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ORIGINAL RESEARCH

Albumin and Associated Biomarkers in Severe Neuropsychiatric Disorders: Acute-Phase Schizophrenia and Bipolar Disorder

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Background: Inflammation is relevant to the pathophysiology of severe neuropsychiatric disorders, schizophrenia (SCZ) and bipolar disorders (BD). Multiple pathophysiological biomarkers are valuable for the study of inflammatory processes. This study investigated albumin-related biomarkers in SCZ and BD to explore their roles in disease.

Methods: A total of 5,577 SCZ, 3442 BD-manic (BD-M) and 1405 BD-depression (BD-D) in acute stage and 5000 health controls (HCs) were enrolled. The differences in these biomarker levels among different groups were compared, and the contributing factors for the occurrence of SCZ, BD, and subgroups of BD were analyzed.

Results: Both SCZ and BD exhibit lower prognostic nutritional index (PNI), but higher neutrophil percentage-to-albumin ratio (NPAR) and creatinine–albumin ratio (CRA) compared with HC. Compared with BD-D, BD-M had higher NPAR and platelet-to-albumin ratio (PAR) and lower CRA. In logistic regression, lower prognostic nutritional index (PNI) and higher CRA were associated with both SCZ and BD, while higher NPAR was associated with BD. In the subgroup of BD, higher NPAR, CRA and lower PNI were associated with BD-M; lower PAR, PNI and higher CRA were associated with BD-D.

Conclusion: Our study reaffirmed the role of inflammation in the pathophysiology of SCZ and BD. Diagnostic value has been demonstrated in NPAR, PAR, PNI and CRA for BD and SCZ.

Keywords: schizophrenia, bipolar disorder, inflammation, albumin, neutrophil percentage-to-albumin ratio, platelet to albumin ratio, prognostic nutritional index

Introduction

Schizophrenia and bipolar disorder are severe neuropsychiatric disorders defined by remarkably heterogeneous clinical symptoms and are high global burden diseases because of multiple and persistent functional impairments including dysfunction in thoughts, perceptions, emotions and behaviour,[1] which share common features with each other considerably in terms of pathophysiological level and risk genes.[2] The etiologies of both schizophrenia and bipolar disorder are yet uncovered completely and precisely, and there still lack of effective biological markers for the diagnosis of both diseases.

Over the last two decades, chronic systemic inflammation and immunity are relevant to the pathophysiology of SCZ[3] and BD.[4] Previous studies demonstrated that multiple pathophysiological biomarkers, which are easily available by use of routine blood examinations, are valuable for the study of inflammatory processes and immune states in psychiatry.[5,6] However, for complicated diseases, like a lot of physical diseases and psychotic illnesses, one single biological marker often could not display satisfactory predictive value, while combined biomarkers can effectively improve the sensitivity of prediction.[7] Along with the finding, combinations of biomarkers have become research hot spot recently.

Albumin is a protein with anti-inflammatory effects,[8] which are down-regulated in response in the process of inflammation.[9] Some biomarkers derived from albumin have been proved prognostic and predictive functions in critically

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ill patients. As a new biomarker, neutrophil percentage-to-albumin ratio (NPAR) has been reported to reflect inflammatory status[10] and might be more effective in reflecting inflammation than albumin, neutrophil percentage, and neutrophil-to-albumin ratio (NLR).[11] The platelet-to-albumin ratio (PAR) was first proposed to assess cancer prognostic and considered as a biomarker for inflammatory status,[12] which has been shown to be effective in predicting inflammation states of affective disorders in previous study.[13] The prognostic nutritional index (PNI) was a biomarker, which was originally used in assessment in malnutritional status and immune state of surgical patients.[14] In recent years, studies showed that not only nutrient intake but also inflammation and oxidation stress played a role in malnutrition. A large number of studies have been performed using PNI as prognosis among patients with inflammation-related disease.[15] Current evidence in the literature showed that elevated serum creatinine reflects inflammation that alters renal endothelial/vascular function leading to decreased renal function, and worsening kidney function may itself be an inflammation.[16] Studies of somatic diseases suggested that creatinine–albumin ratio (CRA) was a new promising and easy-to-measure clinical indicator of prognostic assessment.[7] Some studies has conducted to detect neurobiological markers in schizophrenia and bipolar disorder, NLR, MLR and SII index were significantly higher in patients with BD than in healthy controls;[17] NLR and neutrophil and platelet counts were found to be higher in the patient with schizophrenia as compared to the healthy control group;[18] a functional imbalance in the synthesis of amino acids metabolites causes the appearance of pathophysiologic mechanisms that leads to various neuropsychiatric diseases, such as schizophrenia and bipolar disorder.[19] However, as far as we know, there are limited number of existing studies on NPAR, PNI and PAR and no studies on CRA in patients with SCZ and BD. Limited studies have been conducted using these indicators in psychotic disorders. In this study, we propose that NPAR, PAR, PNI and CRA may participate in the occurrence of BD and SCZ and be biomarkers to reflect the inflammation-immune status of acute SCZ and BD.

