The Serum Uric Acid Level of Bipolar Depression: A Retrospective Real-World Study

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Abstract

Objective

The aim of this study was to evaluate whether serum uric acid can be used as a biomarker to identify bipolar disorder (BD) from unipolar depression (UD).

Methods

We reviewed the medical records of 18-65-year-old depressive patients hospitalized in the first hospital of Shanxi Medical University from October 2015 to October 2020. The main discharge diagnosis of these patients was recurrent depressive disorder(RDD) or BD. The data of gender, age, education level, drug use and serum uric acid level were extracted. The differences of uric acid levels between the two groups at admission and discharge were compared.

Results

The uric acid level of BD decreased after treatment, the uric acid level of BD group was significantly higher than that of UD group at baseline (P=0.02) and after treatment (P=0.025).

Conclusion

UA may be a potential biomarker to distinguish BD from UD.

Introduction

Depression is charactered by depressed mood, loss of interest and lack of energy, with a high prevalence and a recurrent or chronic course[1, 2]. The high prevalence and the associated functional impairment make depression the third major cause of disease burden around the world[3, 4]. Both bipolar disorder (BD) and major depressive disorder (MDD) suffer from depressive mood. BD is defined by mood fluctuations that range from mania or hypomania to depression and periods of euthymia, while MDD patients experience only depressive episodes[1]. Patients with BD are named bipolar depression (BD) when patients are in depression mood, while patients with MDD are suffering depression are named unipolar depression (UD). It is challenging to makes diferential diagnosis of BD or UD in clinical practice. About 60% of individuals with BD are initially diagnosed with UD[5]. This is likely due to earlier onset of depression than hypomania/mania[6, 7]. In the diagnosis of depressive disorder, some first-episode patients are only in transient depressive state (TDS). Depression and depressive state adopt different treatment principles. Due to similar symptoms at the time of attack, it is difficult to distinguish them in clinical diagnosis[8].Therefore, the use of patients with recurrent depressive disorder in the study can avoid the inclusion of patients with TDS to a certain extent.

BD and UD adopt different treatment strategies. Inappropriate drug treatment will increase the risk of suicide and self injury, resulting in deterioration of symptom function and poor prognosis[9–11]. At present, only symptom oriented diagnostic strategies are not enough to support the identification of BD patients with depression as the first feature. Therefore, objective diagnostic biomarkers are needed.

Observations and clinical studies confirm the existence of differences between unipolar and bipolar depression on several levels: age of onset, relapse, family burden[12, 13], or temperamental traits[14]. MRI neuroimaging also confirms that there are differences between the types of depression in terms of activation patterns in neural networks, including the amygdala, anterior cingulate gyrus (ACC), prefrontal cortex (PFC), and striatum during emotional, reward, or cognitive functions[15–17]. However, the cost and availability of the test limit its use in routine differential diagnoses.

Peripheral blood has been the focus of biomarker research because of its easy access, quantifiable and economic characteristics. Previous studies have shown that patients with BD and UD have different inflammatory characteristics, metabolic biomarkers and oxidative stress markers in peripheral blood[18–21].In addition, the decrease of bilirubin level in MDD and the increase of serum lactic acid level in BD are also clues for differential diagnosis[22, 23].Uric acid is the final product of purine metabolism and is produced by xanthine dehydrogenase. The increase of uric acid level is related to the accelerated transformation of purine and the decrease of adenosine transmission[24].There is research evidence that the damage of purinergic system plays a certain role in the pathophysiology of mood disorders, namely BD and UD[25].Previous studies reported different results about the uric acid level in patients with UD and BD.The results of a meta-analysis showed that uric acid levels in patients with MDD were significantly lower than those in healthy controls[26].A cross-sectional control study found that there was no difference in serum UA between patients with bipolar depression and patients with MDD[27], but the results of Wen et al[28] were inconsistent with this. This may be related to age, gender, course of disease and whether to drink.We hypothesized that serum uric acid may be used as a biomarker to identify BD from UD, the uric acid level may be higher in the BD compared to the UD group

Methods

Participants

Participants diagnosed with MDD using DSM-IV-TR were included in psychiatric inpatients in a tertiary hospital in Taiyuan, Shanxi Province, China. The inclusion criteria consisted of: (1) age: between 18 and 65 years old; (2) Hamilton Depression Rating Scale (HDRS) score >14. The exclusion criteria consisted of: (1) any history of neurological diseases, other physical diseases and presence of comorbidities of other disorders; (2) any other mental disorders, e.g., schizophrenia, schizoaffective disorder, substance use disorder, OCD, panic disorder, generalized anxiety disorder, social phobia, post-traumatic stress disorder, Axis II personality disorders, or mental retardation; (3) Pregnancy or breastfeeding. Axis II personality disorders were excluded by using Structured Clinical Interview for DSM-IV and Axis II Personality Disorders (SCID-II) Interview. This study screened the cases in the hospital from October 2015 to October

