Peripheral biomarkers to differentiate bipolar depression from major depressive disorder: a real-world retrospective study

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Abstract

Background Bipolar depression (BPD) is often misdiagnosed as a major depressive disorder (MDD) in clinical practice, which may be attributed to a lack of robust biomarkers indicative of differentiated diagnosis. This study analysed the differences in various hormones and inflammatory markers to explore peripheral biomarkers that differentiate BPD from MDD patients.

Methods A total of 2,048 BPD and MDD patients were included. A panel of blood tests was performed to determine the levels of sex hormones, stress hormones, and immune-related indicators. Propensity score matching (PSM) was used to control for the effect of potential confounders between two groups and further a receiver operating characteristic (ROC) curve was used to analyse the potential biomarkers for differentiating BPD from MDD.

Results Compared to patients with MDD, patients with BPD expressed a longer duration of illness, more hospitalisations within five years, and an earlier age of onset, along with fewer comorbid psychotic symptoms. In terms of biochemical parameters, MDD patients presented higher IgA and IgM levels, while BPD patients featured more elevated neutrophil and monocyte counts. ROC analysis suggested that combined biological indicators and clinical features could moderately distinguish between BPD and MDD. In addition, different biological features exist in BPD and MDD patients of different ages and sexes.

Conclusions Differential peripheral biological parameters were observed between BPD and MDD, which may be age-sex specific, and a combined diagnostic model that integrates clinical characteristics and biochemical indicators has a moderate accuracy in distinguishing BPD from MDD.

Keywords Bipolar depression, Major depressive disorder, Peripheral biomarker

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Introduction

Major depressive disorder (MDD) and bipolar disorder are two common and highly prevalent mood disorders, with high recurrence and low remission rates that impose heavy burdens on families and society [1, 2]. In clinical practice, it is difficult to accurately diagnose bipolar disorder in patients with bipolar depression (BPD) when previous hypomanic or manic experiences are not well recognised. Both MDD and BPD have been defined primarily by the presence of depressive symptoms, and the International Classification of Diseases (ICD)-10 continues the practice of its previous editions by defining the same criteria for depressive episodes [3]. About 60% of BPD patients are misdiagnosed with MDD, and it takes 5–10 years for these patients to be correctly identified with bipolar disorder [4, 5]. Considering that incorrect treatment due to misdiagnosis may exacerbate the illness and cause considerable risk of suicide or self-harm in severe cases of BPD, it is essential to differentiate BPD from MDD. However, despite decades of effort, there is still a lack of valid objective biological markers to distinguish between bipolar and unipolar depression. Although an increasing number of biomarkers have been reported to be capable of distinguishing BPD from MDD, few have been consistently replicated [3, 4, 6, 7]. Therefore, exploring biological markers for rapid and accurate differential diagnosis is of great clinical importance.

The use of differentially expressed biochemicals in peripheral blood as diagnostic, prognostic, and predictive biomarkers for the identification of MDD and BPD has been extensively reported. Given the hypothesis that dysregulation of immune pathways is involved in the aetiology and pathophysiology of mood disorders, some studies have distinguished BPD from MDD by the differential expression of cytokines or soluble receptors in peripheral blood [4, 6, 8, 9]. Martinuzzi et al. [8] summarised and analysed relevant studies [4, 6, 9, 10] and concluded that immune-related biomarkers can distinguish between BPD and MDD. They used clinical data and serum samples from two independent naturalistic cohorts and found that IL-10, IL-15, and IL-27 were positively associated with BPD, which was validated in other independent samples [8]. Furthermore, a meta-analysis suggested that BPD [11] and MDD [12] exhibit altered levels of different inflammatory factors compared with healthy controls. All of these results indicate that immune-related parameters may be essential biomarkers. However, in many primary care hospitals, these inflammatory factors are not included in routine examinations, as they would increase the medical burden of low-income families.

As general screening items, data on leukocytes, C-reactive protein (CRP), complement 3 (C3), complement 4 (C4), immunoglobulins, and peripheral blood leukocyte count are highly accessible, and these immune-associated indicators have been suggested to correlate with mood disorders [13–18]. For example, upregulated concentrations of CRP have been reported in meta-analyses of cross-sectional studies of both bipolar disorder [15] and MDD [18]. C3 [13, 14] and C4 [16] play potential roles in depression by participating in inflammation or regulating neural functions. Significantly higher levels of IgM and IgG were found in psychiatric patients compared to a control group [19, 20]. Excessive influx of immunoglobulin into the brain can induce central nervous system dysfunction because a high concentration of IgG in the cerebrospinal fluid can cause depression-like behaviour [17]. A large prospective cohort study from the UK Biobank computed five-year MDD incidence among individuals on 57 laboratory measures and revealed that a number of inflammation-related indicators (e.g. neutrophil count), endocrine-related molecules (e.g. testosterone), and other biochemical parameters were associated with increased MDD incidence [21]. The results were validated for different ancestries, suggesting the feasibility of differentiating BPD from MDD using laboratory measures. However, only a few studies have reported whether these indicators can be used to differentiate between MDD and BPD.