Methods

Samples

We carried out a retrospective cross-sectional cohort study in Beijing Hui-Long-Guan hospital, in collaboration with Clinical Medical College of Peking University, China. In the study, we extracted and analyzed research data from electronic medical record database in Beijing Hui-Long-Guan hospital, ie, HIS System in six-year (from March 15th, 2015 to March 15th, 2021) period. The research data was extracted without any information that can be used to identify the patients except illness case numbers. The Hui-Long-Guan Hospital Ethics Committee approved the low-risk observational and retrospective research protocol, the ethical approval number 2021-17-KE.

Eligible data in this study should meet the inclusion criteria as follows: patients diagnosed schizophrenia and bipolar disorder in acute stage who were admitted or hospitalized by two attending psychiatrists based on the International Classification of Diseases-10 (ICD-10) coding from F20.0 to F20.9 and F31.1; 31.2; 31.4; 31.5, respectively; subjects were Han Chinese; age from 18 to 65 years old when blood tested. The exclusion criteria were as follows: 1) comorbid psychiatric disorder, 2) somatic diseases that might affect inflammatory, immune or antioxidant status such as hypertensive disease, diabetes, acute infection, acute or chronic autoimmune disease, 3) pregnancy or lactating female, 4) BMI >29.9 kg/m2 or <18.5 kg/m2, 5) smoking more than 20 cigarettes per day, 6) laboratory test showed hepatopathy or nephropathy, anemia. The health control group was consisted of 5000 healthy individuals recruited from the local community of matching age (18 to 65 years old) and sex with the case group, without family history of mental illness and any somatic disease that may disturb stabilization of homeostasis, including inflammatory, immune or antioxidant status. All subjects were Han Chinese and signed informed written consent. The data in this study were collected only from patients admitted inpatient care unit for the first time. We supposed that the blood samples enrolled in our study reflected the characters in acute phase of the diseases, as the blood test was performed the second day after hospitalized as a part of routine checks. Within the designated time frame, this retrospective case–control study enrolled 5,577 patients with SCZ, 4847 patients with BD (3,442 patients with manic episode and 1,405 patients with depressive episode).

Statistical Analysis

In this study, statistical analysis used SPSS (version 19.0) was used for the statistical analysis. The chi-square test was used to test gender. Continuous variable, age, among multiple independent groups, was compared using one-way analysis

of variance (ANOVA). Analysis of covariance (ANCOVA) was performed in the context of the General Linear Model to assess the differences in biomarkers among the different groups. In the ANCOVA analysis process, we consider biomarkers as the dependent variables, and the diagnostic groups were included as fixed factors, while age and sex were included as covariates. Bonferroni-corrected ANCOVA as post hoc analysis was conducted to detect the differences among groups. Binary logistic regression analysis was adopted to investigate the risk factors for SCZ or BD by adjusting gender and age as covariates. Nomogram combined multiple indicators was used to predict the risk of SCZ or BD. Statistical significance threshold was set at $P < 0.05$.

Results

Comparison Among SCZ, BD and HCs

The total sample included 5577 SCZs, 4847 BDs and 5000 HCs. Chi-square test and ANOVA analysis in the study showed that there were no difference in age and gender among the three groups ($F = 1.799$, $P = 0.165$; $\chi2 = 2.799$, $P = 0.061$) (Table 1).

ANCOVA of the biomarker ratios which are related with inflammation and calculated from albumin levels displayed that both SCZs and BDs had higher NPAR, CRA ($F = 318.60$, $P = 0.000$; $F = 410.086$, $P = 0.000$, respectively) and lower PNI ($F = 768.43$, $P = 0.000$) compared to the HCs after adjusting for age and sex, and BDs had lower NPAR compared with the SCZ group. PNI and CRA in BDs exhibited higher level than those in the SCZs after adjusting for age and sex (Table 1).

The levels of WBC, neutrophil, monocyte, platelet counts, albumin and creatinine displayed significant differences ($P < 0.01$) in ANCOVA analysis after adjusting for age and sex among three groups, while there was no difference in the level of lymphocyte. Compared with HCs, the levels of WBC, neutrophil, and monocyte are higher, while levels of platelet counts and albumin are lower in SCZ group ($P < 0.001$, respectively) in post hoc analysis. No difference was found in lymphocyte and creatinine between SCZ group and HC group; compared with the HCs, BDs have slightly higher levels of WBC, neutrophil, monocyte and creatinine while slightly lower levels of platelet counts and albumin ($P < 0.05$, respectively). Furthermore, WBC, neutrophil, monocyte, albumin and creatinine differed between SCZ group and BD group after adjustment for age and sex ($P < 0.05$, respectively) (Table 1).