2020, of which 1391 were diagnosed as MDD, 1088 of them aged 18-65, 362of them were diagnosed with UD and 169 of them were diagnosed with BD. 229 subjects were excluded because of lack of information on UA serum levels and HAMD score.Thus, we included for analyses 302 subjects, 142 with BD and 160 with MDD.See Figure 1.The general demographic information collected includes gender, age, years of education, age of first onset, etc.

For each patient, the drug treatment regimen is divided into mood stabilizer, antipsychotics or antidepressants. The mood stabilizer agents were lithium, valproate, lamotrigine, e.The antipsychotic agents were risperidone, aripiprazole, clozapine, olanzapine, quetiapine, paliperidone, and amisulpride. The antidepressant agents were vortioxetine, ,escitalopram, sertraline, fluoxetine, desvenlafaxine, venlafaxine, paroxetine, duloxetine, trazodone, ,mirtazapine, and fluvoxamine.

Clinical Assessment

24-item Hamilton Depression Rating Scale (HDRS) is used to assess the severity of depresssive symptoms (22), assessed by the psychologist in hospital. The HAMD scale is divided into seven structural parts: anxiety/somatization (items 10–12, 15, 17,20), cognitive disturbance (items 2, 3, 9,19-21), psychomotor retardation (items 1, 7, 8, 14), sleep disturbance (items 4–6), weight loss (item 16), diurnal variation (item 18), and hopelessness (22-24).

Assessing serum UA

Serum UA was measured during routine and standard blood examination of hospitalized patients, and measured by uricase colorimetry.

Data analysis

All the data were analyzed with SPSS Statistics for Windows (version 21.0; IBM, Armonk, NY). For the characteristics of the study sample, measurement data were described as means ± standard deviations (SD) and count data were described in numbers of cases (%). Sociodemographics, clinical characteristics, serum uric acid, HAMD scores were compared using two independant sample t-test and the chi-squared test. Changes in serum uric acid at different timepoints were analyzed by paired T-test.

Results

Sociodemographics, clinical characteristics

There was no significant difference in age, sex, first-episode age and educatioal years between UD group and BD group. There was no significant difference in the total score of HAMD on admission and between the two groups (P>0.05). The total score of HAMD at discharge in BD group was higher than that in UD group. See Table 1.

Table 1
Demographic and clinical characteristics of the sample

		UD group (n=160)	BD group (n=142)	T/χ^2	*P*
Demographic data	age (year)	40.34±11.582	38.04±14.576	-1.527	0.128
	Gender (male/female)	76/84	73/69	0.46	0.564
	Education level	12.43±4.099	12.77±3.604	0.746	0.456
	age of onset	31.33±11.205	31.13±13.583	-0.138	0.890
	Marriage (a/b/c/d/e)	27/129/0/2/2	49/88/4/1	14.092	0.003
HAMD Total score	(on admission)	22.40±6.562	22.04±7.860	-0.426	0.671
HAMD Total score	(at discharge)	8.37±5.007	10.51±5.865	3.323	0.001

P < 0.05 are marked in bold,UD :unipolar depression, BD : bipolar disorder,Marriage a/b/c/d/e:Unmarried / married / separated / divorced / widowed,HAMD: Hamilton Depression Rating Scale

The comparision of serum uric acid between bipolar and unipolar depression.

The level of uric acid in BD group was higher than that in UD group at admission (307.30±88.92 mg/dL.vs.333.19±103.99 mg/dL, p=0.02) and discharge (295.92±90.6234 vs. 320.52±88.40 mg/dL, P=0.025). See Table 2.Figure 2

Table 2
The difference of serum uric acid between the UD and BD groups

	UD group (n=160)	BD group (n=142)	*t*	*P*
uric acid (mg/dL) (on admission)	307.30±88.919	333.19±103.989	2.332	0.02
uric acid(mg/dL) (at discharge)	295.915±90.6234	320.516±88.4049	2.254	0.025
P < 0.05 are marked in bold				

The comparison of serum uric acid before and after treatment in the bipolar depression and unipolar depression.

