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Comparison of Clinical Features, Serum Lipid, and Uric Acid Levels in Patients with Unipolar Depression and Bipolar Depression

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ABSTRACT

Background: The level of uric acid and serum lipids has been suggested as a possible biomarker of bipolar disorder. We aimed to investigate the differences in clinical features and serum levels of lipids and uric acid in patients with bipolar depression or unipolar depression in order to distinguish them.

Methods: The clinical data of 53 patients with unipolar depression (unipolar group) and 61 patients with bipolar depression (bipolar group), who all met the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV of the American Psychiatric Association, were compared with each other retrospectively. The serum levels of uric acid and lipids (including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides) were measured after hospital admission. The Statistical Package for the Social Science version 22.0 software was used for statistical analysis, and logistic regression was employed to identify the susceptible factors of bipolar depression.

Results: Taking into account confounding factors, logistic regression analysis revealed that the high levels of uric acid (odds ratio=1.016, P=.001) and low levels of triglycerides (odds ratio=0.457, P=.025) were significantly correlated with bipolar depression.

Conclusion: It has been demonstrated from this study that individuals with bipolar depression have higher serum uric acid levels and lower triglyceride levels than unipolar depression ones. Therefore, serum levels of uric acid and triglycerides might have the potential to be the biomarkers for differential diagnosis between bipolar and unipolar depression.

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INTRODUCTION

A depressive episode is characterized mainly by persistent depression, lack of interest, and decreased energy. According to the absence or presence of manic/hypomanic episodes, it can be divided into unipolar depression and bipolar depression. The first onset of bipolar disorder is mostly in the depressive phase, and depression takes up a large proportion of the unpredictable and relapsing course throughout the life span, with patients presenting with manic/hypomanic episodes after many years of treatment.[1,2] Because of the highly similar manifestations between unipolar and bipolar depression and the fact that there are no specific biological markers available at present, misdiagnosis or missed diagnosis may occur, ultimately resulting in both inappropriate and inadequate treatment, such as monotherapies with antidepressants. This would greatly increase the risk of patients' symptoms turning to manic episodes, rapid cycling, or mixed episodes and cause delayed treatment and even detrimental prognosis of the patients.[3,4] It has been found that the levels of serum uric acid (UA) in manic episodes, depressive episodes, and the remission stage of patients with bipolar disorder are markedly higher than those of healthy populations, indicating that serum UA levels may become one of the biomarkers of bipolar disorders.[5] Therefore, serum UA level monitoring may provide a basis for distinguishing unipolar depression from bipolar depression. Furthermore, a domestic meta-analysis suggested that serum lipid levels are negatively correlated with suicide rates; for instance, the serum levels of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, and triglycerides are correlated with patients with suicidal tendencies (including depressive episodes) in that their levels are all lower than those who were without suicidal tendencies.[6] Other studies have shown that there

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is state-dependent lipid metabolism in different polarities of patients with bipolar disorder (mania and depression) and unipolar depression; for example, the levels of TC and triglycerides in patients with acute bipolar mania are significantly lower than those of any other mood state. Moreover, typically, cholesterol metabolism may be easily influenced by polarities and severity of affective symptoms, which suggested that the concentration of serum lipids is tightly associated with unipolar and bipolar disorders.[7] Based on the reports mentioned above, in this study, we aimed to investigate potential new biomarkers to distinguish bipolar and unipolar depressions and to discuss both the clinical and laboratory significance of serum levels of UA and lipids in the diagnosis of bipolar disorders.

MATERIAL AND METHODS

Participants

This study was approved by the Institutional Review Boards of the First Affiliated Hospital of Kunming Medical University: 2019 clinical ethical review No. 09-201936FS-2.

Each patient was diagnosed initially by at least 1 psychiatrist at the deputy director level. Two research doctors under consistent training were responsible for determining the patients' exclusion (for patients with other mental disorders or somatic diseases) and patient screening by using the MINI International Neuropsychiatric Interview and the Hamilton Depression Scale (HAMD), the Hamilton Anxiety Scale, and the Young Manic Rating Scale (YMRS) to evaluate the symptoms of the patients enrolled (based on patients' performance over the past 7 days).

