

Original Article

Serum Levels of C-Reactive Protein, Albumin and CRP–Albumin Ratio in Patients with Major Mental Illnesses

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The authors have no conflicts of interest to declare.

DATA AVAILABILITY

The data supporting the findings of this study are included within the article and its supplementary materials.

ABSTRACT:

Background: Increasing evidence implicates immune dysregulation and chronic low-grade systemic inflammation in the pathophysiology and clinical progression of major mental illnesses (MMIs). Elevated levels of acute-phase proteins, pro-inflammatory cytokines, and adhesion molecules have been reported in patients with MMI however, comparative data on differential alterations in inflammatory markers among Nigerians with schizophrenia, bipolar disorder, and depression remain limited.

Objectives: To determine the serum levels of C-reactive protein (CRP), albumin, and CRP–albumin ratio (CAR) in patients with MMI.

Methods: Eighty-six participants were enrolled in this comparative cross-sectional study. They comprised 47 patients with MMIs (18 with schizophrenia, 15 with bipolar disorder and 14 with depression) who were on antipsychotics, and 39 apparently healthy controls. Serum levels of CRP and albumin were determined using semi-quantitative agglutination method and Bromocresol green method, respectively. Thereafter, the CRP–albumin ratio (CAR) was calculated as appropriate.

Results: The mean serum levels of CRP, albumin and CAR did not differ significantly between patients with MMI and controls. However, stratified analyses revealed slightly elevated CRP levels in patients with bipolar disorder compared with those with schizophrenia and depression. Significant inverse correlations were observed between albumin and CAR in patients with depression, bipolar disorder and schizophrenia. Also, CRP showed significant positive correlation with CAR in both the bipolar disorder and schizophrenia groups.

Conclusion: Trends towards differential inflammatory alterations were observed among patients with major mental illnesses, with changes appearing more pronounced in bipolar disorder despite ongoing antipsychotic therapy.

Keywords: Acute phase protein, Bipolar disorder, CRP-albumin ratio, Inflammation.

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INTRODUCTION

Psychiatric disorders are a major public health concern worldwide. They are characterised by significant cognitive disturbances, emotional and behavioural dysregulation with consequent distress or impairment in important areas of functioning (WHO, 2025).

Despite advances in diagnostic criteria and improvements in therapeutic interventions, the prevalence of mental health continues to increase globally. Over a billion people are living with mental disorders globally, with depressive and anxiety disorders being the most prevalent (WHO, 2025). In Africa, the burden of psychiatric disorders continues to rise amid increasing socioeconomic stressors, inadequate mental health infrastructure, and limited access to psychiatric care (Nicholas *et al.*, 2022). In Nigeria, the burden of mental health conditions is high (Adeleke *et al.*, 2025). The most recent estimates from the Global Burden of Disease (GBD) 2023 showed that Nigeria had an estimated 530,000 prevalent cases of schizophrenia, 869,000 cases of bipolar disorder, and 6.69 million cases of major depressive disorder in 2023. The corresponding crude prevalence rates were 305.5, 459.1, and 3,321.2 per 100,000 population, respectively. Major depressive disorder accounted for the highest burden, with a 56.1% increase in the age-standardised prevalence rate between 1990 and 2023, whereas schizophrenia and bipolar disorder showed relatively modest changes (1.1% and 0.3%, respectively) (GBD 2023 Mental Disorder Collaborators, 2026). This indicates the need for adequate attention to factors impeding the optimisation of mental health service delivery in Nigeria.

Growing evidence implicates immune dysregulation and systemic inflammation as key mechanistic contributors to the pathogenesis and clinical progression of neuropsychiatric disorders (Sethi *et al.*, 2019). Findings from both clinical and experimental studies indicate that inflammatory processes can disrupt neurotransmitter metabolism, alter neuroendocrine signalling, and impair neuronal plasticity, thereby contributing to the onset, progression and persistence of psychiatric symptoms (Dean, 2011; Yuan *et al.*, 2019). Reports have also shown that patients with bipolar disorder, depression, and schizophrenia have elevated serum and cerebrospinal fluid levels of proinflammatory cytokines, chemokines, soluble adhesion molecules and acute-phase reactants (Akinlade *et al.*, 2019; Bauer and Teixeira, 2019; Akinlade *et al.*, 2020; Generoso *et al.*, 2021).