Both the uric acid level of BD group (332.87±103.69 mg/dL vs. 320.52±88.40 mg/dL, P=0.019) and UD group (306.65±88.29 mg/dL vs. 295.49±90.56 mg/dL, P=0.019 was lower when discharged than at admission. See Table 3.Figure 3

Table 3
The level of serum uric acid before and after treatment in the BD group

		Before treatment	After treatment	*t*	*P*
uric acid (mg/dL)	BD group (n=142)	332.87±103.694	320.516±88.4049	2.373	0.019
uric acid (mg/dL)	UD group (n=160)	306.65±88.286	295.49±90.556	2.383	0.019
P < 0.05 are marked in bold					

Discussion

This is a retrospective real-world study. Patients aged 18-65 with RDD and BD depressive episodes were selected. Our results showed that the level of uric acid in BD group was higher than that in UD group both at admission and discharge. The uric acid level in BD group decreased after treatment. This suggests that uric acid may be a biomarker for the differential diagnosis of BD and MDD.

The results of this study are basically consistent with previous studies. A case-control cross-sectional study by Albert compared the uric acid levels in different stages of BD (mania, euthymia and bipolar

depression) found no difference, but compared with the age and gender matched control group, it was found that the uric acid levels in BD group were higher than those in Major Depressive Disorder (MDD), Obsessive–Compulsive Disorder (OCD), and Schizophrenia[27].A retrospective study found that uric acid levels with mood stabilizers and antipsychotics were higher than those without these drugs, and there was no difference in uric acid levels with or without antidepressants[28].Another cross-sectional retrospective real-world study found that uric acid levels in the BD group were higher than those in the MDD group in adolescents aged 10-18[29].A 10-year follow-up found that MDD patients with higher uric acid levels had a higher risk of subsequent manic episodes[30].The results of a meta-analysis showed that uric acid levels in BD patients with manic episodes were higher than those in BD patients with depressive episodes[31].

A systematic review pointed out that uric acid level may be a potential biomarker of aggressive behavior in patients with BD[32].Irritability is the core symptom of BD patients.Liu's study on Chinese Han population shows that the uric acid level of BD patients is higher than that of healthy controls matched with their age and gender[33].Elif Tatlıdil Yaylacı found that the uric acid level of BD type I remission was higher than that of RDD remission and HC group, and the uric acid level of RDD group was lower than that of HC group[14].Our results show that the level of uric acid in BD group is still higher than that in RDD group at the time of depression, which plays a supplementary role in the above research and provides evidence for UA as a biomarker for the differential diagnosis of BD.

Limitations

Our study has some limitations: firstly, we only compared BD group and UD group without matched healthy control group and the exact scope. In the future, we need to build a prediction model. Secondly,. uric acid is affected by many factors, such as diet and inflammation. This study did not control the effects of these unrelated factors. Thirdly, the sample size of this study is small, however, this is a real-world study.

Conclusion

In conclusion, although the uric acid level of BD decreased after treatment, the uric acid level of BD group was significantly higher than that of UD group before and after treatment. This suggests that UA may be a potential biomarker to distinguish BD from UD.

Abbreviations

BD: bipolar disorder; UD: unipolar depression ; RDD: recurrent depressive disorder ;TDS: transient depressive state ;MRI: magnetic resonance imaging ;ACC: anterior cingulate gyrus;PFC: prefrontal cortex;UA: uric acid;DSM-IV-TR：American Diagnostic and Statistical Manual of mental disorders, Fourth Edition, Revised Edition;HDRS：Hamilton Depression Rating Scale;OCD: Obsessive compulsive disorder;HAMD: Hamilton Depression Scale;HC:Healthy control

Declarations

Acknowledgements

Not applicable.

Authors' contributions

Dr Li and Huishan Liu contributed equally to the current work. Lei Lei□Xuemin Zhang□Mingxue Gao□ Hongwei TU and Yu Zhang finished the data collection. All authors read and approved the final manuscript.

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Availability of data and materials

The data used to support the findings of this study are included within the article.