Table 1 Comparison of Sociodemographic and Laboratory Variables Among Schizophrenia, BD and Healthy Controls

Variables	SCZ (n=5577)	BD (n=4847)	HC (n=5000)	F/χ^2	*P*
Age (year)	38.90±12.26	39.28±12.84	38.90±10.03	1.799	0.165
Sex (male/female)	2695/2882	2454/2393	2482/2518	2.799	0.061
WBC	6.30±1.41[a]*[b]**	6.51±2.03[a]**	6.20±1.53	46.41	0.000
Neutrophil	3.71±1.18[a]**[b]**	3.87±1.74[a]**	3.61±1.18	46.66	0.000
Lymphocyte	2.00±0.58	2.02±0.66	2.02±0.53	1.05	0.349
Monocyte	0.44±0.14[a]**[b]**	0.47±0.18[a]**	0.40±0.13	210.03	0.000
Platelet	237.53±51.58[a]**	238.46±65.49[a]**	256.03±57.43	169.14	0.000
Albumin	42.99±3.66[a]**[b]**	43.35±4.04[a]**	46.23±2.61	1343.66	0.000
Creatinine	68.58±12.40[b]**	69.99±13.17[a]**	68.75±13.57	17.52	0.000
NPAR	1.36±0.24[a]**[b]*	1.35±0.26[a]**	1.25±0.19	318.60	0.000
PAR	5.56±1.29	5.52±0.1.54	5.57±1.30	0.999	0.368
PNI	53.00±4.74[a]**[b]**	53.43±5.37[a]**	56.30±3.84	768.43	0.000
CRA	1.60±0.28[a]**[b]*	1.62±0.31[a]**	1.48±0.28	410.66	0.000

Notes: *$P < 0.05$; **$P < 0.001$. [a]Compared with the healthy controls group. [b]Compared with the bipolar disorder group.
Abbreviations: SCZ, schizophrenia; BD, bipolar disorder; HC, healthy control; WBC, white blood cell; NPAR, neutrophil percentage-to-albumin ratio; PNI, the prognostic nutritional index; CrA, creatinine–albumin ratio; PAR, platelet to albumin ratio.

Comparison Among BD-M, BD-D and HCs

4847 individuals diagnosed of BD and 5000 HCs were included in the research. A total of 3,442 individuals with BD-M and 1,405 individuals with BD-D were included in data analysis. The ANCOVA analysis demonstrated that after controlling age and sex, there were significant differences in levels of blood cell counts, albumin, creatinine, NPAR, PAR, PNI, and CRA ($P < 0.05$, respectively). Post hoc analysis showed that BD-M group has higher levels of WBC, neutrophil, monocyte and creatinine, NPAR, CRA and lower levels of platelet, albumin and PNI than the HC group ($P < 0.001$, respectively); results demonstrated in BD-D group were not the same, ie, only the levels of mono, creatinine, NPAR and CRA were higher than HC group, while levels of platelet, albumin, PAR and PNI were lower than HC group ($P < 0.001$, respectively). Furthermore, there were differences in blood cell counts, albumin, creatinine, NPAR, PAR and CRA between BD-M and BD-D, after adjustment for age and sex ($P < 0.05$, respectively) (Table 2).

Comparison Among BD-D, BD-M and SCZ

There were no differences in age and male/female ratio among SCZ group, BD-D group and BD-M group ($F = 1.473$, $P = 0.229$; $\chi2 = 2.898$, $P = 0.055$, respectively). In the ANCOVA analysis, after adjusting for age and sex, significant differences were found in the levels of blood cell counts, albumin, creatinine, NPAR, PAR, PNI, and CRA ($p < 0.05$, respectively) among SCZ group, BD-D group and BD-M group. Post hoc analysis displayed that the levels of WBC, neutrophil and monocyte are higher, while levels of platelet, albumin and PNI are lower in BD-M group than SCZ group ($P < 0.001$, respectively); differently, the blood cell counts exhibit similar levels between BD-D group and SCZ group. In BD-D group, only the levels of creatinine, NPAR and CRA were higher than SCZ group, while levels of albumin, PAR and PNI were lower than SCZ group ($P < 0.001$, respectively) (Table 3).

Logistic Regression

This study aimed to explore whether these albumin-based biomarkers could be the contributing factors for SCZ, BD, BD-M or BD-D. Disease status and control were adopted as dependent variables in the stepwise logistic regression model. The potential predictive values of albumin-based markers including NPAR, PAR, PNI and CRA, which were shown to be different between the control group and the acute disease status group, were assessed in the model (Table 4).

