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RESEARCH ARTICLE

CRP/Albumin ratio in schizophrenia and bipolar disorder: Findings from a comparative study

Şizofreni ve bipolar bozuklukta CRP/Albumin oranı: Karşılaştırmalı bir çalışmanın bulguları

Zuhal KOC APAYDIN[1], Nefise DEMIR[1]

[1]Karabük University, Faculty of Medicine, Department of Psychiatry, Karabük, Türkiye

Abstract

Aim: Inflammation plays a pivotal role in the pathogenesis of psychiatric disorders such as schizophrenia and bipolar disorder (BD). The C-reactive protein to albumin ratio (CAR) has emerged as a novel, cost-effective inflammatory biomarker. This study aimed to compare CAR levels among patients with schizophrenia, BD, and healthy controls (HC), and to identify clinical predictors of elevated CAR.

Methods: A retrospective analysis was conducted on 98 schizophrenia patients (acute phase), 100 BD patients (55 manic, 45 depressive), and 76 healthy controls. Sociodemographic data, medication history, and laboratory markers including CRP, albumin, and CAR were collected. Statistical analyses included group comparisons and stepwise linear regression to determine predictors of CAR.

Results: CAR levels were significantly higher in both schizophrenia and BD groups compared to HC, with no significant difference between schizophrenia and BD. Subgroup analysis revealed no significant difference in CRP or CAR between manic and depressive BD episodes. Stepwise regression identified psychiatric diagnosis and clozapine use as significant predictors of CAR levels ($p<0.05$).

Conclusion: Our findings support the involvement of systemic inflammation in schizophrenia and BD. CAR may serve as a practical biomarker for inflammatory activity in psychiatric populations. Future prospective studies are needed to establish its utility in clinical assessment, including diagnosis, prognosis, and treatment response.

Keywords: C-reactive protein/albumin ratio, schizophrenia, bipolar disorder, inflammation, biomarker, clozapine.

Özet

Amaç: Enflamasyon, şizofreni ve bipolar bozukluk (BB) gibi psikiyatrik bozuklukların patogenezinde kritik bir rol oynamaktadır. C-reaktif protein/albumin oranı (CAR), yeni ve maliyet-etkin bir enflamatuvar biyobelirteç olarak öne çıkmaktadır. Bu çalışmada, şizofreni, BB ve sağlıklı kontroller (SK) arasında CAR düzeylerinin karşılaştırılması ve yüksek CAR değerlerinin klinik yordayıcılarının belirlenmesi amaçlanmıştır.

Yöntemler: Retrospektif bir analiz kapsamında, 98 şizofreni hastası (akut dönem), 100 BB hastası (55 manik, 45 depresif) ve 76 sağlıklı kontrol değerlendirilmiştir. Sosyodemografik veriler, ilaç öyküsü ve CRP, albümin ve CAR dahil olmak üzere laboratuvar belirteçleri toplanmıştır. İstatistiksel analizlerde grup karşılaştırmaları ve CAR'ı yordayan değişkenleri belirlemek amacıyla aşamalı doğrusal regresyon kullanılmıştır.

Bulgular: CAR düzeyleri, hem şizofreni hem de BB grubunda SK'ye kıyasla anlamlı derecede yüksek bulunmuş, ancak şizofreni ve BB arasında anlamlı bir fark saptanmamıştır. Alt grup analizinde, manik ve depresif BB epizotları arasında CRP veya CAR açısından anlamlı bir fark görülmemiştir. Aşamalı regresyon analizinde, psikiyatrik tanı ve klozapin kullanımı CAR düzeylerinin anlamlı yordayıcıları olarak belirlenmiştir ($p<0,05$).

Sonuç: Bulgularımız, şizofreni ve BB'de sistemik enflamasyonun rolünü desteklemektedir. CAR, psikiyatrik popülasyonlarda enflamatuvar aktivitenin pratik bir biyobelirteci olarak hizmet edebilir. Gelecekte yapılacak prospektif çalışmalar, bu biyobelirtecin tanı, prognoz ve tedavi yanıtının klinik değerlendirilmesindeki yararlılığını ortaya koyacaktır.

Anahtar Kelimeler: C-reaktif protein/albümin oranı, şizofreni, bipolar bozukluk, enflamasyon, biyobelirteç, klozapin.