Ethics approval and consent to participate

Written informed consent was obtained from all individuals. This study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University and was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

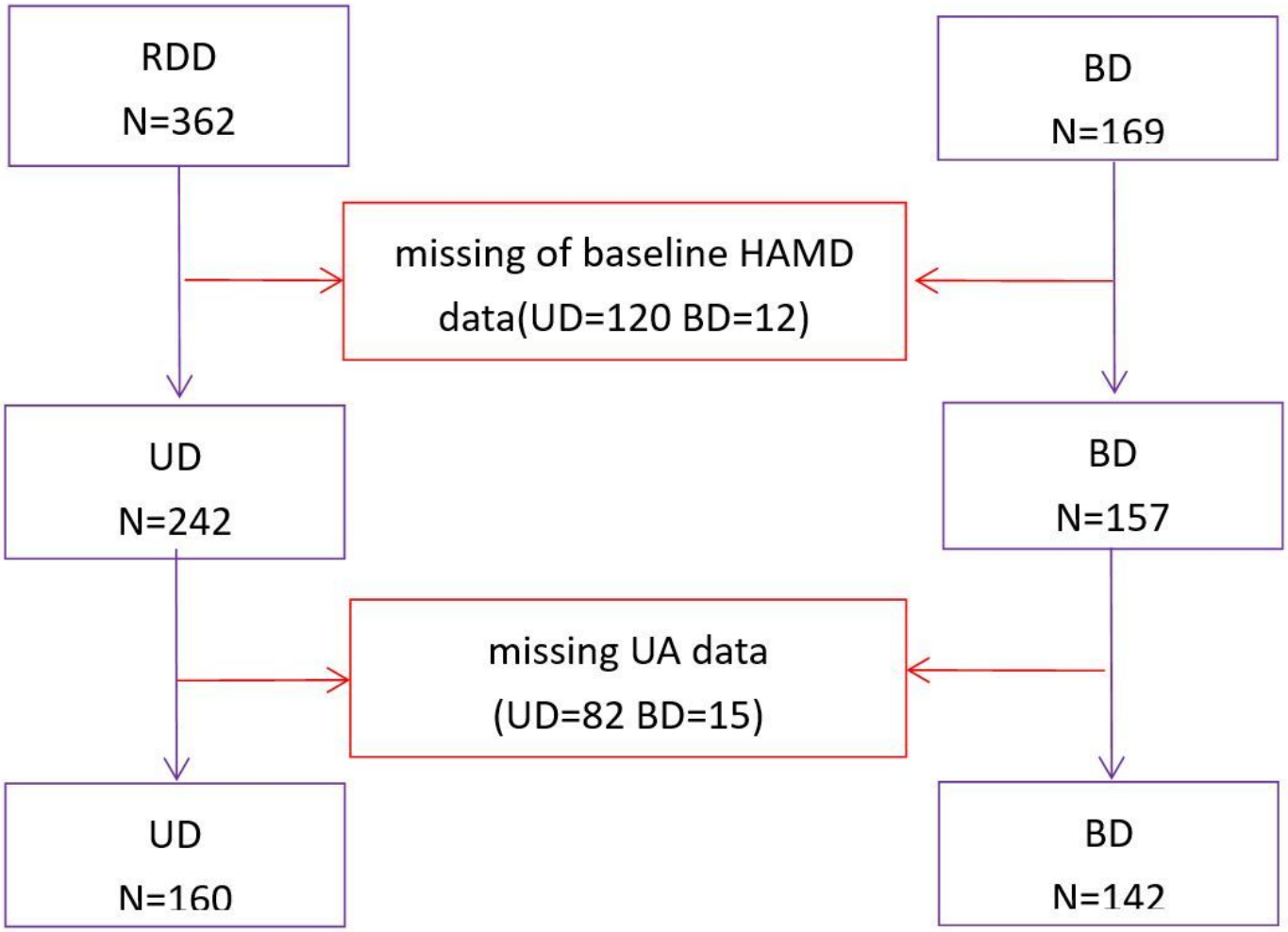

Figure 1

Flowchart of sample selection.