Table 2 Comparison of Sociodemographic and Laboratory Variables Among BD-Depression, BD-Manic and Healthy Controls

Variables	BD-M (n=3442)	BD-D (n=1405)	HC (n=5000)	F/χ^2	*P*
Age (year)	39.21±12.71	39.48±13.15	38.90±10.03	1.68	0.67
Sex (male/female)	1751/1691	703/702	2482/2518	0.62	0.54
WBC	6.64±2.10[a]**[b]**	6.20±1.82	6.20±1.53	69.39	0.000
Neutrophil	3.96±1.79[a]**[b]**	3.66±1.61	3.61±1.18	60.46	0.000
Lymphocyte	2.03±0.67[b]*	1.97±0.63	2.02±0.53	4.27	0.014
Monocyte	0.48±0.19[a]**[b]**	0.43±0.16[a]**	0.40±0.13	245.267	0.000
Platelet	240.23±65.38[a]**[b]*	234.13±65.56[a]**	256.03±57.43	104.92	0.000
Albumin	43.21±4.06[a]**[b]**	43.68±3.99[a]**	46.23±2.61	750.85	0.000
Creatinine	69.46±13.12[b]**	71.30±13.21[a]**	68.75±13.57	30.58	0.000
NPAR	1.36±0.26[a]**[b]**	1.32±0.25[a]**	1.25±0.19	218.79	0.00
PAR	5.58±1.56[b]**	5.37±1.50[a]**	5.57±1.30	12.66	0.00
PNI	53.38±5.43[a]**	53.55±5.20[a]**	56.30±3.84	476.46	0.00
CRA	1.61±0.31[a]**[b]*	1.64±0.30[a]**	1.48±0.28	327.10	0.00

Notes: *P < 0.05; **P < 0.001. [a]Compared with the healthy controls group. [b]Compared with the Bipolar disorder group.

Abbreviations: BD-M, bipolar disorder in manic episode; BD-D, bipolar disorder in depressive episode; HC, healthy control; WBC, white blood cell; NPAR, neutrophil percentage-to-albumin ratio; PNI, the prognostic nutritional index; CRA, creatinine–albumin ratio; PAR, platelet to albumin ratio.

Table 3 Comparison of Sociodemographic and Laboratory Variables Among BD-D, BD-M and SCZ

Variables	BD-M (n=3442)	BD-D (n=1405)	SCZ (n=5577)	F/χ^2	P
Age (year)	39.21±12.71	39.48±13.15	38.90±12.26	1.473	0.229
Sex (male/female)	1751/1691	703/702	2695/2882	2.898	0.055
WBC	6.64±2.10[a]**	6.20±1.82	6.30±1.41	51.56	0.000
Neutrophil	3.96±1.79[a]**	3.66±1.61	3.71±1.18	36.38	0.000
Lymphocyte	2.03±0.67	1.97±0.63	2.00±0.58	4.744	0.009
Monocyte	0.48±0.19[a]**	0.43±0.16	0.44±0.14	87.296	0.000
Platelet	240.23±65.38[a]*	234.13±65.56	237.53±51.58	6.679	0.001
Albumin	43.21±4.06[a]*	43.68±3.99[a]**	42.99±3.66	21.21	0.000
Creatinine	69.46±13.12	71.30±13.21[a]**	68.58±12.40	32.56	0.000
NPAR	1.36±0.26	1.32±0.25[a]**	1.36±0.24	16.04	0.000
PAR	5.58±1.56	5.37±1.50[a]**	5.56±1.29	12.60	0.000
PNI	53.38±5.43[a]*	53.55±5.20[a]**	53.00±4.74	11.41	0.000
CrA	1.61±0.31	1.64±0.30[a]**	1.60±0.28	8.23	0.000

Notes: *P < 0.05; **P < 0.001. [a]Compared with the SCZ group.
Abbreviations: BD-M, bipolar disorder in manic episode; BD-D, bipolar disorder in depressive episode; SCZ, schizophrenia; WBC, white blood cell; NPAR, neutrophil percentage-to-albumin ratio; PNI, the prognostic nutritional index; CRA, creatinine–albumin ratio; PAR, platelet to albumin ratio.

Table 4 The Potential Predictive Values of Albumin-Based Markers in Logistic Regression Between the Control Group and the Acute Disease Status Group

	Age	Sex	PNI	CRA	NPAR	PAR
SCZ	−0.016	−0.120	−0.183	1.657	–	–
BD	−0.011	−0.235	–	–	0.370	–
BD-M	−0.013	−0.168	−0.122	1.669	0.596	–
BD-D	−0.009	−0.387	−0.148	2.031	–	−0.126

Abbreviations: BD-M, bipolar disorder in manic episode; BD-D, bipolar disorder in depressive episode; SCZ, schizophrenia; NPAR, neutrophil percentage-to-albumin ratio; PNI, the prognostic nutritional index; CRA, creatinine–albumin ratio; PAR, platelet to albumin ratio.