INTRODUCTION

Studies seeking to understand the etiology of psychiatric diseases, especially schizophrenia, major depressive disorder, and bipolar disorder (BD), have shown a great deal of interest in the inflammatory theory. Inflammation-related high pro-inflammatory molecules and acute-phase reactants, such as CRP (C- Reaktive Protein), have been observed in the plasma of individuals with various neuropsychiatric disorders. These increases have been detected in both peripheral blood and cerebrospinal fluid (1–5). Inflammation has been shown to contribute

Corresponding Author: Zuhal KOC APAYDIN zuhalapaydin@karabuk.edu.tr
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to psychiatric symptoms by affecting neurotransmitter levels, neuroendocrine responses, and brain plasticity (6). Based on these findings, studies on inflammation and its effects have significantly increased over the past 20 years, particularly in schizophrenia (7-9) and BD (10,11).

Previous studies on schizophrenia have suggested that the disorder has a genetic predisposition to certain inflammatory processes and that this inflammation may be exacerbated by environmental stress factors and immune system alterations. It has been suggested that this pathophysiological mechanism in the brain may disturb the equilibrium of neurotransmitters, resulting in the emergence and continuation of schizophrenia symptoms (8). Studies have demonstrated increased microglial density in individuals with schizophrenia, along with elevated levels of cytokines in peripheral blood (12,13). Moreover, elevated concentrations of IL-6, TNF, and IL-1β have been measured in the bloodstream of individuals with first-episode and chronic schizophrenia (14). While individuals diagnosed with schizophrenia have been shown to consistently exhibit higher CRP levels compared to healthy controls (HC) (15-18), elevated CRP levels have also been observed in both the acute and stable phases of schizophrenia. Moreover, patients in the acute phase have been found to have significantly higher CRP levels than those in the stable phase (15). Cross-sectional studies have demonstrated that atypical antipsychotics such as olanzapin and aripiprazole can reduce pro-inflammatory cytokine levels (19). In addition, lumateperone, a novel antipsychotic, has also been shown to decrease levels of IL-1β, IL-6, and TNF-α, suggesting its potential anti-inflammatory properties in the treatment of schizophrenia (20). This has led researchers to explore the use of anti-inflammatory strategies as a potential adjunctive treatment in schizophrenia. Meta-analysis findings indicate that anti-inflammatory medications may confer advantages regarding both positive and negative symptoms of schizophrenia (21).

Research indicate that neuroinflammatory and systemic mediators of inflammation are associated with the neuropathogenesis of BD (22). Elevated concentrations of pro-inflammatory cytokines and acute-phase reactants have been noted during manic and depressive phase, as well as across various forms of BD (23). Studies have shown a link between CRP, a marker of low-grade inflammation, and BD. Compared to healthy controls (HC), individuals with BD exhibit higher CRP levels (2). Moreover, increased CRP levels have been correlated with the intensity of manic episodes in BD24 and cognitive impairments (25).

In both schizophrenia and BD, increased inflammatory markers have been demonstrated in both the brain and peripheral circulation through various studies (26-28). Research indicates that individuals with schizophrenia and BD demonstrate heightened inflammation in various brain regions (29-32). IL-6 levels are elevated in schizophrenia patients in comparison to BD and HC groups. Furthermore, the inflammatory dysregulation in BD correlates with episodic occurrences, whereas in schizophrenia, this phenomenon seems to be more chronic (33).

CRP and albumin are acute-phase reactants that react to systemic inflammation (34), with CRP levels increasing (35) and albumin levels decreasing (36) in response to inflammation. The CRP/albumin ratio (CAR) has recently been suggested as a superior indication of inflammatory response compared to CRP or albumin individually (37). Research on this ratio indicates its potential as a marker of increased inflammation in neurological disorders like Parkinson's disease and migraine (38,39), as well as in schizophrenia (40). In a study conducted on patients with first-episode mania in BD, no statistically significant difference was found in the CAR compared to HC (41).

Multiple studies have shown the role of inflammation in schizophrenia and BD, we could not find a study in the literature that investigates how the CAR differs among schizophrenia, BD, and HC. Therefore, we aimed to compare patients with schizophrenia and BD with HC in terms of the CAR to examine whether this ratio reflects disease-specific inflammatory processes. Our research targets evaluating the usefulness of CAR as a predictive marker in distinguishing different diseases.