Neuroendocrine system dysfunction may play an important role in the mechanisms underlying the pathophysiology of mood disorders. Primary abnormalities in the adrenal and gonadal axes are associated with mood alterations. Numerous studies have reported hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis and impairment in its sensitivity to negative feedback regulation in bipolar disorder [22, 23] and MDD [24, 25]. Cortisol and adrenocorticotropic hormone (ACTH) are important biological indicators of a dysfunctional HPA axis and have been included as routine clinical test items to evaluate the status of the axis. Some studies have found variability in patients with MDD and BPD, such as lower cortisol levels in women with BPD and higher cortisol levels in patients with MDD [26]. Nonetheless, this variability has not been verified by other studies. Women experience depression at about twice the rate of men, while for bipolar disorder the difference is not so pronounced [27], suggesting that gonadal hormones are of different importance in the two disorders or may have a different percentage of influence on the condition. In fact, considerable clinical evidence demonstrates that fluctuations in ovarian hormones are associated with an increased risk of depressive states [27, 28], but the impact of ovarian hormones on mood is complex. Compared with women with MDD, women with BPD are more likely to have early-onset menstrual cycle

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dysfunction [29]. However, studies on gonadal hormone differences between patients with BPD and MDD are limited. In addition, it is important to emphasise sex- and age-related differences when examining the correlation between neuroendocrine hormone levels and mood disorders, because of either the different prevalence of men and women, or the different levels of various hormones between sexes or ages.

Based on the above information, we explore a relatively objective diagnostic method using traditional inflammatory or biochemical indicators and hormones in peripheral blood to differentiate between BPD and MDD. Furthermore, we also attempt to explore the differences between sexes and ages.

Methods

Study sample

The study cohort was selected from inpatients at Beijing Anding Hospital Capital Medical University between January 2013 and December 2019. The inclusion criteria were as follows: 1) patients who were diagnosed with recurrent depressive disorder or bipolar disorder, currently with a depressive episode according to the International Statistical Classification of Diseases and Related Health Problems-10th revision (ICD-10). The diagnosis was made by two experienced psychiatrists. All participants enrolled in this study were in the acute phase of MDD or BPD; 2) patients aged between 12 and 80 years; and 3) availability of reliable medical records, without any important information missing. The exclusion criteria were as follows: 1) those diagnosed with other mental disorders such as bipolar manic episodes, rapid cycling bipolar disorder, schizoaffective disorder, and schizophrenia; 2) those with severe physical diseases, such as acute infection, autoimmune diseases, severe liver and kidney dysfunction; 3) those with acute infection and CRP > 10 mg/dL; 4) those with drug or alcohol dependence or abuse issues; 5) pregnant and lactating women; and 6) those taking hormones, including sex steroids or glucocorticoid medications. All data carrying patient identity information were de-labelled.

Study protocol

This was a retrospective study. Medical data from electronic health records were transformed into the Observational Medical Outcomes Partnership Common Data Model, and the Beijing-Hebei-Tianjin Mental Health big data platform was developed, which has been described in previous studies [30, 31]. Clinical and demographic data were extracted from the medical records available in the database. Peripheral blood tests were repeated within 24–72 h after admission from the hospital. Biochemical parameter data, including oestrogen, testosterone, progesterone, cortisol, ACTH, and CRP levels, were extracted from the big data platform. ACTH and Cortisol were analyzed using a metabolic assay, while oestradiol, testosterone and progesterone were measured through a reproductive endocrinology assay. These analyses were conducted on the Atellica Solution analyser (immunoassay and clinical chemistry analyser manufactured by Siemens, Erlangen, Germany; https://www.siemens-healthineers.com/en-uk/integrated-chemistry/systems/atellica-solution-analyzers) based on a competitive immunoassay using direct chemiluminescence technology. Serum CRP concentration was measured by the Image 800 immunochemistry system using immunoassay (Beckman Coulter, United States; https://www.beckmancoulter.com/en/products/protein-chemistry/immage-800). Accuracy and reliability of experimental data were ensured through rigorous quality control procedures and all experimental procedures strictly adhered to the manufacturer's guidelines and standard operating procedures.

Covariates and PSM

Propensity score matching (PSM) was used to control for potential confounding factors in the MDD and BPD groups. Demographic covariates, including age, sex, and body mass index (BMI), were matched between the two groups according to the method of 1-to-1 nearest neighbour matching, without replacement, and the caliper value was set at 0.01. Matched pairs of participants with equal numbers in each group were generated by PSM, and all demographic covariates included in the PSM analysis showed no differences in sex, age, and educational level. PSM was performed using the package 'MatchIt' in R software. Statistical significance was set at $P < 0.05$.

Statistical methods

Statistical Product and Service Solutions version 26.0 (SPSS, Inc., Chicago, IL, USA) was used to perform the statistical analyses. None of the continuous variables in this study conformed to the normal distribution and homogeneity of variance. Data were presented as median and quartile ranges. The Kruskal–Wallis H-test was used to compare the differences in laboratory indicators between the two groups. All categorical variables were expressed as numbers and percentages (%) and compared using the chi-square test. Two-tailed *P* values were used for all statistical analyses, and $P < 0.05$ was considered statistically significant. Stepwise logistic regression analysis was used to measure the impact of variables and construct regression models. Receiver operating characteristic (ROC) curve analysis was used to assess the discriminatory effects of the continuous variables and logistic regression models by calculating the area under the ROC curve (AUC). Maximising Youden's index (J;

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where J = sensitivity + specificity − 1) was calculated to determine the optimal cut-off values between sensitivity and specificity.

Results

We included a total of 3782 patients in our study. Following propensity score matching, we retained 1024 patients with MDD and 1024 patients with BPD. Among these patients, there were 886 males and 1522 females. Specifically, there were 431 male patients in the MDD group and 455 male patients in the BPD group. The number of patients aged ≤ 25 years was 522 (274 in the MDD group and 248 in the BPD group), while the number of patients aged between 25 and 50 years was 1149 (562 in the MDD group and 587 in the BPD group). Additionally, there were 737 patients aged 50 years or older (368 in the MDD group and 369 in the BPD group).