In binary logistic regression model of occurrence of acute SCZ, the result showed age (β = −0.016, P = 0.000), sex (β = −0.120, P = 0.035), PNI (β = −0.183, P = 0.000) and CRA (β = 1.657, P = 0.000) were independent influencing factors. We performed nomogram that combined multiple indicators to predict the risk of acute schizophrenia (Figure 1).

In binary logistic regression model of occurrence of acute BD group, the result showed age (β = −0.011, P = 0.000), sex (β = −0.235, P = 0.000), NPAR (β = 0.370, P = 0.004), PNI (β = −0.118, P = 0.000) and CRA (β = 1.849, P = 0.000) were independent influencing factors. We performed nomogram that combined multiple indicators to predict the risk of acute BD (Figure 2).

In binary logistic regression model of occurrence of acute BD-M group the result showed age (β = −0.013, P = 0.000), sex (β = −0.168, P = 0.009), NPAR (β = 0.596, P = 0.004), PNI (β = −0.122, P = 0.000) and CRA (β = 1.669, P = 0.000) were independent influencing factors. We performed nomogram that combined multiple indicators to predict the risk of acute BD-M (Figure 3).

In binary logistic regression model of occurrence of acute BD-D group the result showed age (β = −0.009, P = 0.000), sex (β = −0.387, P = 0.005), PAR (β = −0.126, P = 0.000), PNI (β = −0.148, P = 0.000) and CRA (β = 2.031, P = 0.000) were independent influencing factors. We performed nomogram that combined multiple indicators to predict the risk of acute BD-D (Figure 4).

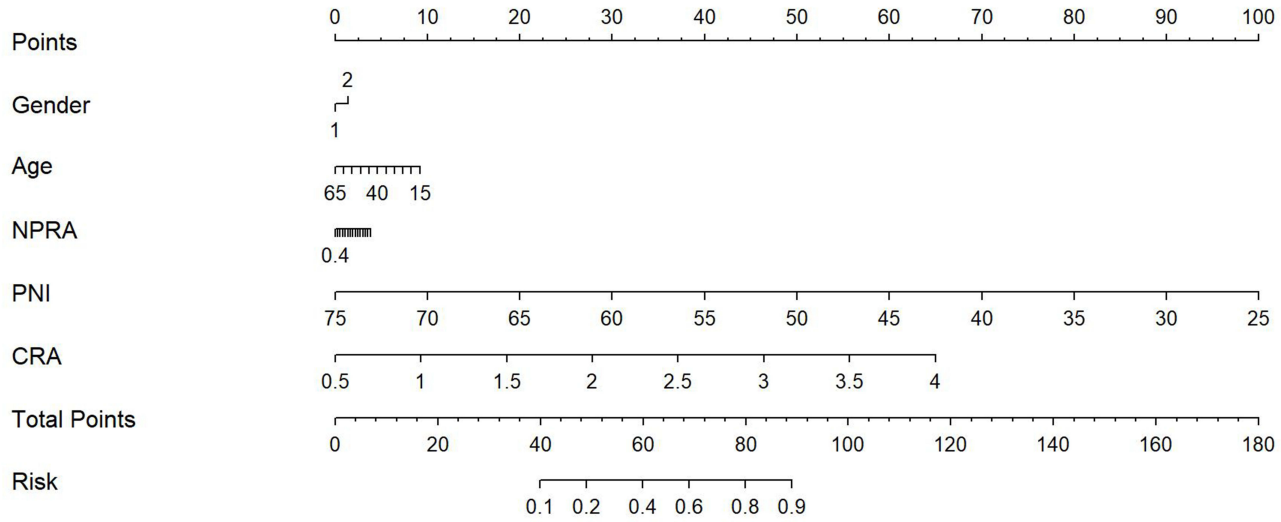

Figure 1 Risk factors of SCZ nomogram. (Code of sex, 1: male, 2: female) (To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the Risk of SCZ axes to determine the SCZ risk).
Abbreviation: SCZ, schizophrenia.