A total of 114 inpatients in the First Affiliated Hospital of Kunming Medical University from April 2019 to January 2020 were selected, which include unipolar (n = 53) and bipolar (n = 61) groups.

Patients in the bipolar group who met the following criteria were enrolled in this study: (1) diagnosed as bipolar depression according to Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV); (2) age between 18 and 65 years, regardless of gender; (3) Chinese, irrespective of nationality; (4) total scores of HAMD $\geq$ 17 points; screening positive using the Mood Disorder Questionnaire (MDQ) or the Hypomania/Mania Symptom Checklist (HCL-32); and (5) provided written informed consent signed by all the subjects.

Patients in the unipolar group who met the following criteria were included in this study: (1) diagnosed as unipolar depression according to DSM-IV; (2) age between 18 and 65 years, regardless of gender; (3) Chinese, irrespective of nationality; (4) the total scores of HAMD $\geq$ 17 points; the scores of YMRS $\leq$ 8 points; MDQ or HCL-32 screening negative; and (5) provided written informed consent signed by all the subjects.

The exclusion criteria included: (1) any one of the following primary or comorbid diagnosis based on DSM-IV: organic mental disorder, dementia, schizophrenia, delusional disorder or schizoaffective disorder, and drug or alcohol abuse/dependence; (2) patients with severe somatic diseases associated with lipid and UA elevation, such as liver disorders, diabetes, autoimmune disorders, hypertension, and thyroid disorders; (3) patients on medication that would affect serum lipids and UA, such as corticosteroids and anti-inflammatory drugs; (4) pregnancy; (5) electroconvulsive therapy within 3 months before joining the group; and (6) those who could not cooperate or complete the test themselves.

Methods

The total scores of HAMD-17 were used to assess the severity of depressive symptoms, with MDQ or HCL-32 used to evaluate the past manic or hypomanic episodes. The general demographic data, such as age, gender, body mass index (BMI), course of the disease, family history, pre-disease psychosocial factors, clinical presentation, and medication usage (including the use of second-generation antipsychotics, mood stabilizers, and antidepressants), were collected. Fasting blood samples from patients were collected between 7:00 and 10:00 AM to detect the concentration of serum triglycerides, TC, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, and uric acid.

Statistical Analysis

All data were analyzed with Statistical Package for the Social Science version 22 (IBM SPSS Corp., Armonk, NY, USA) statistical software (IBM SPSS Corp., Armonk, NY, USA). Data were tested for normality by using the Kolmogorov–Smirnov test and Levene's test to decide if equal variances could be assumed between 2 groups. For normal distribution data, such as age, HAMD-17 total scores, TC, BMI, HDL cholesterol, and serum UA, the *t*-test was used to compare between the unipolar group and bipolar group, expressed as mean $\pm$ SD. For data not distributed normally, including triglycerides and LDL cholesterol, the Mann–Whitney *U* test was used, expressed as [median (lower quartile, upper quartile)]. The difference between proportions (sex, history of multiple

MAIN POINTS

- We discussed the differences in clinical manifestations between unipolar and bipolar depression and studied the differences in serum levels of uric acid and lipids.
- The serum uric acid and triglyceride levels may be independently related factors for bipolar depression.
- The serum levels of uric acid and lipids may be potential predictors of bipolar disorder.

depressive episodes, agitation, antipsychotic use, and mood stabilizer use) was analyzed with the Pearson's chi-square test. Given that drug administration may affect the serum UA and lipid levels, confounding variables in medication users and non-user groups were selected with the independent *t*-test. Multinomial logistic regression analysis was carried out for the analysis of the levels of serum UA and lipids, with sex, BMI, and the confounding factors as covariates. Odds ratios (ORs) with 95% CI were calculated using logistic regression to analyze the independent risk factors for bipolar depression. A level of $P < .05$ was considered as statistically significant.

RESULTS

Demographic and clinical data are shown in Table 1.