Difference of demographic and clinical features between BPD and MDD

The demographic and clinical characteristics and biochemical parameters of the patients with BPD and MDD before and after PSM are summarised in Table 1. After PSM, there were no significant differences in age, sex, education, occupation, marital status, BMI, tobacco use, or alcohol consumption between BPD and MDD. Compared to patients with MDD, those with BPD had a longer duration of illness (median seven vs. eight years, $P < 0.001$), more hospitalisations within five years (median 1 vs. 2 times, $P < 0.001$), an earlier age of onset (28 vs. 26 years, $P < 0.001$), and fewer accompanying psychotic symptoms (59.9% vs. 29.1%, $P < 0.001$). These results suggest that it is feasible to distinguish between BPD and MDD based on the clinical features of the patients.

Potential biomarkers for distinguishing BPD from MDD

To investigate BPD-specific biochemical parameters, we compared sex, stress hormones, and inflammatory factors between BPD and MDD patients. As shown in Table 1 and Fig. 1, MDD patients presented higher levels of IgA ($P = 0.040$) and IgM ($P = 0.004$), whereas BPD patients had higher neutrophil ($P = 0.004$) and monocyte ($P = 0.002$) counts. There were no differences in testosterone, oestradiol, progesterone, cortisol, ACTH, CRP, C3, C4, IgG, or lymphocyte count (all $P > 0.05$) between the groups (Table 1).

To further verify the relationship between biochemical changes and diseases, we used stepwise logistic analysis to incorporate clinical characteristics and biological parameters that were statistically different between the two groups. As shown in Table 2, after controlling for confounding factors, such as clinical features, the

significant linkage between age of onset, duration of illness, psychotic symptoms, number of hospitalisations within five years, monocyte count, and IgM levels remained statistically different ($P < 0.05$, Table 2).

ROC analysis was conducted to investigate the efficacy of characteristic variables as potential biomarkers of BPD. As presented in Table 3, each indicator was not specific enough to differentiate between BPD and MDD, with an AUC ranging from 0.534 to 0.629. The combination model of several indicators, including clinical features, IgM, and monocyte count, improved the differential effect with an AUC value of 0.677.

Age- and sex-specific biochemical characteristics

Sex and biological age affect gonadal hormone, stress, and inflammatory marker levels. Therefore, we performed refined stratification analysis by age and sex, as shown in Table 4. Among male patients, BPD patients had lower peripheral concentrations of immunoglobulin IgG (Z = -2.157, $P = 0.031$) but higher white blood cell counts, including lymphocytes (Z = 3.023, $P = 0.003$), monocytes (Z = 2.918, $P = 0.004$), and neutrophils (Z = 2.422, $P = 0.015$). Meanwhile, these differences were not observed in female patients. Female patients with BPD had significantly lower IgM levels (Z = -2.681, $P = 0.007$) compared to patients with MDD.

We used the interquartile age range of 25–50 years as the basis for stratification, as shown in Table 4. In patients aged 25 years or below, BPD patients had higher levels of cortisol (Z = 2.933, $P = 0.003$) and lower levels of immunoglobulin IgA (Z = -2.815, $P = 0.005$) in peripheral blood. In patients aged 25–50 years, we found that BPD patients had higher monocyte (Z = 2.081, $P = 0.037$, Table 5) and neutrophil (Z = 3.717, $P < 0.001$, Table 5) counts than MDD patients. The other parameters showed no significant differences between the two groups. In BPD patients aged 50 years or older, in contrast to MDD patients, peripheral blood levels of progesterone (Z = -2.961, $P = 0.003$) and immunoglobulin IgM (Z = -2.198, $P = 0.028$) were lower, while monocyte counts (Z = 2.108, $P = 0.035$) were higher.

Discussion

In this study, a large sample of real-world data was analysed, and sex hormones, stress, and inflammatory markers were compared to explore the biochemical indicators between BPD and MDD. We found that IgA, IgM, neutrophil, and monocyte counts in peripheral blood differed between BPD and MDD. There were also significant differences in clinical features, including age at onset, duration of illness, psychotic symptoms, and number of hospitalisations within five years. These clinical characteristics and IgM and monocyte counts remained

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Table 1 Demographic features and biochemical parameters

