and depressive groups were approximately equal. Euthymic patients had a higher CRP levels. When CRP levels of all sub-groups including controls were compared to each other a significant difference was found between the groups, $p = 0.009$ (Table 5, Fig. 1)

Table 5: Comparison of CRP levels among different Stages of BD

Stages of Bipolar	Number of Subjects	Mean CRP Levels (mg/l)	F	P-value
Manic	50	14.84±18.69	4.051	0.009*
Depressive	25	14.84±16.06		
Euthymic	07	18.85±20.30		
Control	30	3.88±1.12		

F= degree of freedom, p= probability

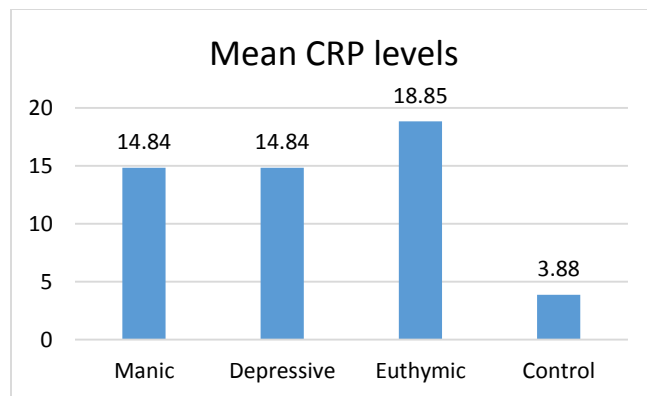


Fig. 1: Comparison of Mean CRP levels among controls and various stages of BD

DISCUSSION

The present research was conducted to assess C - reactive protein (CRP) levels in bipolar subjects and to compare it with the control. Moreover, association of CRP levels was evaluated with gender.

We found that bipolar patients have a significantly higher CRP levels as compared to controls ($p=0.001$). Similar results were demonstrated in a study which indicated that CRP levels were elevated in manic bipolar patients before any treatment. But after treatment the levels of CRP decreased⁽¹⁷⁾. In another study similar results were depicted, which showed increased CRP levels in bipolar II patients as compared to controls⁽¹⁸⁾. Dickerson

reported that increased CRP level in bipolar patients is related to deteriorated cognition of the patients⁽¹⁵⁾.

Wysokinski et al., demonstrated a contrasting finding⁽¹⁰⁾. He analyzed serum CRP levels among patients with acute schizophrenia, unipolar depression, bipolar depression and bipolar mania and found that there was no significant difference in the CRP levels among these clinical groups ($p=0.58$). Although the difference in the CRP levels were non-significant among the above mentioned groups but it was found that one-third of the total subjects in the study group had CRP levels $>3\text{mg/l}$.

We divided the patient group according to the stage of bipolar disorder into manic, euthymic and depressive groups. We found a significant difference in CRP levels among control and these groups ($p=0.009$). Patients with euthymic condition had a higher CRP level as compared to manic and depressive subjects. Levels of CRP were also analyzed among male and female subjects of these groups. In all the groups males had a higher CRP level as compared to females but the difference was non-significant. Berardis reported a higher CRP levels in manic and depressive bipolar patients as compared to controls⁽¹⁴⁾. Similarly, in another study elevated CRP levels were found in manic as compared to euthymic and depressive patients⁽¹³⁾. CRP levels were moderately increased in euthymic and depressive bipolar subjects and more significantly increased in manic subjects in a study conducted by Fernandes⁽¹⁹⁾. Moreover, CRP levels were found to be elevated in manic bipolar subjects as compared to euthymic and depressive patients in a study conducted by Cunha et al⁽²⁰⁾. Conversely, CRP levels were decreased in depressive patients as compared to euthymic and manic subjects in a recent study⁽²¹⁾.