The mean age (mean ± SD) in the 2 groups was: bipolar group 27.38 ± 9.72 years and unipolar group 42.40 ± 9.88 years. It was shown that the age in the bipolar group was lower than that in the unipolar one, and the difference was significant ($t = 8.167$, $P < .001$). The proportion of frequency of depression in the bipolar group (n = 32, 52.46%) was substantially higher than the unipolar group (n = 15, 28.30%), showing a significant difference ($\chi^2 = 6.830$, $P = .009$). Moreover, the total scores of HAMD in the bipolar group were markedly lower than those in the unipolar one (22.98 ± 4.66 points vs. 25.25 ± 4.73 points, $t = 2.565$, $P = .012$). The patients with bipolar depression used more antipsychotics compared with the unipolar depression patients (n = 56, 91.80% vs. n = 23, 43.40%, $\chi^2 = 31.234$, $P < .001$). The rate of mood stabilizer use in the bipolar group (n = 48, 78.69%) was significantly higher than that in the unipolar group (n = 21, 39.62%) ($\chi^2 = 18.115$, $P < .001$). The TC levels in patients with bipolar depression were markedly lower than those of patients with unipolar depression (3.98 ± 0.98 mmol/L vs. 4.45 ± 1.01 mmol/L, $t = 2.496$, $P = .014$). The concentration of serum UA in the bipolar group was remarkably higher than that in the unipolar group (366.35 ± 88.46 μmol/L vs. 300.69 ± 88.68 μmol/L, $t = -3.902$, $P < .001$). No significant difference was found in sex ($P = .507$), agitation symptoms ($P = .136$), BMI ($P = .374$), the levels of triglycerides ($P = .205$), HDL cholesterol ($P = .057$), and LDL cholesterol ($P = .065$) between the 2 groups.

Independent *t*-tests were performed on serum levels of UA and lipids of medication users and non-users. The specific values are presented in Tables 2 and 3. Serum UA levels were significantly higher in patients using mood stabilizers than those not using these drugs (349.54 ± 107.64 μmol/L vs. 313.66 ± 65.15 μmol/L, $t = 2.184$, $P = .031$). In the antidepressant group, the UA levels of the user group were lower than those of the non-users (327.63 ± 91.39 μmol/L vs. 386.03 ± 100.28 μmol/L, $t = -2.208$, $P = .029$). In the antipsychotics group, there was no difference in UA levels in the 3 kinds of drug user groups relative to those of the non-user groups. Therefore, we confirmed that mood stabilizer and antidepressant administration may be relevant confounding variables.

Table 1. Comparison of Clinical Characteristics Between the 2 Groups

Clinical Features	Bipolar Depression (n = 61)	Unipolar Depression (n = 53)	$t/z/x^2$	*P*
Sex (%)				
Male	25 (40.98)	25 (47.17)	0.441[c]	.507
Female	36 (59.02)	28 (52.83)		
Age (years)	27.38 ± 9.72	42.40 ± 9.88	8.167[a]	<.001
Multiple depressive episodes (%)				
Yes	32 (52.46)	15 (28.30)	6.830[c]	.009
No	29 (47.54)	38 (71.70)		
Agitation symptoms (%)				
Yes	26 (42.62)	30 (56.60)	2.218[c]	.136
No	35 (57.38)	23 (43.40)		
BMI	23.49 ± 4.39	22.84 ± 3.21	-0.893[a]	.374
Total score of HAMD (points)	22.98 ± 4.66	25.25 ± 4.73	2.565[a]	.012
Antipsychotic use (%)				
Yes	56 (91.80)	23 (43.40)	31.234[c]	<.001
No	5 (8.20)	30 (56.60)		
Mood stabilizer use (%)				
Yes	48 (78.69)	21 (39.62)	18.115[c]	<.001
No	13 (21.31)	32 (60.38)		
TC (mmol/L)	3.98 ± 0.98	4.45 ± 1.01	2.496[a]	.014
Triglycerides (mmol/L)	1.26 (0.85, 1.74)	1.34 (0.99, 1.77)	-1.268[b]	.205
LDL-C (mmol/L)	2.45 (1.99, 2.95)	2.76 (2.14, 3.30)	-1.847[b]	.065
HDL-C (mmol/L)	1.16 ± 0.36	1.28 ± 0.32	1.927[a]	.057
UA (μmol/L)	366.35 ± 88.46	300.69 ± 88.68	-3.902[a]	<.001

BMI, body mass index; HAMD, Hamilton Depression Scale; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; UA, uric acid.
[a]*t*-Value of the comparison between groups with bipolar depression and the unipolar depression.
[b]Z-value.
[c]χ^2 value.