Variables	Before matching (*n* = 3782)				After matching (*n* = 2408)			
	MDD (*n* = 2298)	BPD (*n* = 1484)	Z/χ2	*P value	MDD (*n* = 1204)	BPD (*n* = 1204)	Z/χ2	*P value
Age (years)	50 (34, 60)	34 (24, 50)	-17.60	< 0.001	38 (27, 53)	39 (27, 53)	0.652	0.515
Male (%)	716 (31.2)	611 (41.2)	39.71	< 0.001	431 (35.8)	455 (37.8)	1.029	0.310
Alcohol consumption (yes, %)	148 (6.4)	95 (6.4)	0.002	0.124	76(6.31)	86 (7.14)	0.662	0.416
Tobacco use (yes, %)	335 (14.6)	285 (19.2)	14.09	< 0.001	197(16.4)	225 (18.7)	2.253	0.133
Level of education (n, %)			89.63	< 0.001			0.640	0.887
Elementary school or below	261 (11.4)	83 (5.6)			80 (6.6)	78 (6.5)		
Secondary school	584 (25.4)	312 (21.0)			247 (20.5)	258 (21.4)		
High school	942 (41.0)	690 (46.5)			541 (44.9)	547 (45.4)		
University or above	511 (22.2)	399 (26.9)			336 (27.9)	321 (26.7)		
Occupation (n,%)			54.71	< 0.001			1.049	0.790
Students	61 (2.7)	128 (8.6)			59 (4.90)	54 (4.49)		
Farmer/worker	1952 (84.9)	1138 (76.7)			980 (81.3)	990 (82.2)		
Retirement	164 (7.1)	89 (6.0)			80 (6.6)	85 (7.1)		
Unemployed	121 (5.3)	129 (8.7)			85 (7.1)	75 (6.2)		
Marital status (n, %)			219.0	< 0.001			0.221	0.974
Unmarried	478 (20.8)	616 (41.5)			412 (34.2)	405 (33.6)		
Married	1698 (73.9)	759 (51.1)			707 (58.7)	714 (59.3)		
Divorced	78 (3.4)	87 (5.9)			65 (5.4)	63 (5.2)		
Widowed	44 (1.9)	22 (1.5)			20 (1.7)	22 (1.8)		
BMI (kg/m^2)	23.7 (21.0, 26.2)	24.1 (21.2, 27.1)	3.602	< 0.001	23.8 (20.9,26.5)	23.8 (21.1, 26.7)	0.977	0.328
Clinical characteristics								
Age of onset	36 (24, 49)	24 (18, 33)	-17.84	< 0.001	28 (20, 40)	26 (20, 35)	-4.830	**< 0.001**
Duration of illness (years)	8 (3, 16)	8 (4, 15)	1.428	0.153	6 (3,11)	8 (4, 15)	7.327	**< 0.001**
Psychotic symptoms (yes, n.%)	640 (27.9)	632 (42.6)	87.74	< 0.001	351 (29.2)	500 (41.5)	40.35	**< 0.001**
Number of hospitalisations within five years (n.%)	1 (1,2)	2 (1,3)	13.59	< 0.001	1 (1,2)	2 (1,3)	12.29	**< 0.001**
Biochemical parameters								
Testosterone (ng/dL)	43.1 (26.8, 279.9)	59.2 (33.0, 321)	7.405	< 0.001	49.6 (30.9, 320)	53.4 (30.7, 298.0)	0.543	0.587
Oestradiol (pg/mL)	21.1 (9.05, 39.8)	28.4 (16.2, 52.0)	9.530	< 0.001	28.0 (14.4, 54.4)	27.4 (14.9, 54.7)	-0.219	0.827
Progesterone (ng/mL)	0.44 (0.28, 0.75)	0.51 (0.30, 0.91)	4.572	< 0.001	0.49 (0.32, 0.88)	0.50 (0.30, 0.90)	-0.420	0.674
Cortisol (μg/dL)	17.5 (13.5, 21.5)	17.0 (12.9, 21.3)	-1.965	0.049	16.7 (12.9, 20.8)	17.1 (13.3, 21.4)	1.951	0.051
ACTH (pg/mL)	44.1 (28.8, 64.2)	44.0 (29.0, 67.7)	0.527	0.599	43.2 (28.7, 63.4)	43.6 (29.1, 66.8)	0.780	0.435
CRP (mg/dL)	0.21 (0.16, 0.33)	0.21 (0.16, 0.34)	-0.204	0.838	0.21 (0.16, 0.32)	0.21 (0.16,0.33)	-0.242	0.809
C3 (g/L)	0.85 (0.73, 0.98)	0.87 (0.74, 1.02)	3.575	< 0.001	0.85 (0.73, 0.98)	0.85 (0.74, 1.01)	1.338	0.181
C4 (g/L)	0.20 (0.16, 0.24)	0.19 (0.16, 0.24)	-2.085	0.037	0.19 (0.16, 0.24)	0.19 (0.16, 0.24)	-0.671	0.502
IgA (g/L)	2.05 (1.51, 2.73)	1.90 (1.35, 2.53)	-5.386	< 0.001	1.99 (1.50, 2.66)	1.94 (1.40, 2.62)	-2.057	**0.040**
IgM (g/L)	1.00 (0.73, 1.40)	0.99 (0.71, 1.40)	-1.337	0.181	1.04 (0.76, 1.46)	0.98 (0.70, 1.40)	-2.848	**0.004**
IgG (g/L)	11.1 (9.70, 12.7)	11.0 (9.45, 12.5)	-2.603	0.009	11.1 (9.59, 12.7)	11.0 (9.47, 12.50)	-1.223	0.221
Neutrophil count (*10^9/L)	4.56 (3.61, 5.80)	4.78 (3.71, 6.08)	6.232	< 0.001	4.56 (3.60, 5.77)	4.78 (3.66, 6.05)	2.851	**0.004**
Monocyte count (*10^9/L)	0.34 (0.27, 0.43)	0.37 (0.29, 0.47)	6.053	< 0.001	0.35 (0.28, 0.44)	0.36 (0.29, 0.46)	3.030	**0.002**
Lymphocyte count (*10^9/L)	1.72 (1.36, 2.13)	1.84 (1.47, 2.26)	3.550	< 0.001	1.79 (1.43, 2.21)	1.83 (1.44, 2.26)	1.326	0.185

Continuous data are presented as median (lower quartile, upper quartile) and compared using the Kruskal–Wallis H test, and categorical data are indicated by (number/total number) and percentage (%) and compared using the Chi-square test

Abbreviations: *MDD* major depressive disorder, *BPD* bipolar depression, *CRP* C-reactive protein, *ACTH* adrenocorticotropic hormone, *BMI* body mass index, *C3* complement 3, *C4* complement 4, *Ig A* immunoglobulin A, *IgG* immunoglobulin G, *IgM* immunoglobulin M