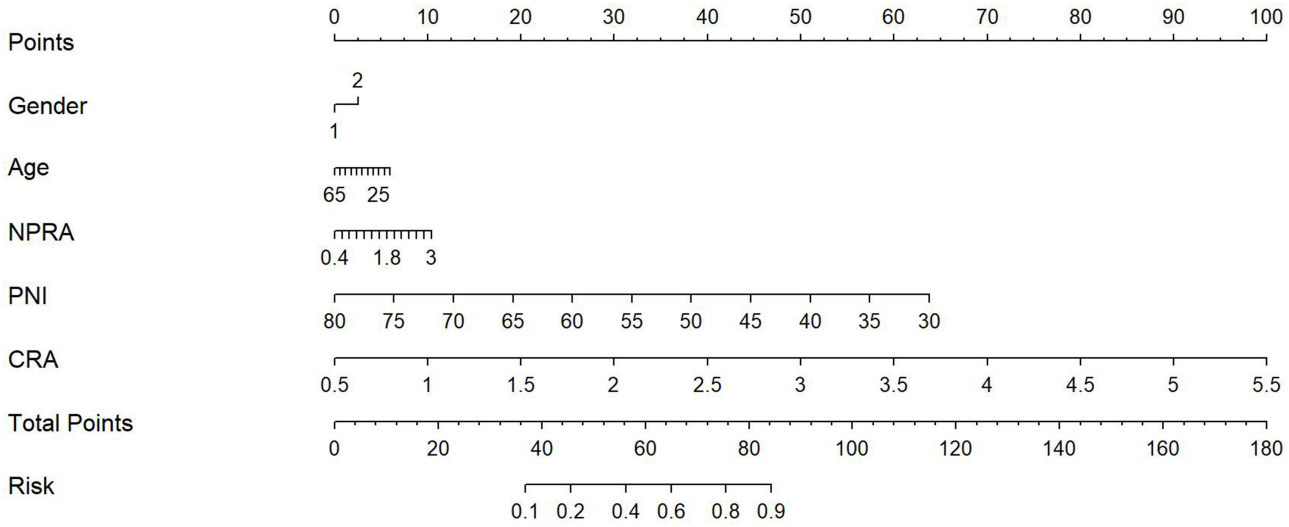

Figure 2 Risk factors of BD nomogram. (Code of sex, 1: male, 2: female) (To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the Risk of BD axes to determine the BD risk).
Abbreviation: BD, bipolar disorder.

Discussion

This was a large-scale research, as far as we known, which was the first time explored albumin and related biomarkers, including NPAR, PAR, PNI and CRA, in schizophrenia and bipolar disorder patients at acute stage. Furthermore, the data of manic episode and depressive episode were analyzed separately. Our study showed that both SCZ and BD patients exhibited lower albumin and PNI, but higher NPAR and CRA compared with health controls. Compared with SCZ, BD had lower NPAR and higher PNI and CRA. Both BD-M and BD-D had higher NPAR, CRA and lower PNI than health

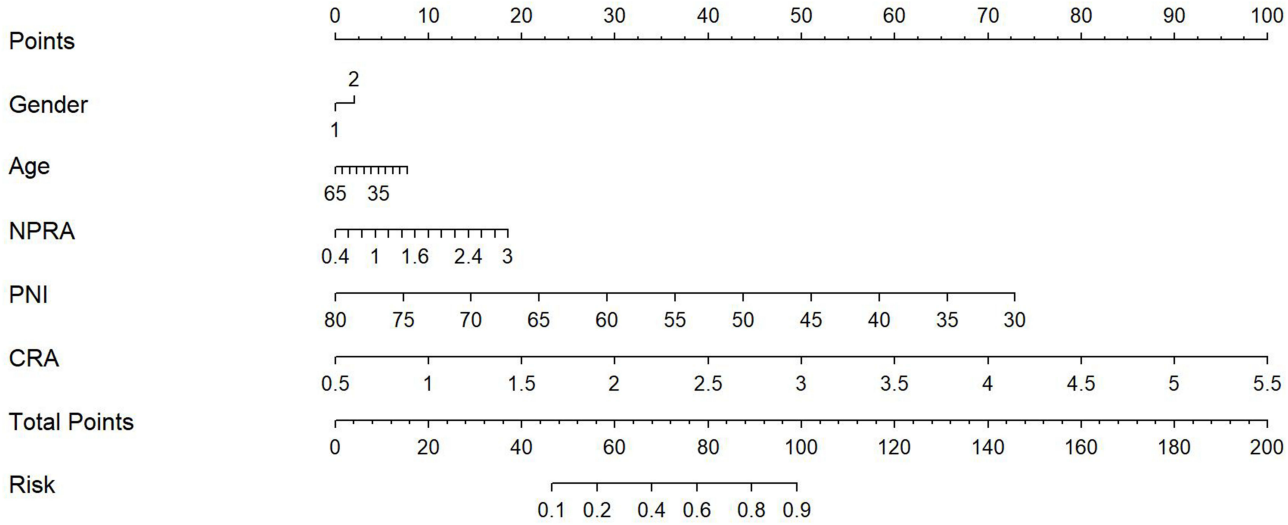

Figure 3 Risk factors of BD-M nomogram. (Code of sex, 1: male, 2: female) (To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the Risk of BD-M axes to determine the BD-M risk).
Abbreviation: BD-M, bipolar disorder manic episode.