Considering the presence of multicollinearity and the small sample size, even if triglycerides, HDL cholesterol, and LDL cholesterol were not statistically significant in the *t*-test, we still treated them as covariates and included them separately in logistic regression analysis. Results revealed that the levels of serum UA (OR = 1.016, $P = .001$) and triglycerides (OR = 0.457, $P = .025$) may be independently related factors for bipolar depression after controlling for age, sex, and BMI (Table 4). There

Table 2. Independent *t*-Test Results Comparing the UA Levels (μmol/L) Between Groups

Medication Usage	Mean ± SD	*t*	*P*
All groups			
Antipsychotic use (%)			
Yes (n = 76, 68.47%)	345.92 ± 93.44	1.821	.071
No (n = 35, 31.53%)	311.28 ± 92.46		
Mood stabilizer use (%)			
Yes (n = 66, 59.46%)	349.54 ± 107.64	2.184	**.031**
No (n = 45, 40.54%)	313.66 ± 65.15		
Antidepressant use (%)			
Yes (n = 97, 87.39%)	327.63 ± 91.39	-2.208	**.029**
No (n = 14, 12.61%)	386.03 ± 100.28		
Bipolar depression group			
Antipsychotic use (%)			
Yes (n = 53, 91.38%)	362.68 ± 83.65	-1.030	.308
No (n = 5, 8.62%)	405.26 ± 135.93		
Mood stabilizer use (%)			
Yes (n = 45, 77.59%)	388.18 ± 84.66	3.911	**<.01**
No (n = 13, 22.41%)	290.78 ± 54.01		
Antidepressant use (%)			
Yes (n = 44, 75.86%)	360.09 ± 84.65	-0.955	.344
No (n = 14, 24.14%)	386.03 ± 100.28		
Unipolar depression group			
Antipsychotic use (%)			
Yes (n = 23, 43.40%)	307.30 ± 104.85	0.472	.639
No (n = 30, 56.60%)	295.62 ± 75.49		
Mood stabilizer use (%)			
Yes (n = 21, 39.62%)	266.75 ± 106.46	-2.353	**.022**
No (n = 32, 60.38%)	322.96 ± 67.72		
Antidepressant use (%)			
Yes (n = 53, 100%)	300.69 ± 88.68		
No (n = 0, 0%)	/		

UA, uric acid.

Table 3. Independent *t*-Test Results Comparing the TC Levels (mmol/L) Between Groups

Medication Usage	Mean ± SD	*t*	*P*
All groups			
Antipsychotic use (%)			
Yes (n = 77, 68.75%)	4.143 ± 1.022	0.918	.361
No (n = 35, 31.25%)	4.334 ± 1.012		
Mood stabilizer use (%)			
Yes (n = 67, 59.82%)	4.177 ± 1.012	0.321	.749
No (n = 45, 40.18%)	4.240 ± 1.037		
Antidepressant use (%)			
Yes (n = 98, 87.50%)	4.195 ± 1.052	0.208	.836
No (n = 14, 12.50%)	4.256 ± 0.772		
Bipolar depression group			
Antipsychotic use (%)			
Yes (n = 52, 91.23%)	4.010 ± 0.860	0.985	.329
No (n = 5, 8.77%)	4.398 ± 0.570		
Mood stabilizer use (%)			
Yes (n = 44, 77.19%)	4.040 ± 0.838	0.060	.952
No (n = 13, 22.81%)	4.056 ± 0.893		
Antidepressant use (%)			
Yes (n = 44, 77.19%)	4.029 ± 0.802	0.246	.807
No (n = 13, 22.81%)	4.095 ± 1.000		
Unipolar depression group			
Antipsychotic use (%)			
Yes (n = 23, 43.40%)	4.624 ± 0.906	1.096	.278
No (n = 30, 56.60%)	4.317 ± 1.078		
Mood stabilizer use (%)			
Yes (n = 21, 39.62%)	4.564 ± 0.892	0.663	.510
No (n = 32, 60.38%)	4.375 ± 1.087		
Antidepressant use (%)			
Yes (n = 53, 100%)	4.450 ± 1.010		
No (n = 0, 0%)	/		

TC, total cholesterol.

were no statistically significant differences found for the levels of TC, HDL cholesterol, and LDL cholesterol. It is worth mentioning that the levels of UA and triglycerides were still significantly associated with the diagnosis of bipolar disorder after further controlling for antipsychotic use (UA: OR = 1.013, *P* = .007; triglycerides: OR = 0.453, *P* = .031), antidepressant use (UA: OR = 1.015, *P* = .002; triglycerides: OR = 0.505, *P* = .048), and mood stabilizer use (UA: OR = 1.014, *P* = .003; triglycerides: OR = 0.422, *P* = .026).