* Corrected *P* value. [a]s Compared with the depression group, *P* < 0.05;[b] compared with the mania group, *P* < 0.05
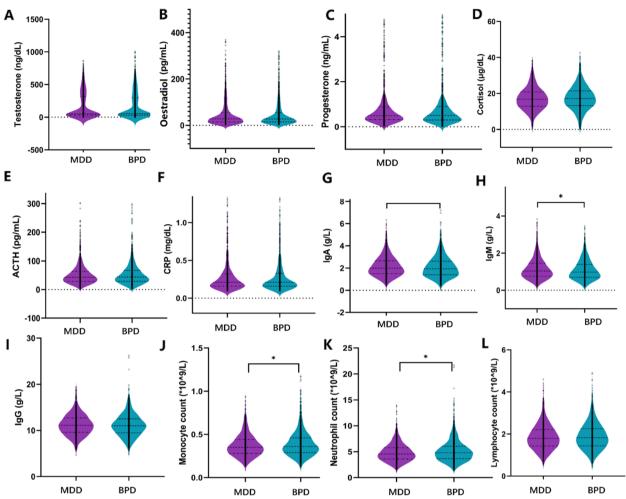
Fig. 1 Serum concentrations of twelve proteins between MDD and BPD. The data is presented in the form of a violin plot. The horizontal lines in the violin plot represents the median, upper quartile, and lower quartile, respectively, and the asterisk means *P* < 0.05. **A** Statistical results of testosterone. **B** Statistical results of estradiol. **C** Statistical results of progesterone. **D** Statistical results of cortisol. **E** Statistical results of ACTH. **F** Statistical results of CRP. **G** Statistical results of IgA. **H** Statistical results of IgM. **I** Statistical results of IgG. **J** Statistical results of monocyte count. **K** Statistical results of Neutrophil count. **L** Statistical results of lymphocyte count. Abbreviations: MDD, major depressive disorder; BPD, bipolar depression; CRP, C-reactive protein; ACTH, adrenocorticotropic hormone; C3, complement 3; C4, complement 4. Ig A, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M

Table 2 Stepwise logistic regression results between MDD and BPD

Variables	B	Standard Error	Wald χ2	*P* value	OR	95%*CI*
Age of onset	-0.017	0.003	25.02	< 0.001	0.983	0.976–0.989
Duration of illness	0.021	0.005	16.12	< 0.001	1.021	1.011–1.031
Psychotic symptoms	0.490	0.091	28.23	< 0.001	1.632	1.365–1.951
Number of hospitalizations within five years	0.333	0.036	82.30	< 0.001	1.395	1.298–1.498
Monocyte count (*10^9/L)	0.901	0.312	8.357	0.004	2.463	1.337–4.538
IgM (g/L)	-0.179	0.077	5.447	0.020	0.836	0.720–0.972
Constant	-0.616	0.221	8.515	0.004	0.540	—

Abbreviations: *MDD* major depressive disorder, *BPD* bipolar depression, *IgM* immunoglobulin M, *OR* odds ratio, *CI* confidence interval

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Table 3 Results of ROC analysis between MDD and BPD

Variables	AUC	Cutoff	SE	*P* value	95% CI^a	Sensitivity	Specificity	LR+	LR-
Age of onset	0.549	30	0.012	<0.001	0.519–0.580	57.72	51.66	1.194	0.818
Duration of illness	0.571	12.5	0.012	<0.001	0.541–0.601	79.65	33.39	1.196	0.610
Number of hospitalizations within five years	0.629	2.0	0.011	<0.001	0.600–0.658	68.77	52.74	1.455	0.592
Monocyte count (*10^9/L)	0.536	0.415	0.012	0.002	0.506–0.566	0.700	0.359	1.092	0.836
IgM (g/L)	0.534	0.845	0.012	0.004	0.503–0.564	39.20	67.86	1.220	0.896
Logistic model	0.677	0.514	0.011	<0.001	0.649–0.705	74.59	52.24	1.541	0.506

Abbreviations: *MDD* major depressive disorder, *BPD* bipolar depression, *AUC* area under the curve, *LR +* positive likelihood ratio, *LR-* negative likelihood ratio