The present study indicated that males have higher CRP levels as compared to females. Previously, effect of gender has been studied with respect to CRP levels in multiple studies. However, females depicted a higher CRP level as compared to males in a recent study conducted in Kenya⁽²²⁾. In another study gender differences in hsCRP were evaluated and it was found that females have higher CRP levels as compared to males⁽²³⁾. These differences can be due to the fact that we analyzed CRP levels in bipolar patients while in these studies the study group comprised of normal subjects.

CONCLUSION

In conclusion, the values of C-reactive protein (CRP) are significantly elevated in bipolar patients as compared to controls, so CRP is positively associated with BD. CRP levels were also significantly different among sub-groups of bipolar disorder. Moreover, males from all the subgroups have higher CRP levels as compared to females.

REFERENCES

- American Psychiatric Association, American Psychiatric Association, editors. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, D.C: American Psychiatric Association; 2013. 947 p.
- World Health Organization. World health statistics 2021: monitoring health for the SDGs, sustainable development goals [Internet]. Geneva: World Health Organization; 2021 [cited 2022 Sep 30]. Available from: <https://apps.who.int/iris/handle/10665/342703>
- Pillai A, Terry AV, Mahadik SP. Differential effects of long-term treatment with typical and atypical antipsychotics on NGF and BDNF levels in rat striatum and hippocampus. *Schizophr Res* [Internet]. 2006 Feb [cited 2022 Sep 30];82(1):95–106. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0920996405005256>
- Dome P, Rihmer Z, Gonda X. Suicide Risk in Bipolar Disorder: A Brief Review. *Medicina (Mex)* [Internet]. 2019 Jul 24 [cited 2022 Sep 30];55(8):403. Available from: <https://www.mdpi.com/1648-9144/55/8/403>
- McIntyre RS, Berk M, Briezke E, Goldstein BI, López-Jaramillo C, Kessing LV, et al. Bipolar disorders. *The Lancet* [Internet]. 2020 Dec [cited 2022 Jan 4];396(10265):1841–56. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0140673620315440>
- Schaffer A, Isometsä ET, Azorin JM, Cassidy F, Goldstein T, Rihmer Z, et al. A review of factors associated with greater likelihood of suicide attempts and suicide deaths in bipolar disorder: Part II of a report of the International Society for Bipolar Disorders Task Force on Suicide in Bipolar Disorder.