Table 4. Logistic Regression Analysis of Bipolar Depression

Variables	*β*	Standard Error	OR	95% CI	*P*
UA	0.016	0.005	1.016	1.007-1.025	**.001**
Triglycerides	-0.784	0.349	0.457	0.230-0.905	**.025**
Age	-0.150	0.030	0.860	0.811-0.913	**<.001**
Female	0.628	0.677	1.873	0.497-7.065	.354
BMI	0.107	0.083	1.113	0.946-1.311	.197

BMI, body mass index; OR, odds ratio; UA, uric acid. The following values verify that the created model of logistic regression analysis fits the observed data well: the value of Cox and Snell R^2 is 0.473, the value of Nagelkerke's R^2 is 0.631, the values of Omnibus test are statistically significant ($P < .001$), and the value of Hosmer-Lemeshow test is 0.198.

DISCUSSION

Bipolar depression is easily misdiagnosed as unipolar depression due to their similarities in the clinical presentation of depressive episodes, which could delay effective treatment and worsen prognosis. Nowadays, the clinical diagnosis is mainly dependent on some screening instruments like MDQ or HCL-32 for assessing mania/hypomania and HAMD, the Beck Depression Inventory, the Patient Health Questionnaire, and the Montgomery-Asberg Depression Rating Scale for evaluating depression, combined with prodromal symptoms (such as insomnia, decreased need for sleep and increased irritability), risk syndromes (such as a family history of BD), course of the disease, and clinical presentation (including mood symptoms and abnormal behaviors) which is more subjective. If we can find effective biological markers to distinguish between unipolar and bipolar depression according to their mechanisms of depressive episodes, including differences in biochemical metabolism, it will be of great significance to guide correct diagnosis and early intervention and to avoid misdiagnosis or missed diagnosis.

Our finding that patients with bipolar depression have an earlier age of onset and more episodes than those with unipolar depression is also supported by the study of Schaffer et al.[8] The above results are in line with the characteristics of bipolar disorder. In the present study, no patients in the unipolar group were found to have adolescent onset. Furthermore, the age difference was prominent between the unipolar group and bipolar group, which is inconsistent with the results of Benazzi and Aksikal[9] and Hegerl et al.[10] Therefore, age may interfere with our research findings. The results of this study may be related to the retrospective sample selection and small sample size, and it is necessary to further expand the sample and extend the observation time. There should also be vigilance about whether teenagers are misdiagnosed or not, and this factor should be taken into account in future research.

Furthermore, because patients with bipolar depression suffer from a higher risk of suicidal behavior, more detrimental social function, and more frequent depressive episodes than those with unipolar depression, it is important to control acute mood symptoms as soon as possible. At this time, adequate and effective drug therapy is the critical strategy for achieving fast mood stability. Therefore, our results support the notion that the proportion of antipsychotic usage in patients with bipolar depression is markedly larger than that in patients with unipolar depression.