^{a} 95% *CI* for AUC

Table 4 Results of comparisons of biochemical parameters stratified by sex

Groups		Testosterone (ng/dL)	Oestradiol (pg/mL)	Progesterone (ng/mL)	Cortisol (µg/dL)	ACTH (pg/mL)	CRP (mg/dL)	C3 (g/L)
Male	MDD	396.8 (295.5, 512.5)	24.6 (17.2, 32.0)	0.48 (0.33, 0.74)	16.9 (13.4, 20.8)	51.7 (35.7, 74.3)	0.21 (0.16, 0.33)	0.88 (0.76, 1.00)
(*N*=886)	BPD	368.1 (262.4, 508.7)	24.1 (17.5, 32.6)	0.52 (0.31, 0.79)	17.0 (13.2, 21.2)	53.3 (34.8, 77.0)	0.21 (0.17, 0.32)	0.87 (0.75, 1.02)
	Z	-1.729	0.358	1.043	0.63	0.052	0.368	0.128
	P value	0.084	0.721	0.297	0.528	0.958	0.713	0.898
Female	MDD	36.2 (25.6, 47.1)	36.8 (11.3, 86.1)	0.50 (0.31, 1.08)	16.4 (12.5, 20.9)	38.8 (25.8, 57.2)	0.21 (0.15, 0.32)	0.83 (0.72, 0.97)
(*N*=1522)	BPD	35.6 (24.5, 49.3)	34.7 (12.5, 87.1)	0.49 (0.29, 1.09)	17.2(13.3, 21.6)	39.4 (26.5, 59.7)	0.21 (0.15, 0.33)	0.85 (0.72, 1.00)
	Z	0.087	0.039	-1.014	1.926	0.679	-0.599	1.449
	P value	0.931	0.969	0.311	0.054	0.497	0.549	0.147
		C4 (g/L)	IgA (g/L)	IgM (g/L)	IgG (g/L)	Lymphocyte count *10^9/L	Monocyte count *10^9/L	Neutrophil count *10^9/L
Male	MDD	0.20 (0.16, 0.24)	2.03 (1.51, 2.70)	0.84 (0.63, 1.11)	10.8 (9.21, 12.3)	1.78 (1.45, 2.16)	0.36 (0.30, 0.44)	4.70 (3.74, 5.84)
(*N*=886)	BPD	0.19 (0.16, 0.24)	1.87 (1.33, 2.62)	0.80 (0.59, 1.09)	10.3 (8.98, 12.0)	1.92 (1.49, 2.38)	0.38 (0.31, 0.49)	4.95 (3.89, 6.25)
	Z	-0.669	-2.259	-1.025	-2.157	3.023	2.918	2.422
	P value	0.504	0.024	0.305	**0.031**	**0.003**	**0.004**	**0.015**
Female	MDD	0.19 (0.16, 0.24)	1.98 (1.48, 2.64)	1.18 (0.88, 1.61)	11.2 (9.8, 12.8)	1.80 (1.42, 2.24)	0.34 (0.27, 0.43)	4.50 (3.51, 5.71)
(*N*=1522)	BPD	0.19 (0.15, 0.24)	1.97 (1.42, 2.61)	1.12 (0.79, 1.57)	11.2 (9.9, 12.8)	1.78 (1.40, 2.19)	0.35 (0.28, 0.44)	4.70 (3.54, 5.90)
	Z	-0.443	-0.843	-2.681	0.234	-0.67	1.601	1.656
	P value	0.658	0.399	**0.007**	0.815	0.503	0.109	0.098

Abbreviations: *MDD* major depressive disorder, *BPD* bipolar depression, *CRP* C-reactive protein, *ACTH* adrenocorticotropic hormone, *C3* complement 3, *C4* complement 4, *Ig A* immunoglobulin A, *IgG* immunoglobulin G, *IgM* immunoglobulin M

different following stepwise logistic regression analysis after controlling for confounding factors. ROC analysis suggested that the combination of these biological indicators and clinical features could moderately distinguish between BPD and MDD. In addition, there were different biochemical parameters in patients with BPD and MDD of different sexes and ages.

In the present study, we found that patients with BPD had an earlier age of onset compared to those with MDD, consistent with previous findings [4, 6, 32]. Similarly, we also found that patients with BPD experienced a longer duration of illness, consistent with the results of most

studies [4, 7, 33]. In addition, we also found that BPD patients had a higher rate of psychotic symptoms and more hospitalisations within five years, in contrast to MDD patients. These findings were validated in a similar study [34]. Some studies indicate that psychotic symptoms (especially delusion) may have more relevance to bipolar type I depression. Differences in clinical features remained after correcting for confounders using logistic regression. It is suggested that the clinical features of MDD and BPD are worth exploring.

For inflammatory markers in peripheral blood, we found that IgA and IgM levels in peripheral blood were

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Table 5 Results of comparisons of biochemical parameters stratified by age