METHODS

This research was structured as a retrospective cohort study. The study examined data collected from persons aged 18 to 65, encompassing patients diagnosed with schizophrenia or BD, as well as HC, who attended the Karabuk Training and Research Hospital for reasons such as report renewals or employment-related medical assessments. The study included individuals

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who presented to the hospital between 2020 and 2024, underwent psychiatric evaluation by a psychiatrist, and were diagnosed with bipolar disorder or schizophrenia according to the DSM-5. The biochemistry and CRP test results of these individuals were available in the hospital's electronic medical record system, as these laboratory parameters had been obtained during their admission for an acute episode. The data were obtained through a review of past medical records.

Inclusion Criteria:

- Age between 18 and 65 years
- Diagnosed with schizophrenia or bipolar disorder
- Availability of complete biochemistry and CRP test results in hospital records

Based on the hospital records review, patients with the following conditions were excluded:

- History of substance use (alcohol or any addictive substance)
- History of inflammatory diseases (e.g., rheumatoid arthritis, lupus)
- Acute or chronic infections
- Autoimmune diseases
- History of cancer or tumors
- Neurological diseases (e.g., epilepsy, Parkinson's disease)
- Use of corticosteroids or immunosuppressive treatment
- Body Mass Index (BMI) lower than 18.5 (underweight) or higher than 30 (obese)
- Absence of biochemistry, or CRP test results in hospital records

Although smoking is typically considered an exclusion criterion due to its potential impact on inflammatory markers, the number of non-smoking patients in our sample was too limited. Therefore, in order to maintain adequate sample size, smoking was not used as an exclusion criterion. However, statistical analyses revealed no significant difference in smoking status between patient groups and healthy controls, suggesting that this factor did not introduce substantial bias into the study findings.

Due to the retrospective nature of the study, standardized scale scores indicating the severity of psychiatric symptoms were not available in the medical records. Therefore, analyses based on symptom severity could not be performed.

The data of patients who met the inclusion criteria were reviewed from the hospital's electronic record system. Per hospital procedure, blood samples are obtained within the initial 24 hours of hospitalization or upon outpatient admission using routine venipuncture from the antecubital veins.

As part of the preliminary assessment, the records of 556 patients who applied to the outpatient treatment unit or were hospitalized, along with healthy controls, were reviewed.

The research protocol received approval from the Non-Interventional Ethics Committee of Karabuk University (Protocol No: 2024/2040, Date: 10/12/2024), thereby assuring compliance with the Declaration of Helsinki.

Statistical Analyses

The data were analyzed utilizing the SPSS 29.0 software suite. The Kolmogorov-Smirnov test was utilized to evaluate normalcy. Demographic information was analyzed by summarizing categorical data with frequencies and percentages, and presenting normally distributed data as means and standard deviations. Non-parametric data were presented as medians together with minimum and maximum values. To analyze continuous variables, one-way ANOVA was applied when the assumptions of normality and homogeneity of variance were met, while the Kruskal-Wallis test was used for non-parametric data. For post-hoc comparisons, the Tukey test was performed on parametric data, whereas non-parametric data were analyzed using the Mann-Whitney U test, with Bonferroni correction for p-value adjustment. Categorical variables were evaluated via the chi-square test. A stepwise multiple linear regression analysis was conducted to assess the predictive effects of psychiatric diagnosis, antipsychotic medication use (including clozapine and other agents), medication dosage, age, sex, BMI, smoking status, and clinical phase on inflammatory parameters, specifically the C-reactive protein to albumin ratio (CAR). Variables were entered into the model using a stepwise method based on significance levels. Multicollinearity was evaluated using Tolerance and Variance Inflation Factor (VIF) values.

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RESULTS

The study was conducted on a sample consisting of 98 patients with schizophrenia in the acute phase, 100 patients with bipolar disorder (55 in a manic episode and 45 in a depressive episode), and 76 healthy controls.

The age distribution was comparable throughout the groups, with no statistically significant differences detected (p>0.05). Similarly, the sex composition exhibited no significant difference between the groups (p>0.05).