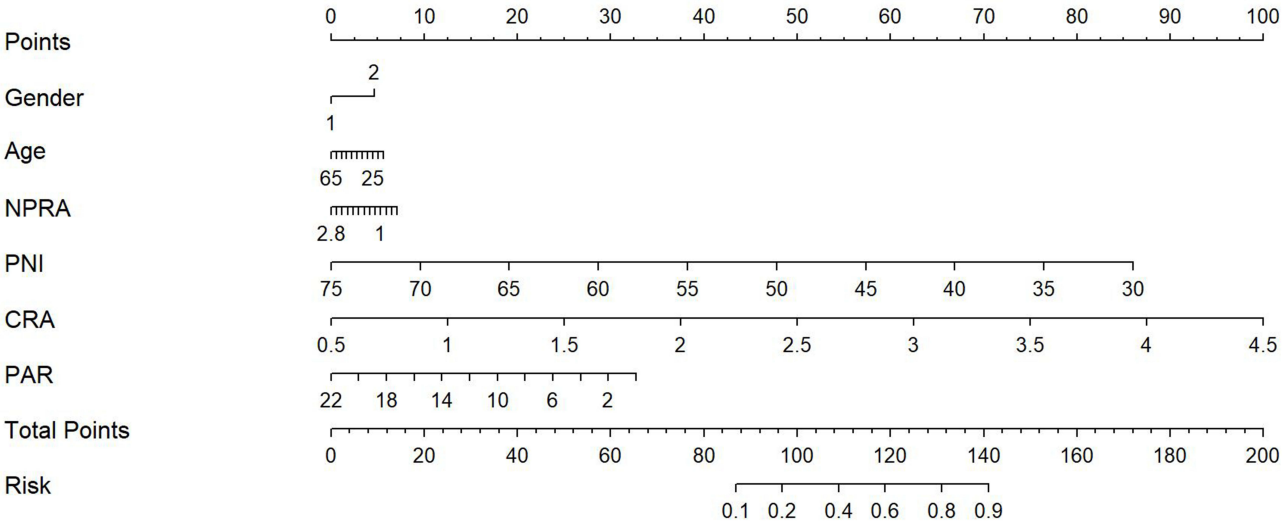

Figure 4 Risk factors of BD-D nomogram. (Code of sex, 1: male, 2: female) (To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the Risk of BD-D axes to determine the BD-D risk).
Abbreviation: BD-M, bipolar disorder manic episode.

controls, as well as lower PNI than SCZ. However, in BD-D, the level of PAR was lower than both health control and SCZ and the levels of NPAR and CRA were higher than SCZ. Compared with BD-D, BD-M had higher levels of NPAR and PAR and lower level of CRA. In multiple logistic regression, lower PNI and higher CRA were found to be strongly associated with both SCZ and BD, while higher levels of NPAR were associated with BD. In subgroup of BD, higher levels of NPAR, CRA and lower level of PNI were significantly associated with BD-M; lower levels of PAR, PNI and higher level of CRA were associated with BD-D.

There were some reasons why we have chosen these parameters calculated from albumin: first, unlike other inflammatory markers, albumin has a long half-life and can be easily obtained in daily clinical work in a real-life

setting;[6] second, these parameters were easily obtained from blood screening and have been proven effective in reflecting inflammatory processes and immune states in physical illness.