Groups		Testosterone (ng/dL)	Oestradiol (pg/mL)	Progesterone (ng/mL)	Cortisol (µg/dL)	ACTH (pg/mL)	CRP (mg/dL)	C3 (g/L)
≤ 25 years	MDD	53.1 (36.1, 335.3)	40.9 (27.5, 82.9)	0.60 (0.38, 1.19)	14.2 (10.9, 18.4)	38.4 (26.1, 60.9)	0.19 (0.14, 0.25)	0.82 (0.69, 0.96)
(N = 522)	BPD	65.9 (38.1, 342.0)	42.0 (25.9, 95.1)	0.70 (0.43, 1.28)	16.2 (11.9, 20.9)	40.6 (25.9, 65.2)	0.18 (0.14, 0.24)	0.81 (0.70, 0.95)
	Z	1.466	0.287	1.245	2.933	0.606	-0.465	-1.40
	P value	0.143	0.774	0.213	**0.003**	0.544	0.642	0.888
25 ~ 50 years	MDD	53.4 (34.3, 324.2)	34.4 (21.0, 75.7)	0.57 (0.34, 1.09)	16.5 (13.0, 20.8)	43.5 (29.1, 62.0)	0.21 (0.16, 0.32)	0.85 (0.73, 0.98)
(N = 1149)	BPD	58.1(32.2, 292.5)	33.3 (19.6, 70.8)	0.62 (0.34, 1.12)	17.2 (13.5, 21.2)	42.9 (29.3, 66.6)	0.21 (0.16, 0.34)	0.88 (0.73, 1.03)
	Z	-0.067	-1.243	0.722	1.585	0.411	-0.181	1.703
	P value	0.947	0.214	0.470	0.113	0.681	0.856	0.089
≥ 50 years	MDD	39.5 (23.3, 296.5)	11.4 (5.00, 22.2)	0.38 (0.24, 0.58)	18.3 (14.6, 22.1)	45.1 (30.4, 69.9)	0.24 (0.17, 0.35)	0.88 (0.76, 0.99)
(N = 737)	BPD	42.0 (23.2, 277.5)	13.9 (5.00, 23.3)	0.32 (0.21, 0.51)	17.8 (13.6, 22.6)	45.9 (31.6, 69.2)	0.23 (0.17, 0.35)	0.87 (0.77, 1.01)
	Z	-0.038	1.452	-2.961	-1.298	0.199	-0.109	0.213
	P value	0.970	0.147	**0.003**	0.194	0.842	0.913	0.831
		C4 (g/L)	IgA (g/L)	IgM (g/L)	IgG (g/L)	Lymphocyte count *10^9/L	Monocyte count *10^9/L	Neutrophil count *10^9/L
≤ 25 years	MDD	0.17 (0.14, 0.21)	1.82 (1.40, 2.49)	1.16 (0.88, 1.61)	11.1 (9.46,12.6)	1.90 (1.59, 2.38)	0.35 (0.28, 0.44)	4.29 (3.21, 5.53)
(N = 522)	BPD	0.17 (0.14, 0.21)	1.59 (1.27, 2.26)	1.10 (0.83, 1.56)	10.8 (9.30, 12.1)	1.92 (1.60, 2.36)	0.35 (0.28, 0.47)	4.47 (3.48, 5.76)
	Z	-0.608	-2.815	-1.502	-1.474	-0.042	0.934	1.803
	P value	0.543	**0.005**	0.133	0.141	0.967	0.350	0.071
25 ~ 50 years	MDD	0.19 (0.16, 0.23)	1.99 (1.49, 2.67)	1.07 (0.78, 1.51)	11.0 (9.62, 12.6)	1.84 (1.49, 2.25)	0.36 (0.29, 0.45)	4.64 (3.68, 5.93)
(N = 1149)	BPD	0.19 (0.16, 0.24)	1.94 (1.42, 2.62)	1.03 (0.75, 1.46)	10.9 (9.61, 12.5)	1.85 (1.51, 2.26)	0.37 (0.30, 0.48)	5.02 (3.82, 6.54)
	Z	-0.237	-1.397	-1.438	-0.768	0.424	2.081	3.717
	P value	0.813	0.162	0.150	0.443	0.672	**0.037**	**< 0.001**
≥ 50 years	MDD	0.21 (0.18, 0.25)	2.13 (1.57, 2.71)	0.91 (0.65, 1.21)	11.2 (9.64, 12.8)	1.57 (1.25, 2.02)	0.34 (0.27, 0.42)	4.73 (3.74, 5.83)
(N = 737)	BPD	0.21 (0.17, 0.25)	2.17 (1.46, 2.84)	0.81 (0.60, 1.17)	11.2 (9.56, 12.9)	1.66 (1.31, 2.18)	0.35 (0.28, 0.44)	4.62 (3.61, 5.72)
	Z	-0.771	0.210	-2.198	-0.027	1.942	2.108	-1.181
	P value	0.441	0.834	**0.028**	0.979	0.052	**0.035**	0.238

Abbreviations: *MDD* major depressive disorder, *BPD* bipolar depression, *CRP* C-reactive protein, *ACTH* adrenocorticotropic hormone, *C3* complement 3, *C4* complement 4, *Ig A* immunoglobulin A, *IgG* immunoglobulin G, *IgM* immunoglobulin M

lower in BPD patients than in MDD patients. After correcting for confounders, IgM levels remained the same. To the best of our knowledge, few studies have reported differences in immunoglobulins between BPD and MDD. Some studies have compared the differences in immunoglobulin levels between BPD patients and healthy controls. The current findings are inconsistent [20, 35–37], which may be related to different inclusion criteria and relatively small sample sizes. Nevertheless, a growing number of studies have found that both BPD and MDD are associated with underlying infections and oxidative stress [38, 39]. The differences in IgA and IgM levels, which are important components of humoral immunity, suggest that different patterns of humoral immunity may exist between BPD and MDD. In addition, our follow-up analysis revealed that a difference in IgM levels was mainly observed in female patients. Earlier studies revealed that IgM levels were higher in female patients than in male patients in both bipolar and unipolar depressive groups [20]. Unfortunately, this study did not

directly compare the two groups. Nonetheless, this finding suggests that identifying both complex psychiatric disorders requires more refined subgroups.

For peripheral blood leukocyte counts, we found that neutrophil and monocyte counts differed between BPD and MDD, whereas lymphocytes did not. After correcting for confounders, the monocyte counts still differed. A previous cross-sectional study found no difference in neutrophil, lymphocyte, and monocyte counts between BPD (*n* = 40) and MDD (*n* = 36) [40]. However, Dionisie et al. [41] found differences in neutrophil and lymphocyte counts between BPD (*n* = 34) and MDD (*n* = 83) but not in monocytes. It is important to note that both similar studies had small sample sizes, which may have contributed to the inconsistent results. Fang et al. [33, 42] analysed the differences in peripheral blood tests between bipolar disorder and MDD in different age groups using real-world data. They found significant differences in neutrophil counts between the two groups in patients aged 16–55 years, while no differences were

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found in adolescent patients. This suggests that the age of the subjects also significantly influenced the outcome. In our subsequent comparisons stratified by age, we found similar age-related differences. In addition, no differences in CRP levels between BPD and MDD patients were observed in this study. Although we performed separate stratification tests by age and sex, we still did not observe any differences between the groups. A cross-sectional study aimed at examining differences in CRP levels among patients with acute episodes of MDD ($n=319$), schizophrenia ($n=458$), BPD ($n=114$), and bipolar mania ($n=32$) did not find significant differences between the groups [43]. However, another study concluded that the CRP level may be a biomarker to differentiate between MDD and BPD [44]. Moreover, CRP has been found to correlate with mood state and severity of illness [15, 45], which may partly account for the inconsistent results.