Aspartate aminotransferase (AST) levels exhibited a statistically significant difference between the groups (p<0.001). The Mann-Whitney U test results indicate that both the schizophrenia and BD cohorts exhibited significantly elevated AST levels relative to the control group (schizophrenia: MR=103.96-66.27, p<0.001, p-adjusted<0.003; BD: MR=98.90-74.82, p=0.002, p-adjusted=0.006).

Significant differences were observed in serum albumin levels among the groups (p<0.001). In both the schizophrenia and BD groups, albumin levels were markedly lower than in the HC (schizophrenia: MR=70.86-108.95, p<0.001, p-adjusted<0.003; bipolar disorder: MR=71.04-111.48, p<0.001, p-adjusted<0.003).

Significant differences in CRP levels and the CAR were observed among the groups (both p<0.001). In the schizophrenia and BD groups, CRP levels and CAR were significantly greater than in the HC group (schizophrenia: CRP: MR=104.95-65.00, p<0.001, p-adjusted<0.003; CAR: MR=105.78-63.93, p<0.001, p-adjusted<0.003; BD: CRP: MR=105.99-65.49, p<0.001, p-adjusted<0.003; CAR: MR=106.89-64.30, p<0.001, p-adjusted<0.003).

The schizophrenia and bipolar disorder groups did not show any statistically significant differences in any parameter (p>0.05). o evaluate whether there were differences in CRP, albumin, and CAR levels between depressive and manic episodes in individuals with bipolar disorder, the Mann-Whitney U test was conducted. The results indicated no statistically significant differences between the bipolar depression group (n=45) and the bipolar mania group (n=55) in terms of CRP (Z=-0.395, p=0.693), albumin (Z=-0.894, p=0.371), or CAR levels (Z= -0.312, p=0.755). Table 1 provides an overview of the data analysis. The comparison of parameters showing statistically significant differences between groups is presented in Table 2.

Table 1. Comparison of demographic, hematological, and biochemical parameters across schizophrenia, bipolar disorder, and control groups

	Schizophrenia (n=98)	Bipolar Disorder (n=100)	Healthy Control (n=76)	p
Age (Mean± SD)	45.41±12.46	43.91±12.51	42.02±11.86	0.199[a]
Sex	-	-	-	0.639[b]
Male	56 (57.1%)	51 (51.0%)	43 (56.6%)	-
Female	42 (42.9%)	49 (49.0%)	33 (43.4%)	-
Smoking Status	-	-	-	0.893[b]
Smoker	69 (70.4%)	68 (68.0%)	54 (71.1%)	-
Non-Smoker	29 (29.6%)	32 (32.0%)	22 (28.9%)	-
Types of Medications	-	-	-	-
Risperidone	19 (19.4%)	12 (12.0%)	-	-
Olanzapine	21 (21.4%)	11 (11.0%)	-	-
Clozapine	12 (12.2%)	4 (4.0%)	-	-
Paliperidone	19 (19.4%)	9 (9.0%)	-	-
Aripiprazole	16 (16.3%)	12 (12.0%)	-	-
Quetiapine	21 (21.4%)	22 (22.0%)	-	-
Haloperidol	12 (12.2%)	3 (3.0%)	-	-
Zuclopenthixol	17 (17.3%)	5 (5.0%)	-	-
Lithium	0 (0%)	44 (44.0%)	-	-
Valproate	0 (0%)	43 (43.0%)	-	-
BMI (median, min–max)	24.0 (18.5–29.7)	23.9 (18.7–29.2)	23.6 (18.7–29.3)	0.912[c]
AST	19.0 (9–83)	18.0 (4–80)	19.0 (2–43)	<0.001[c]
ALT	18.0 (4–108)	17.0 (1–70)	19.0 (5–70)	0.495[c]
GGT	17.0 (3–412)	19.0 (2–148)	21.0 (6–78)	0.434[c]
Albumin	4.40 (3.0–5.5)	4.40 (3.0–5.4)	4.70 (3.7–5.3)	<0.001[c]
Urea	25.0 (4–51)	25.0 (9–155)	27.0 (10–46)	0.139[c]
Creatinine	0.70 (0.3–1.7)	0.70 (0.4–1.6)	0.80 (0.5–1.2)	<0.001[c]
CRP	4.75 (0.2–94.3)	3.95 (3.0–5.4)*	2.00 (0–11)	<0.001[c]
CAR	1.06 (0.04–21.93)	0.94 (0.04–14.41)	0.41 (0–2.39)	<0.001[c]