Alteration in the serum levels of acute phase proteins, which are key components of the systemic inflammatory response, has been reported in patients with psychiatric disorders. Miller *et al.* (2014) reported elevated CRP level in patients with schizophrenia. Expectedly, lower level of serum albumin was reported in patients with schizophrenia compared to healthy controls (Chen *et al.*, 2018). In patients with depression, elevated CRP level has been associated with greater symptom severity, a specific pattern of depressive symptoms, and a worse response to treatment (Orsolini *et al.*, 2022).

Although acute phase proteins such as CRP and albumin are established biomarkers of inflammation, evidences continue to emerge showing that CRP-albumin ratio (CAR) is a more reliable measure of inflammatory response than either CRP or

albumin due to its incorporation of both positive and negative acute phase reactants (Ranzani *et al.*, 2013). CAR has been shown to reflect hyperinflammation and to be associated with poor prognosis in septic patients (Ranzani *et al.*, 2013). CAR has demonstrated similar properties in patients with neurological illnesses such as Parkinson's disease, migraine and restless leg syndrome (Olgun Yazar *et al.*, 2019; Yazar and Yazar, 2019; Yazar *et al.*, 2020). In patients with schizophrenia, Balcioglu and Kirlioglu (2020) showed that CAR and neutrophil-albumin ratio (NAR) are reliable biomarkers of inflammation that could reflect inflammatory status, independent of relapse or remission in patients with schizophrenia. Also, McFarland *et al.* (2020) reported that an association exists between depression severity and CAR.

Despite significant progress in psychiatry immunology, there is limited information on potential differences in inflammatory profiles among patients with major psychiatric disorders, particularly in Sub-Saharan African populations where comparative studies involving schizophrenia, bipolar disorder, and depression are scarce. Availability of this information might facilitate the development of disease-specific adjunctive immunotherapeutic interventions. Based on previous reports implicating inflammation in the pathophysiology of MMI and the limited comparative data from the Sub-Saharan African populations, we hypothesised that patients with schizophrenia, bipolar disorder, and depression would exhibit distinct patterns of inflammatory marker alterations relative to healthy controls and that the magnitude of these alterations might differ among the clinical subgroups. This study was therefore designed to determine the serum levels of CRP, albumin, and CAR in patients with schizophrenia, bipolar disorder, and depression.

MATERIALS AND METHODS

Study participants

A total of 86 adults consisting of 18 patients with schizophrenia, 15 patients with bipolar disorder, 14 patients with depression and 39 age-and sex-matched apparently healthy adults who served as controls were enrolled in this comparative cross-sectional study. All the patients with MMI were enrolled from the New World Psychiatry Hospital, Ibadan, Nigeria.

Clinical diagnostic assessment

The diagnosis of schizophrenia, depression or bipolar disorder was made using the Structured Clinical Interview for Diagnostics and statistical manual IV Axis I Disorder (SCID) version 2.0 (First and Gibbon, 2004).

Exclusion criteria

Patients with substance use disorder, liver disorder or infection were excluded from the study.

Ethical consideration

Before the commencement of the study, the study protocol was reviewed and approved (UI/EC/22/0164) by the University of Ibadan, University College Hospital (UI/UCH) Joint Ethics Committee. Also, before enrolment into the study, written informed consent or assent was obtained from the study participants or their relatives/guardians as appropriate.

Blood sample collection

Venous blood sample (5 mL) was obtained from each study participant using standard phlebotomy techniques and dispensed into anticoagulant-free sample bottles. Serum was appropriately obtained and stored at -20°C until analysed.

Laboratory analysis

Serum level of CRP was determined using a semi-quantitative agglutination method following the manufacturer's instruction (DIALAB, Austria). Briefly, positive samples were serially diluted to determine the highest dilution exhibiting visible agglutination (titre), and the CRP concentration was calculated according to the manufacturer's instructions using the formula: CRP (mg/L) = $S \times D$, where S is the reagent sensitivity (6 mg/L) and D is the highest serum dilution showing agglutination. The calculated concentrations (mg/L) were used for statistical analyses. The bromocresol green (BCG) colorimetric method was used to determine the serum level of albumin following the

manufacturer's instruction (DIALAB, Austria). Thereafter, the CRP-albumin ratio (CAR) was calculated as the ratio of the serum level of CRP (mg/L) to the serum level of albumin (g/L). Albumin concentrations originally measured in g/dL were converted to g/L prior to ratio calculation.