In the neuroendocrine system, we focused on the differences in the related molecules of the HPA and hypothalamic-pituitary–gonadal (HPG) axes in peripheral blood between BPD and MDD. However, we did not identify any statistically significant differences. For cortisol levels, BPD showed an upregulation trend compared to MDD ($P=0.051$), with stratified comparisons suggesting that the difference was mainly observed in patients younger than 25 years old. Elevated cortisol levels are among the most robust pathophysiological findings in mood disorders [23, 46, 47]. All patients included in this study were in the acute phase of depressive episodes, and cortisol and ACTH levels may be abnormal in both groups; however, this may not be a potential biological marker to distinguish BPD from MDD. In addition, higher levels of cortisol were found in patients with psychotic symptoms [48], and patients with BPD in this study were more prone to psychotic symptoms, which may further explain the elevated cortisol levels compared to those in the MDD group.

For gonadal hormone profiles, we only found a significantly higher progesterone level in MDD patients aged ≥ 50 years compared to those with BPD. Similar studies have found differences in oestradiol and testosterone levels between patients with bipolar disorder and MDD using real-world data, but no difference in progesterone [32]. This difference seems to be related to age [42]. The main reason for this inconsistency is related to the fact that the study included all patients with bipolar disorder, including manic episodes. Previous studies have reported lower peripheral testosterone levels during depression, and higher testosterone levels during the manic phase [49, 50], increased progesterone levels in manic episodes in contrast to controls [51]. Furthermore, the HPA axis is involved in complex interactions with the HPG axis [47]. Briefly, testosterone inhibits the responsiveness of the HPA axis in relation to peripheral stress; conversely, stress exposure inhibits gonadotropin release, which leads to the suppression of oestrogen and testosterone production [52–54].

The accuracy of the above individual indicators as biomarkers for differentiating BPD from MDD is relatively low. Given that both bipolar disorder and depressive disorder are complex disorders, combining multiple biological indicators for analysis is more effective, and this study also found that combining multiple indicators can improve the accuracy of diagnosis. In this study, the age of onset, duration of illness, number of hospitalisations within five years, monocyte count, and IgM level were used as joint predictors, resulting in an ROC analysis with an AUC of 0.677. This value was higher than that of other single indicators (the AUC ranged from 0.534 to 0.629) and exhibited greater accuracy in predicting BPD. As a comparison, this AUC was similar to that of a proteomic profile outcome predictor model, which was 0.67 [55]. Nevertheless, the accuracy of the diagnostic model established in this study is still modest, which is lower than that based on plasma lipidomic results to distinguish BPD from MDD in women [56]. Hence, more biomarkers need to be explored in future studies to improve the accuracy of the diagnostic model.

This study had some limitations. First, since BPD and MDD have similar clinical presentations, we only included patients with recurrent depressive disorder to avoid misdiagnosis of BPD as MDD. However, the downside of this study is that these patients may have been in treatment prior which may have affected some indicators. Secondly, since the electronic medical record system of psychiatric hospitals does not include data from healthy individuals, we were unable to establish a healthy control group in this study. However, previous studies demonstrated that the biological indicators selected for this study are disease specific when they were compared with healthy controls [15, 37, 54, 57–59]. Therefore, although our investigation suggested significant differences in clinical characteristics and the levels of some hormonal and inflammatory markers between MDD and BPD patients, including healthy controls would promote our ability to evaluate the specificity of the identified biomarkers for further clinical application. Furthermore, since retrospective data analysis may introduce biases and limit causal inference compared to prospective studies, relying on previously collected data in this study may inadvertently influence confounding factors, thereby compromising the validity and reliability of the results. Therefore, in future research, more supplementation with prospective studies is particularly important to enhance our understanding of these biomarkers.

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Conclusion

This study found that MDD and BPD patients had significant differences in clinical characteristics and the levels of some hormonal and inflammatory markers, which were demonstrated across sexes and ages. We established a diagnostic model that integrated clinical features and biochemical indicators with moderate accuracy. Additional biomarkers and follow-up should be included in future studies.

Abbreviations

BPD	Bipolar disorder
MDD	Major depressive disorder
PSM	Propensity score matching
CRP	C-reactive protein
BMI	Body mass index
C3	Complement 3
C4	Complement 4
ACTH	Adrenocorticotropic hormone
ROC	A receiver operating characteristic curve
HPA	Hypothalamic-pituitary-adrenal axis
HPG	Hypothalamic-pituitary–gonadal axis
ICD-10	International Statistical Classification of Diseases and Related Health Problems-10th revision

Authors' contributions
RL and LZ conceived and designed the study. NL, HW, QZ performed the data analysis. NL, HW and ZY contributed to manuscript preparation, ZQ interpretated the results. FB, JL, JH, FY and HL helped collect data and organize data. All the authors reviewed and approved the final version of the manuscript.

Availability of data and materials
The datasets generated and analyzed during the current study are not publicly available due to ethical restrictions and personal data protection, but are available from the corresponding authors Rena Li and Ling Zhang on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Beijing Anding Hospital Capital Medical University. All methods were performed in accordance with the Declaration of Helsinki and the relevant guidelines. The requirement for informed consent was exempted by the Ethics Committee of Beijing Anding Hospital Capital Medical University, owing to the use of anonymous and de-identified data of medical database of Beijing Anding Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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