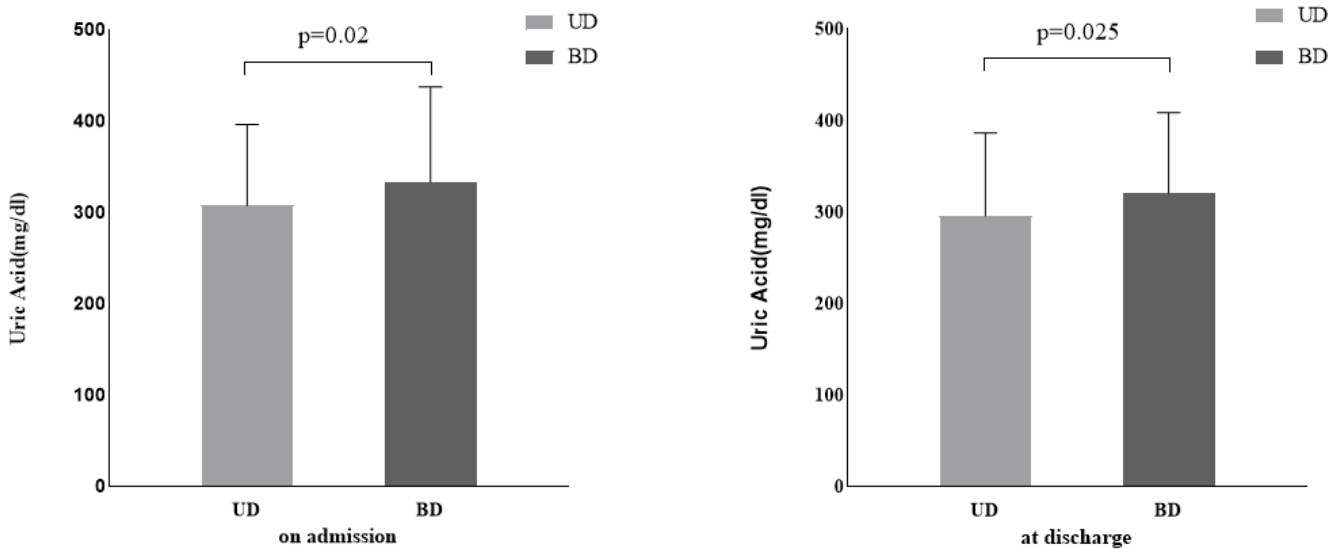

Figure 2

Comparison of mean uric acid between UD group and BD group at admission and discharge.

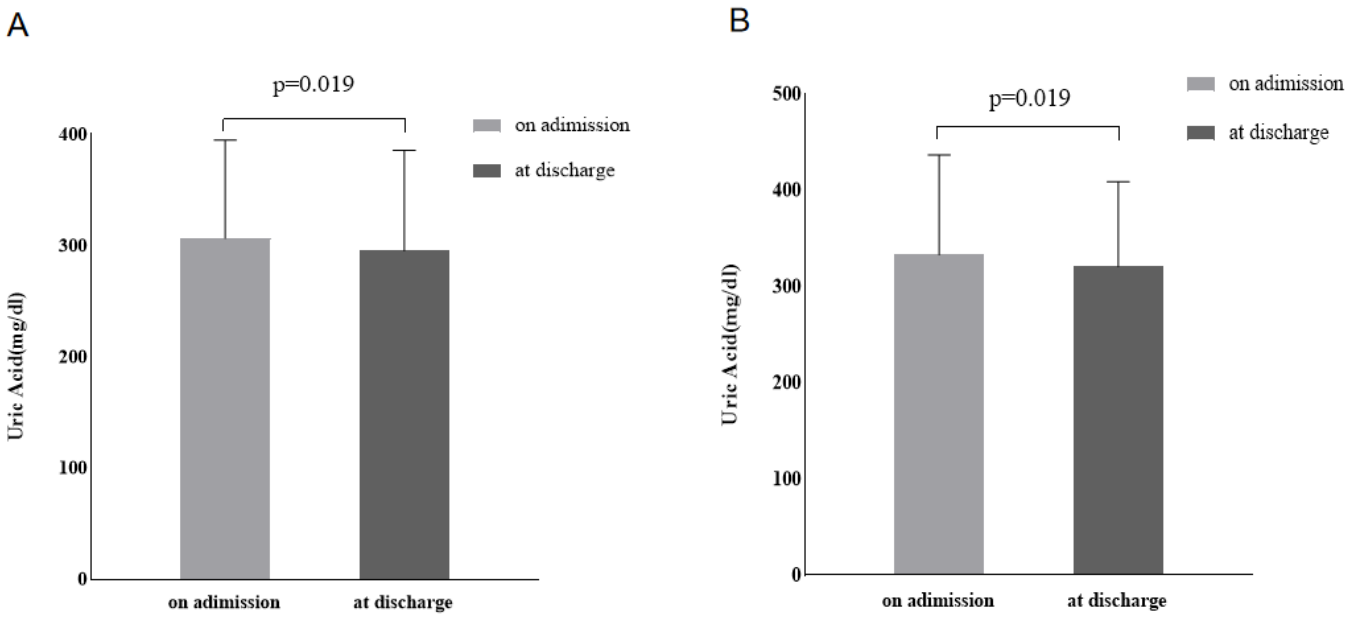

Figure 3

The level of serum uric acid before and after treatment in the BD and UD group A:UD,B:BD