Data analysis

Data obtained were carefully cross-checked to ensure accuracy and completeness. The data entry and analysis were done using the SPSS software, version 23.0. Data were assessed for Gaussian distribution using the Shapiro-Wilk test. Thereafter, differences in means were determined using the Student's t-test and ANOVA, as appropriate. Association between categorical variables was determined using the Chi-square test, while Pearson's correlation test was used to determine the correlation between the variables. Results are presented as mean $\pm$ standard deviation. P-values less than 0.05 were considered as statistically significant.

RESULTS

Age and the serum levels of albumin and CRP in the study participants are shown in Table 1. There was no significant difference in the mean ages of the patients with MMI and controls. The mean levels of albumin and CRP were similar between the two groups (Table 1). Similarly, the mean CAR in patients with MMI (0.10 ± 0.03) was not significantly different compared with the controls (0.09 ± 0.01) (Figure 1).

Table 1: Serum levels of albumin and C-reactive protein in the study participants

	MMI (n = 47)	Controls (n = 39)	P-value
Sex (Male, Female)	31, 16	23, 16	0.654†
Age (years)	32.98 $\pm$ 10.31	31.14 $\pm$ 6.78	0.447
Albumin (g/dL)	4.83 $\pm$ 1.26	4.79 $\pm$ 1.04	0.886
CRP (mg/L)	4.53 $\pm$ 0.89	4.44 $\pm$ 0.84	0.650

MMI = Major mental illness, CRP = C-reactive protein, †P-value derived from chi-square test

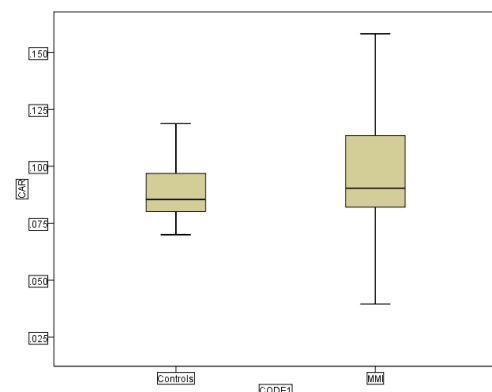


Figure 1: CRP-albumin ratio in patients with major mental illness and controls.

The central horizontal line within each box represents the median. The lower and upper boundaries of the box indicate the first (25th percentile) and third (75th percentile) quartiles, respectively, while the box spans the interquartile range (IQR). The whiskers extend to the smallest and largest observations within 1.5 $\times$ IQR of the lower and upper quartiles. The difference was not statistically significant ($P = 0.059$).

Stratifying MMI into subgroups, the mean levels of albumin and CRP were slightly higher in patients with bipolar disorder compared with patients with depression, schizophrenia and controls (Table 2). However, CAR values were insignificantly different when patients with MMI were compared with one another (Depression; 0.11 ± 0.03 , Bipolar disorder; 0.10 ± 0.03 , Schizophrenia; 0.08 ± 0.01 ; F-value = 3.074, P-value = 0.058) (Figure 2).

Table 2: Serum levels of albumin and C-reactive protein in patients with depression, bipolar disorder, schizophrenia and controls

	Depression (n = 14)	Bipolar disorder (n = 15)	Schizophrenia (n = 18)	Controls (n = 39)	P-value
Albumin (g/dL)	4.18 $\pm$ 1.14	5.27 $\pm$ 1.71	4.96 $\pm$ 0.59	4.79 $\pm$ 1.04	0.075
CRP (mg/L)	4.31 $\pm$ 0.75	4.80 $\pm$ 1.01	4.47 $\pm$ 0.87	4.44 $\pm$ 0.84	0.466

CRP = C-reactive protein

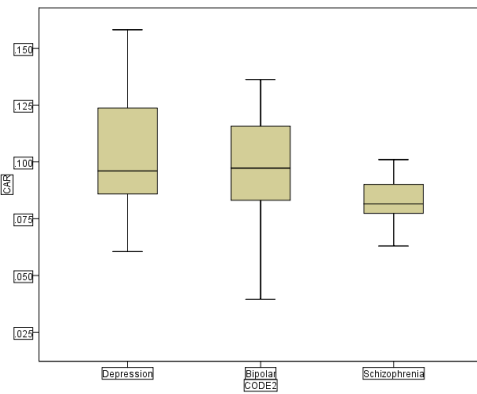


Figure 2: CRP-albumin ratio in patients with depression, bipolar disorder, schizophrenia and controls

The central horizontal line within each box represents the median. The lower and upper boundaries of the box indicate the first (25th percentile) and third (75th percentile) quartiles, respectively, while the box spans the interquartile range (IQR). The whiskers extend to the smallest and largest observations within $1.5 \times$ IQR of the lower and upper quartiles. The difference was not statistically significant ($P = 0.058$).