BMI: Body Mass Index, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, GGT: Gamma-Glutamyl Transferase, Albumin: Serum Albumin, CRP: C-Reactive Protein, CAR: C-Reactive Protein to Albumin Ratio, a : One-Way ANOVA, b : Chi-Cquare, c : Kruskal- Wallis test, p<0.05

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Table 2. Comparison of blood parameters showing statistically significant differences between groups

	SCH-BD	p	p-adj	SCH-HC	p	p-adj	BD-HC	p	p-adj
AST (MR)	106.10-93.03	0.101	0.320	103.96-66.27	<0.001	<0.003	98.90-74.82	0.002	0.006
Albumin (MR)	101.10-97.98	0.704	1.000	70.86- 108.95	<0.001	<0.003	71.04- 111.48	<0.001	<0.003
Creatinine (MR)	98.01-100.97	0.713	1.000	73.20- 105.94	<0.001	<0.003	76.40-104.42	<0.001	<0.003
CRP (MR)	99.07-99.93	0.912	1.000	104.95- 65.00	<0.001	<0.003	105.99-65.49	<0.001	<0.003
CAR (MR)	98.54-100.45	0.817	1.000	105.78- 63.93	<0.001	<0.003	106.89-64.30	<0.001	<0.003

AST: Aspartate Aminotransferase, , CRP: C-Reactive Protein, CAR: C-Reactive Protein to Albumin Ratio , SCH: Schizophrenia, BD: Bipolar Disorder, Cntrl: Control, MD: Mean Difference, MR: Mean Rank. Mann- Whitney U test Adjusted p-values (padj) are corrected for Bonferroni adjustment, with the adjusted significance level (aadjusted) set at <0.0167 for three comparisons

To identify the most relevant predictors of inflammation (measured by the CRP/albumin ratio, CAR), a stepwise linear regression analysis was performed. Stepwise regression was selected due to the exploratory nature of the study and the relatively large number of potential predictors, which included demographic variables (age, sex), psychotropic medication use, clinical diagnosis, and illness phase. This method allowed for the identification of variables that contributed significantly to the variance in CAR levels, while excluding non-contributory covariates, thereby improving model parsimony and interpretability.

The final model was statistically significant, $F(2, 271)=7.849$, $p<0.001$, accounting for approximately 5.5% of the variance in CAR levels (adjusted $R^2=0.048$). Two variables remained in the model: psychiatric diagnosis and clozapine use. Psychiatric diagnosis was significantly associated with CAR (B=0.558, β=0.188, p=0.002), indicating that patients with schizophrenia or bipolar disorder exhibited higher inflammation levels compared to healthy controls. Additionally, clozapine use was positively associated with CAR (B=1.475, β=0.132, p=0.026), suggesting that patients using clozapine had significantly elevated CRP/albumin ratios.

Other variables, including age, sex, use of other antipsychotics (e.g., risperidone, olanzapine, aripiprazole), lithium, valproate, equivalent medication dosage, BMI, smoking status, and clinical phase, were not significantly associated with CAR levels in the final model (all p>0.05). Notably, multicollinearity diagnostics revealed acceptable VIF values (<1.35) for all included predictors, supporting the stability of the model. The relevant data are presented in Table 3.

Table 3. Stepwise linear regression predicting CAR levels

Included Variables:

Predictor	B	SE B	β	t	p	Tolerance	VIF
(Constant)	0.802	0.238	-	3.370	<0.001	-	-
Psychiatric Diagnosis	0.558	0.176	0.188	3.176	0.002	0.998	1.002
Clozapine	1.475	0.659	0.132	2.240	0.026	0.998	1.002

Excluded Variables:

Excluded Variable	β	t	p	Tolerance	VIF
Age	0.084	1.409	0.160	0.986	1.014
Sex	-0.038	-0.638	0.524	0.993	1.007
Risperidone	0.078	1.299	0.195	0.975	1.026
Olanzapine	0.072	1.200	0.231	0.980	1.020
Aripiprazole	0.000	-0.005	0.996	0.979	1.021
Quetiapine	0.034	0.557	0.578	0.937	1.067
Haloperidol	0.078	1.309	0.192	0.991	1.009
Lithium	-0.048	-0.704	0.482	0.744	1.344
Valproate	-0.051	-0.743	0.458	0.755	1.324
Antipsychotic Equivalent Dose	0.097	1.534	0.126	0.093	1.151
Lithium Dose	-0.056	-0.824	0.411	0.762	1.312
Valproate Dose	-0.066	-0.980	0.328	0.778	1.286
BMI	0.047	0.785	0.433	0.990	1.011
Smoking	0.022	0.366	0.715	0.994	1.006
Clinical Phase	-0.176	-0.901	0.368	0.091	10.989