NPAR is a newly exploited predictor related with systemic inflammation stage in somatic diseases, such as cancer and stroke.[11] Increased neutrophil percentage and decreased albumin levels have been demonstrated in patients with SCZ[5,20] and BD.[21,22] Along with the above observation, we found that NPAR, the combination of albumin and neutrophil percentage, displayed a valuable prediction of occurrence of BD, especially BD-M. Platelet played an important role in inflammatory response.[23] Studies have demonstrated that a series of inflammatory conditions, including cancer progression,[12] atherosclerosis[24] and the pathophysiology of COVID-19,[25] can be mediated by platelets. Platelet albumin ratio (PAR) is a combined indicator of inflammation and nutritional status and has been shown to be a useful and potentially prognostic biomarker for various cancers.[12] There was limited data about PAR and psychotic disorders. In our team's early work, we found that the BD-D patients had the lowest PAR among major depression disorders, BD-M and BD-D patients.[13] The present study had found PAR levels in BD-D patients are also lower than those of SCZ patients, hence PAR could be a protective factor for BD-D which is contrary to the findings in other inflammation diseases.[26] The reason could be related to the fact that platelet can regulate 5-HT[23] which plays a key role in depression episode.[27] PNI calculated peripheral blood lymphocyte count and albumin concentration as an indicator of the inflammatory response[28] and linked nutritional status to immune response for patients.[29] To our knowledge, this is the first study to detect PNI in acute psychotic disorders. We found both schizophrenia patients and BD patients have lower PNI than health control, and schizophrenia has the lowest PNI among schizophrenia, BD manic and depressive episodes, while PNI could play a protective role in both SCZ and BD patients. Further research should pay attention to PNI to back up these results. Creatinine is not only a metabolite of creatine phosphate as an energy storage but also had distinct effects for systemic inflammatory response[7] and capacity to contribute to the total antioxidant.[30] Previous study[31] showed no difference in creatine levels among major depression disorder, BD-M and BD-D, which have been evaluated only in small single-center series. In the present study, we found BD-D has higher creatinine level than BD-M, SCZ and health controls, and the results were similar among the creatine levels of BD-M, SCZ and HCs. The inconsistency of results could be due to differences in the population studied and sample sizes of these studies. Studies of digestive diseases,[7] suggested that creatinine-albumin ratio (CRA) was a negative prognostic factor with worse disease specific survival. Our results displayed that both BD and SCZ groups had higher levels of CRA than HC group, and both BD-D and BD-M had higher levels of CRA than HC group. Compared to the patients with SCZ and BD-M, the BD-D patients had higher CRA level. Our findings were not consistent with previous studies[32,33] in that hypo(manic) phases of BD was associated with more obvious changes in inflammatory process than BD-D, but supports another point of view that heterogeneity existed between BD-D and BD-M.[31] We speculate that there exist different inflammation mechanisms in BD-M and BD-D. CRA was showed to be a risk factor for the occurrence of BD and SCZ in the logistic regression analysis. However, limited studies were carried out on the association of the CAR with psychiatry diseases, and we speculated that elevated CRA may reflect the level of system inflammation as a peripheral sign and marker. Thus far, the mechanisms underlying BD and SCZ are shown to be complex and still not completely elucidated. And it is possible that inflammation and immune are only partial contributing factors of occurrence of SCZ and BD, which may explain why our study found these serum markers had minor relevance in logistic regression. This study can also reflect clinical phenomena more truly and facilitates an entry point in clinical application that combined biomarkers and model of biological markers can effectively improve the sensitivity of prediction.

The present study was a real-world research aimed to take the advantage of a large size database of patient medical information, the finding of which had potential for clinical transformation. However, there are still some limitations that need to be considered and caution should be taken when interpreting the findings of our study. First, as a retrospective study, certain clinical information is absent, such as course of disease, first episode of psychosis, BMI of subjects, and the severity of the disease. Second, due to the nature of cross-sectional study, the conclusion lacks of causal relationships between albumin-related parameters (NPAR, PAR, PNI and CRA) and BD or SCZ. Third, since information on dietary supplementation and pharmacotherapy is unreliable and fragmented, we could not assess whether albumin-related parameters (NPAR, PAR, PNI and CRA) might be at-least partly explained by these confounding factors.

Conclusions

In the present study, the albumin-related ratios, including the NAPR, PAR, PNI and CRA, were found to exhibit different levels in both BD and SCZ compared to in HCs. PNI could be a protective factor, and CRA could be a risk factor for both SCZ and BD. In BD-D, PAR could only be explained to a limited extent by inflammation but can reflect to a larger extent the critical role of platelets in the occurrence of the disease. Compared to the patients with BD-M, the BD-D subgroup had higher CRA level, suggesting that inflammatory changes are not more significant during manic episodes of BD than during depressive phases. Higher levels of NPAR, CRA and lower level of PNI were significantly linked to BD-M; lower levels of PAR, PNI and higher level of CRA were associated with BD-D, which support the previous literature which demonstrated heterogeneity existed between BD-D and BD-M, especially in the process of inflammation. The present research reaffirmed the role of systemic inflammation in the pathophysiology of SCZ and BD; along with the findings of our present study, more attention should be paid to NPAR, PAR, PNI and CRA to detect the mechanisms of inflammation in BD and SCZ, and heterogeneity in different episodes of BD, which could help find new ways of preventing BD and SCZ. Moreover, diagnostic value has been demonstrated in NPAR, PAR, PNI and CRA for BD and SCZ, and more detailed studies are needed to investigate on this point to help fill in gaps in the field of diagnostic biomarkers for BD and SCZ.

Abbreviations

SCZ, schizophrenia; BD, bipolar disorders; BD-M, BD-manic; BD-D, BD-depression; HCs, health controls; NPAR, neutrophil percentage-to-albumin ratio; CRA, creatinine–albumin ratio; PAR platelet-to-albumin ratio; PNI, prognostic nutritional index.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Hui-Long-Guan Hospital, no.2021-17-KE. Written informed consent was obtained from individuals or guardian participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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