As shown in Table 3, there was significant negative correlation between albumin and CAR in patients with depression, bipolar disorder, schizophrenia and controls. Also, there was significant positive correlation between CRP and CAR in patients with bipolar disorder, schizophrenia and controls. However, no significant correlation was observed in patients with depression (Table 3).

Table 3: Correlation between albumin, C-reactive protein and their ratio in the study participants

	Depression		Bipolar disorder		Schizophrenia		Controls	
	r-value	P-value	r-value	P-value	r-value	P-value	r-value	P-value
Albumin vs CRP	0.151	0.622	-0.078	0.781	-0.138	0.597	-0.188	0.272
Albumin vs CAR	-0.790	0.001**	-0.764	0.001**	-0.575	0.016*	-0.630	<0.001**
CRP vs CAR	0.435	0.137	0.641	0.010**	0.880	<0.001**	0.834	<0.001**

CRP = C-reactive protein, CAR = CRP-albumin ratio. *Significant at $P < 0.05$, **Significant at $P < 0.01$.

DISCUSSION

Reports continue to show that significant relationship exists between MMI and inflammation (Fond, 2014; Akinlade et al., 2019; Dregan et al., 2019; Yuan et al., 2019; Akinlade et al., 2020). In this study, the serum levels of albumin, a negative acute phase protein, were similar in patients with MMI and controls. This observation is in contrast to previous reports. Maes et al. (1995), Van Hunsel et al. (1996) and Al-Marwani et al. (2023) reported significantly lower level of albumin in patients with depression compared with healthy individuals and that the albumin level correlated with disease severity and could serve as a novel indicator for evaluating the progress and severity of depression. Also, Chen et al. (2018) reported lower level of albumin in patients with schizophrenia compared with the controls. Furthermore, Xu et al. (2023) reported lower level of albumin in patients with bipolar disorder compared with the controls. These reports considered each psychiatry disorder separately and not as a group of major mental illnesses. This could be responsible for the observed differences in albumin levels. Also, the observed differences could be due to differences in selection of participants. Most of the studies enrolled drug naïve patients while our patients were on antipsychotic treatment. Previous studies have suggested that serum albumin levels may gradually increase following antidepressant therapy, possibly reflecting attenuation of inflammatory activity and improvement in nutritional or metabolic status (Zhang et al., 2023).

Although serum albumin levels have been reported to be similar in patients with major depressive disorder and bipolar disorder, lower serum albumin levels have been associated with greater symptom severity in both major depressive disorder and bipolar disorder, suggesting that serum albumin may better reflect clinical severity than diagnostic classification (Sayed et al., 2025). Comparing the MMI subgroups, albumin levels were slightly lower in patients with schizophrenia and depression

compared with the patients with bipolar disorder. This observation supports the report of Xu et al. (2023) which showed that albumin level was significantly lower in patients with schizophrenia compared with patients with bipolar disorder. These observations could suggest that there is differential alteration pattern or post-antipsychotic response pattern in albumin level, and by extension, acute phase proteins in patients with schizophrenia, depression and bipolar disorder, highlighting the heterogeneity of inflammatory responses across psychiatric disorders.

The serum CRP levels were insignificantly different in patients with major mental illness (MMI) compared with the controls. Although studies evaluating pooled MMI populations are scarce, previous reports have demonstrated increased CRP levels in patients with depression, bipolar disorder, and schizophrenia, further supporting the involvement of systemic inflammation in the pathophysiology of these disorders (Evers et al., 2019; Pitharouli et al., 2021). The absence of a statistically significant difference in CRP levels between patients and controls in the present study may, however, reflect the immunomodulatory effects of antipsychotic medications, as all the patients were on antipsychotics at the time of enrolment into the study. Antipsychotics have been shown to exert variable effects on inflammatory pathways in patients with MMI (Sobiš et al., 2015; Juncal-Ruiz et al., 2018). Furthermore, our finding is consistent with reports indicating no significant association between CRP levels and certain psychiatric conditions, including depression (Howren et al., 2009; Figueroa-Hall et al., 2022).