Model Summary (Final Model – Model 2): $F(2, 271) =7.849$, $p<0.001$ $R^2=0.055$, Adjusted $R^2=0.048$ Standard Error of the Estimate=2.315, Note. BMI: Body Mass Index, CAR= C-reactive protein to albumin ratio; VIF=Variance Inflation Factor. Psychiatric diagnosis:1= schizophrenia, 2=bipolar disorder, 0=healthy controls (reference). Clinical phase: 0=healthy control, 1=schizophrenia–acute episode, 2=bipolar disorder–depressive episode, 3=bipolar disorder–manic episode

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DISCUSSION

This study evaluated acute-phase reactants, such as CRP, as indicators of inflammation in individuals with schizophrenia and bipolar disorder, as well as CAR, which is considered a novel biomarker for inflammation. Our results indicated a statistically significant variation in inflammatory markers between individuals with schizophrenia and BD relative to HC, implying an elevated inflammatory state in these psychiatric conditions. Prior research has demonstrated that both neuroinflammation and systemic inflammation markers are heightened in patients with schizophrenia and BD compared to HC (26,42,43). While inflammation in bipolar disorder has been shown to correlate more closely with disease episodes (10,44,45), in schizophrenia, a link with inflammation has been observed in both chronic and first-episode contexts (9,46,47).

Studies suggest that chronic inflammation at both the brain and systemic levels may lead to disruptions in the neurotransmitter system in psychiatric disorders (48,49) and contribute to the emergence of disease symptoms (8,10). Moreover, the administration of anti-inflammatory therapies in individuals with schizophrenia and bipolar illness has demonstrated enhancements in cognitive performance and a reduction in symptom intensity (21,50). The data indicate that inflammation may substantially influence the etiopathogenesis of these two diseases. Multiple research examining the correlation between systemic inflammation and psychiatric diseases, both historically and contemporaneously, have assessed biomarkers such as CRP, a marker of inflammation (2,15). These studies have particularly identified findings supporting chronic inflammation in schizophrenia (16). Similarly, research investigating the correlation between BD and CRP has yielded evidence that supports the involvement of inflammation (25). In a recent longitudinal study on bipolar disorder, CRP as well as other inflammatory markers were found to be elevated relative to healthy controls (51).Our research aligns with the existing literature on this matter. CRP levels were elevated in both diseases relative to HC. Research examining the disparity in CRP levels between BD and schizophrenia has revealed no significant difference between the two groups (52,53). Likewise, our analysis revealed no significant variation in CRP levels across the schizophrenia and BD cohorts. Certain studies indicate that inflammation in BD may correlate with episodes of the condition (54). However, our study did not reveal a significant difference in CRP and CAR levels between manic and depressive episodes. Nevertheless, evaluating a dataset that includes comparisons between remission and episode periods may be more appropriate for obtaining clearer insights on this issue.

Albumin is also a negative acute-phase reactant (36), and studies on schizophrenia and bipolar disorder have shown that albumin levels are lower in both groups compared to healthy controls, indicating a pro-inflammatory state (55). In our study, findings consistent with the literature were also observed.

CAR is a low-cost inflammatory marker with the potential to serve as a psychiatric biomarker, potentially indicating neuroinflammation, medication side effects, and cardiometabolic status (56). Research has indicated that levels are elevated in neuropsychiatric illnesses such as Parkinson's disease, migraine, and depression, in comparison to healthy individuals (38-40). In one study, when the CAR cut-off value for schizophrenia was set at 0.388, sensitivity and specificity were both found to be 81% when compared to healthy controls (40). This finding suggests that CAR may serve as a potential biomarker to support the diagnostic process in schizophrenia and could be used as a practical indicator, particularly for assessing the inflammatory burden.