- Aust N Z J Psychiatry [Internet]. 2015 Nov [cited 2022 Sep 30];49(11):1006–20. Available from: <http://journals.sagepub.com/doi/10.1177/0004867415594428>
- Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychol Med* [Internet]. 2019 Sep [cited 2022 Oct 3];49(12):1958–70. Available from: https://www.cambridge.org/core/product/identifier/S0033291719001454/type/ejournal_article
- Ng A, Tam WW, Zhang MW, Ho CS, Husain SF, McIntyre RS, et al. IL-1 β , IL-6, TNF- α and CRP in Elderly Patients with Depression or Alzheimer's disease: Systematic Review and Meta-Analysis. *Sci Rep* [Internet]. 2018 Dec [cited 2022 Oct 3];8(1):12050. Available from: <http://www.nature.com/articles/s41598-018-30487-6>
- de Ferranti SD, Rifai N. C-reactive protein: a nontraditional serum marker of cardiovascular risk. *Cardiovasc Pathol* [Internet]. 2007 Jan [cited 2022 Sep 30];16(1):14–21. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1054880706000718>
- Wysokiński A, Margulska A, Strzelecki D, Kłoszewska I. Levels of C-reactive protein (CRP) in patients with schizophrenia, unipolar depression and bipolar disorder. *Nord J Psychiatry* [Internet]. 2015 Jul 4 [cited 2022 Sep 30];69(5):346–53. Available from: <http://www.tandfonline.com/doi/full/10.3109/08039488.2014.984755>
- Becking K, Haarman BCM, van der Lek RFR, Grosse L, Nolen WA, Claes S, et al. Inflammatory monocyte gene expression: trait or state marker in bipolar disorder? *Int J Bipolar Disord* [Internet]. 2015 Dec [cited 2022 Sep 30];3(1):20. Available from: <http://www.journalbipolar disorders.com/content/3/1/20>
- Courtet Ph, Jaussent I, Genty C, Dupuy AM, Guillaume S, Ducasse D, et al. Increased CRP levels may be a trait marker of suicidal attempt. *Eur Neuropsychopharmacol* [Internet]. 2015 Oct [cited 2022 Sep 30];25(10):1824–31. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0924977X15001522>
- Evers AK, Veeh J, McNeill R, Reif A, Kittel-Schneider S. C-reactive protein concentration in bipolar disorder: association with genetic variants. *Int J Bipolar Disord* [Internet]. 2019 Dec [cited 2022 Sep 30];7(1):26. Available from: <https://journalbipolar disorders.springeropen.com/articles/10.1186/s40345-019-0162-z>
- De Berardis D, Conti CM, Campanella D, Carano A, Scali M, Valchera A, et al. Evaluation of C-Reactive Protein and Total Serum Cholesterol in Adult Patients with Bipolar Disorder. *Int J Immunopathol Pharmacol* [Internet]. 2008 Apr [cited 2022 Sep 30];21(2):319–24. Available from: <http://journals.sagepub.com/doi/10.1177/039463200802100208>
- Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Yolken R. Elevated C-reactive protein and cognitive deficits in individuals with bipolar disorder. *J Affect Disord* [Internet]. 2013 Sep [cited 2022 Sep 30];150(2):456–9. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0165032713003406>
- Hornig M, Goodman DBP, Kamoun M, Amsterdam JD. Positive and negative acute phase proteins in affective subtypes. *J Affect Disord* [Internet]. 1998 Apr [cited 2022 Sep 30];49(1):9–18. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0165032797001808>
- Uyanik V, Tuglu C, Gorgulu Y, Kunduracılar H, Uyanik MS. Assessment of cytokine levels and hs-CRP in bipolar I disorder before and after treatment. *Psychiatry Res* [Internet]. 2015 Aug [cited 2022 Oct 16];228(3):386–92. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0165178115003911>
- Chang HH, Wang TY, Lee IH, Lee SY, Chen KC, Huang SY, et al. C-reactive protein: A differential biomarker for major depressive disorder and bipolar II disorder. *World J Biol Psychiatry* [Internet]. 2017 Jan 2 [cited 2022 Oct 16];18(1):63–70. Available from: <https://www.tandfonline.com/doi/full/10.3109/15622975.2016.1155746>
- Fernandes BS, Steiner J, Molendijk ML, Dodd S, Nardin P, Gonçalves CA, et al. C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry* [Internet]. 2016 Dec [cited 2022 Sep 30];3(12):1147–56. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2215036616303704>
- Cunha ÁB, Andreazza AC, Gomes FA, Frey BN, da Silveira LE, Gonçalves CA, et al. Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. *Eur Arch Psychiatry Clin Neurosci* [Internet]. 2008 Aug [cited 2022 Sep 30];258(5):300–4. Available from: <http://link.springer.com/10.1007/s00406-007-0797-0>
- Jacoby AS, Munkholm K, Vinberg M, Pedersen BK, Kessing LV. Cytokines, brain-derived neurotrophic factor and C-reactive protein in bipolar I disorder – Results from a prospective study. *J Affect Disord* [Internet]. 2016 Jun [cited 2022 Sep 30];197:167–74. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0165032715314439>
- Ileri JM. C-Reactive Protein Levels in Male and Female Blood Donors at Kenyatta National Hospital, Kenya. *Adv Soc Sci Res J* [Internet]. 2022 Feb 23 [cited 2022 Oct 16];9(2):222–7. Available from: <https://journals.scholarpublishing.org/index.php/ASSRJ/article/view/11748>
- Kapur S, Kapur S, Zava D. Gender Differences in High-Sensitivity C-Reactive Protein as Determined by Dried Blood Spot Assay. :1.