Comparative analysis across schizophrenia, depression, and bipolar disorder groups revealed that the serum level of CRP was slightly higher in patients with bipolar disorder compared with patients with schizophrenia, depression and even, the controls. This observation further highlights the presence of differential immune profiles in MMI subgroups and suggests increased inflammatory activation in bipolar disorder compared with other psychiatric conditions. Presently, there is limited information on studies evaluating differences in the serum levels of CRP in patients with bipolar disorder, schizophrenia, and depression. However, (Evers et al., 2019) reported elevated serum CRP level in bipolar disorder compared with healthy controls.

The CRP-albumin ratio (CAR) has been shown to be a superior indicator of inflammation. Presently, there is little information on CAR in patients with MMI especially, patients with bipolar disorder and depression. Balcioglu and Kirlioglu (2020) reported that CAR is a reliable marker of inflammation and could be used to reflect increased inflammatory status in patients with schizophrenia. In this study, CAR was not significantly different among the MMI subgroups. This observation could suggest that inflammatory responses in the patients are relatively similar.

Expectedly, serum level of negative acute phase proteins such as albumin reduces, while that of positive acute phase proteins such as CRP increases during inflammation. The significant inverse correlation between albumin level and CAR observed in patients with depression, bipolar disorder, and schizophrenia mirrors the expected physiological interplay between the parameters as demonstrated in the control group. This observation could suggest that initiation of antipsychotic therapy may attenuate inflammatory dysregulation in patients with MMI.

Also, there was significant positive correlation between CRP and CAR in patients with bipolar disorder, schizophrenia and controls. This observation is also not surprising as CRP and CAR are markers of inflammation. However, no significant correlation was observed between CRP and CAR in patients with depression. Using Mendelian randomization analysis, Palmos et al. (2023) reported no evidence of a bidirectional causal relationship between CRP levels and major depressive disorder.

CONCLUSION

It could be concluded from this pilot exploratory study that trends towards differential inflammatory alterations were

observed among patients with major mental illnesses, with changes appearing more pronounced in bipolar disorder despite ongoing antipsychotic therapy. The observed trend towards greater inflammatory alterations in bipolar disorder should be explored further in larger longitudinal studies to clarify its clinical significance and temporal relationship with the disease progression.

Limitations

Findings from this study should be interpreted in light of several limitations. The relatively small overall and subgroup sample sizes may have limited the statistical power to detect subtle differences between groups. Furthermore, the comparative cross-sectional design precludes causal inference regarding the observed associations. Although all patients were receiving antipsychotic therapy, the heterogeneity of the antipsychotic medications administered may have introduced an unmeasured treatment-related confounder that could have affected the comparability of the inflammatory biomarkers across groups. In addition, potential confounding factors, including body mass index, smoking status, and duration of illness, were not fully controlled. Future studies involving larger, well-characterised cohorts and longitudinal designs are warranted to validate these findings and further elucidate the role of inflammatory biomarkers in major mental illnesses.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Before the commencement of the study, the study protocol was reviewed and approved (UI/EC/22/0164) by the University of Ibadan, University College Hospital (UI/UCH) Joint Ethics Committee. Also, before enrolment into the study, written informed consent or assent was obtained from the study participants or their relatives/guardians as appropriate.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES

The authors acknowledge that AI-assisted technologies were partially used in the preparation of this manuscript. Specifically, ChatGPT was used for language refinement and grammar correction. All content was critically reviewed, edited, and approved by the authors. No AI tools were used to generate data, interpret results, or replace the authors' intellectual contribution.

DATA AVAILABILITY

The data supporting the findings of this study are included within the article and its supplementary materials.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING

The study was self-funded.

AUTHORS' CONTRIBUTIONS

SKR conceived and designed the study; SKR, DDO, OOA and VOL collected the samples; SKR and DDO did the laboratory analysis, SKR wrote the initial draft, SKR, DDO, OOA and VOL reviewed the final draft, SKR supervised the entire research.

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