A prior study investigating CAR levels in individuals with BD reported no notable variation compared to HC (41). The fact that the study in the literature only examined first-episode mania (42) may explain why no difference was found between bipolar disorder and healthy controls. The relationship between inflammation and bipolar disorder, whether inflammation is a causative factor or a result of episodic phases, remains ambiguous. In our study, patients were evaluated only during their acute phases, which may account for the different results obtained.

Although CRP is a widely used marker of inflammation, its specificity is limited due to elevations in various physiological and pathological conditions. In contrast, the CAR (CRP-to-albumin ratio) combines a positive acute-phase reactant (CRP) with a negative one (albumin), potentially offering a more accurate and

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balanced representation of inflammatory status. This ratio may serve as a more sensitive and specific indicator of systemic inflammation compared to CRP alone(41). Considering the limited number of studies assessing CAR in psychiatric populations, our study contributes significantly to the literature by addressing this gap and exploring the potential utility of CAR as a novel biomarker in schizophrenia and bipolar disorder.

Our study also has several limitations. Firstly, since the patients were not classified according to whether they were in an acute episode or remission phase and were only evaluated during acute episodes, the effects of inflammation during the remission phase could not be determined. Consequently, future longitudinal studies are essential to elucidate the dynamic impact of inflammation across the duration of these illnesses. Additionally, since our study has a retrospective design, establishing a causal relationship is challenging. In addition, although the retrospective design posed limitations, the effects of medications on inflammation were still addressed through statistical analyses, providing preliminary insights into their potential impact on inflammatory biomarkers. Another limitation of the study is related to smoking behavior. Although smoking is a known factor influencing inflammatory markers, particularly CRP, the exclusion of smokers was not feasible due to the high prevalence of smoking among individuals with psychiatric disorders. As a result, smoking status was included in the analyses as a covariate; however, the potential confounding effects of smoking on inflammation could not be fully eliminated.

In the literature, the effects of certain psychotropic medications on inflammatory responses have also been investigated. In particular, clozapine has been associated with pro-inflammatory changes due to its effects on cytokine modulation and immune activation (57). In our study, the observed association between elevated CAR levels and the use of clozapine is consistent with the existing literature. Although elevated AST levels in the patient groups could potentially be explained by drug interactions or comorbid conditions such as metabolic syndrome, this aspect was not specifically evaluated in our study.

Although some studies have reported a significant association between age and inflammatory markers due to a phenomenon known as “inflammaging” -a chronic low-grade inflammation associated with aging (58) -our findings did not show a statistically significant relationship between age and CAR levels in the regression analysis. This may suggest that, in our sample, age did not independently contribute to CAR variation when other factors such as diagnosis and medication use were accounted for.

In conclusion, our findings indicate that systemic inflammation is elevated in both schizophrenia and bipolar disorder, and that this increase is shaped not only by disease-specific pathophysiological processes but also by antipsychotic treatments such as clozapine

Given that CAR is an economical and easily measurable inflammatory marker, it holds promise as a valuable biomarker in psychiatry. Our findings support the growing body of literature regarding the role of inflammation in psychiatric disorders and highlight the need for future research to establish the clinical applicability of CAR in diagnosis, prognosis, and treatment response evaluation. Future prospective studies are necessary to explore the causal nature of these associations and to assess the potential benefits of treatment strategies targeting inflammation.

CONCLUSION

This study is notable as it is the inaugural comparison of the CAR across schizophrenia, BD, and HC. Our results demonstrate that CAR levels are markedly elevated in both the schizophrenia and BD cohorts relative to HC. This shows that systemic inflammation may have a role in the pathogenesis of certain psychiatric illnesses. No substantial variation in CAR levels was seen between the schizophrenia and BD groups. The retrospective design of our study and the absence of classification of patients by episode status (acute or remission) render it ambiguous whether inflammation initiates the disorder or if disease episodes provoke inflammatory processes. Future prospective research examining the temporal variations in CAR and its correlation with other inflammatory biomarkers may yield additional insights into the link between inflammation and psychiatric symptoms. CAR is an economical and readily quantifiable inflammatory marker, rendering it a viable biomarker in psychiatry. Our findings enhance the literature about the role of

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inflammation in psychiatric diseases and underscore the necessity for future research to ascertain the therapeutic relevance of CAR in diagnosis, prognosis, and therapy response.

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