Although no statistical difference in the levels of HDL cholesterol or LDL cholesterol was found between the 2 groups in this study, there is still evidence showing possible correlation between suicidal behavior and low levels of serum lipids (particularly cholesterol) in patients with depression.[11] Moreover, previous reports revealed that depressed patients (including unipolar and bipolar ones) with anhedonia had lower LDL cholesterol levels, while patients with suicidal thoughts commonly had higher levels of TC and HDL cholesterol.[12] Additionally, another study used techniques of next-generation sequencing and pathway analyses to examine the effects of 4 drugs commonly prescribed for bipolar disorder on human neuronal cells and rats. Its results showed that the combinations of drugs might affect the cholesterol biosynthesis pathway and increase intracellular cholesterol production, thereby increasing neurite outgrowth and neural plasticity as the newly synthesized cholesterol may be used in cells to synthesize new cell membranes. The mechanism reported in that study may be the basis of the clinical efficacy of drugs when used in combination with patients with bipolar disorder.[13] The levels of serum triglycerides might be involved in patients with severe depressive disorder and related to cognitive impairment, especially in delayed memory,[14] and triglyceride levels may be correlated with cognitive dysfunction in patients with bipolar disorders.[15] All these suggested that the levels of serum lipids in patients with bipolar depression and unipolar depression were closely related to the occurrence and development of not only the course but also the severity and the risks of self-injury and suicide of these 2 kinds of depression. In this study, using a *t*-test, we found that the concentration of TC in the bipolar group was significantly lower than that in the unipolar one, which is inconsistent with the findings of Kłoszewska et al, who reported that although the level of TC is not significantly different between the 2 groups, it is significantly higher than that in the healthy population.[16] Triglyceride levels were statistically significant in the logistic regression analysis but not in the *t*-test, which we considered to be related to the presence of multicollinearity and the small sample size. Our results show that the low triglyceride levels may be related to bipolar disorder. Moreover, there is no difference in the serum lipid levels between the medication user group and the non-user group, which is not consistent with what we anticipated (antipsychotics influence lipid metabolism). We considered this may be related to confounding factors. Age matching is essential in further research, as it is an important factor in the assessment of suicide and the severity of the depression.

In addition, it has been demonstrated that purine metabolism may also play an important role in the pathophysiological mechanism of bipolar disorder, but the monitoring of purine metabolism in the central nervous system remains a challenge; UA is the only end product of purine metabolism and is more convenient to monitor. Therefore, purine metabolism can be reflected indirectly by monitoring the level of serum UA. Some studies have suggested that the serum levels of UA of patients with

bipolar depression are higher than those of patients with unipolar depression and healthy controls, and the patients with higher serum UA levels have a higher risk of a subsequent hypomanic or manic episode; so the level of serum UA can be used as a characteristic marker to predict the transformation of patients with unipolar depression to bipolar disorder. However, there is no correlation between UA levels and the severity of manic episodes.[5,17,18] The purinergic system may be one of the promising ways to find biomarkers of bipolar disorder, which still remain elusive. A review reported that UA levels were positively associated with hallucinations and suicidality.[19] This not only indicates that the purinergic system is related to clinical symptoms and severity of diseases but also suggests that we need to further explore it in future studies to understand how this system influences the development of disease, for example by affecting certain brain regions, neurotransmitters, or neuroendocrine systems. Our study showed that the levels of serum UA in the bipolar group were substantially higher than those of the unipolar group, and the serum UA levels might be a risk factor for bipolar depression, which suggests that the level of serum UA may provide great predictive value in distinguishing bipolar disorder from unipolar depression. Both serum UA and lipids may be risk factors for bipolar depression. On this basis, future studies, on links between serum UA and lipids and clinical symptoms, should attract increased attention. We will be more rigorous in controlling for confounding factors in future studies.

We acknowledge there are some limitations in this study. Our study targeting patients already diagnosed with bipolar disorder (and multiple depressed episodes) could not lead to resolving an unpredictable depressive course. If the different clinical phases of patients could be compared longitudinally, it would provide a more reliable clinical basis for the pathogenesis of unipolar depression and bipolar depression. It is better to conduct a longitudinal study for depressed patients before they suffer from manic/hypomanic episodes. Therefore, in future experiments, we will conduct a long-term follow-up of patients with unipolar depression and collect information on patients with manic/hypomanic episodes so as to find effective and novel biomarkers that can predict the conversion of unipolar depression to bipolar disorder.

The sample size in our study is relatively small; so future research should further expand it and control the influencing factors. It is a single-center retrospective research, with recall bias existent. But this study mainly focused on the comparison of clinical characteristics, reducing the impact of recall bias as much as possible. This study also needs to be confirmed by a large sample size, multicenter, prospective cohort study. Whether unipolar depression and bipolar depression have other specific clinical characteristics and risk factors needs to be further examined by follow-up studies.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Kunming Medical University (Approval No: 09-201936FS-2).

Informed Consent: Written informed consent was obtained from participants who participated in this study.

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