ORIGINAL ARTICLE

Clinical Risk Score for Predicting Bipolar Depressive Disorder in Adults with Depressive Disorder

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Objective: To develop a predictive diagnosis model for bipolar disorder using clinically and statistically significant factors.

Materials and Methods: The present study was a diagnostic prediction research, registered with the TCTR identification number TCTR20230629004. It collected data from psychiatric outpatients at Naresuan University Hospital's Psychiatric Outpatient Department between July 17, 2023, and February 13, 2024. Participants were categorized into bipolar disorder cases and major depressive disorder controls based on diagnoses. The researchers assessed clinical characteristics through medical history reviews and patient interviews. The prediction model was created using predictive factors through multivariable logistic regression. Risk scores were generated to predict bipolar disorder.

Results: The present study involved 81 participants that included 13 or 16%, diagnosed with bipolar disorder and 68 or 84%, diagnosed with major depressive disorder. The model considered predictive factors such as age of illness onset, atypical depression, treatment-resistant depression, history of self-harm or suicide, and the number of depressive episodes. The model demonstrated good discriminatory ability with the area under the receiver operating characteristic curve (AuROC) of 87.1% (95% CI 74.6 to 99.5). Internal validation via bootstrapping with 500 replications and yielded an AuROC of 87.1% (95% CI 76.8 to 101.0%) with a bootstrap shrinkage of 1.025. Clinical risk scores were stratified into low risk at 2.5 or less, moderate risk at 3 to 12, and high risk at 12.5 or higher. The likelihood ratios of positive (LHR+) were 0.27 for the low risk, 0.81 for the moderate risk, and 12.21 for the high risk groups.

Conclusion: Clinical risk scores from the present study model may enable a more accurate and rapid diagnosis of bipolar disorder, particularly in high-risk individuals treated by psychiatrists in tertiary care hospitals.

Keywords: Bipolar disorder; Depression; Early diagnosis; Tertiary healthcare; Treatment resistant depression; Predictive model

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Psychiatric disorders significantly impact patients' quality of life and global health. Depression, ranking among the top ten diseases causing health loss[1], has a prevalence of 27% among all outpatients seeking services[2]. Similarly, bipolar disorder is one of the five most prevalent psychiatric disorders and is highly common among teenagers and young adults, making a substantial contribution to years lived with disability (YLDs)[1]. Studies indicate a misdiagnosis rate of 10% to 22% among patients presenting with symptoms of bipolar depressive disorder, often receiving a diagnosis of unipolar depressive disorder[3-6]. This diagnostic challenge arises because 67% of patients with bipolar disorder initially seek medical attention during a depressive episode, often overlooking previous mania or hypomania experiences[7,8]. Delayed diagnosis leads to inappropriate treatment and elevates the risk of self-harm or suicide[6,9]. Studies reveal that patients may take more than four years to receive a bipolar disorder diagnosis, with up to 46% previously misdiagnosed with major depressive disorder (MDD)[9].

Furthermore, besides a history of hypomanic or manic episodes, studies highlight several clinical characteristics associated with bipolar disorder during depressive episodes. These include an earlier age of illness onset, atypical depressive symptoms, treatment-resistant depression, frequent self-harm or suicide attempts, antidepressant-induced mania or hypomania, multiple depressive episodes, and a family history of bipolar disorder[3,9-20]. These clinical characteristics could potentially aid in diagnosing or predicting bipolar disorder.

Previous research has attempted to leverage these clinical characteristics to develop predictive models

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for bipolar disorder. For instance, a study aimed to predict the development of bipolar disorder within five years in children of parents with the disorder, using six predictive factors such as mania, depression, anxiety, mood lability, psychosocial functioning, and parental age at mood disorder onset. Although the prediction model demonstrated good accuracy and internal validation, it was limited to children and adolescents with known parental bipolar disorder history[21].

Another large population study compared diagnostic predictors between 467 patients with bipolar disorder and 4,145 individuals with depression. Despite achieving a high predictive value, the study included numerous predictors chosen solely for statistical reasons, hampering its practical application in clinical settings[17].

Despite existing diagnostic prediction models, there remains a need for a comprehensive model incorporating both clinically and statistically significant predictors to create a risk scoring system for diagnosing bipolar disorder. Hence, the present research aimed to develop a diagnosis prediction model along with a scoring system to assess individual risks from some important clinical characteristics and statistically significant for bipolar disorder, ensuring internal validation and clinical relevance for each individual.

Materials and Methods

Study design and setting

The present study was a diagnostic prediction research collected data from interviews with the participants selected through disease-based criteria at the Psychiatric Outpatient Department, Naresuan University Hospital, a tertiary care hospital, between July 17, 2023, and February 13, 2024.

Participants

Domain of patients studied: Outpatients who sought treatment during the planning phase for data collection at the Psychiatric Outpatient Department, Naresuan University Hospital. The selected outpatients were the ones who had a history of major depressive episodes and were diagnosed with MDD, for a control group, and the patients who had a history of major depressive episodes diagnosed with bipolar disorder, for the case group. They were conscious, able to read and write in Thai, and aged between 18 and 60 years old.

Patients included in the case group had a current diagnosis of bipolar disorder, with a history of major depressive episodes, according to DSM-5[22] or ICD-10[23] criteria. Patients were excluded from this group if they presented with a psychiatric emergency or physical condition requiring urgent treatment, had a diagnosis of schizophrenia, schizoaffective disorder, neurodevelopmental disorders such as intellectual disabilities or autism spectrum disorder, neurocognitive disorders such as delirium or dementia, stroke, or traumatic brain injury, were currently experiencing symptoms of psychosis, were currently using substances including alcohol, marijuana, amphetamines, cigarettes/tobacco, opium and its derivatives, hallucinogenic substances, or volatile substances, or those who had ceased substance use within the past month.

The control group consisted of patients with a current diagnosis of MDD according to DSM-5[22] or ICD-10[23] criteria. Exclusion criteria were the same as for the case group, with the additional exclusion of any patients currently using mood stabilizers such as anticonvulsant drugs or lithium, or antipsychotic medications and those with a prior diagnosis of manic or hypomanic episodes unrelated to antidepressant use.

Sample size calculation

The sample size was based on a pilot study using statistical software, with a bipolar-to-depressive disorder ratio of 0.18 to 1 (2:10 patients)[6]. Predictive factors included atypical depression, present in 10% of depressive disorder cases and 50% of bipolar cases. Using a two-sided test with a 0.05 alpha error and 80% power, 68 depressive and 13 bipolar disorder cases were required, reflecting actual patient proportions at Naresuan University Hospital. A final sample of 81 patients was selected, comprising 68 with depressive disorder and 13 with bipolar disorder. Limitations included analysis of only three factors, mean age of onset, atypical depression, and antidepressant-induced mania.

Data collection

The participants were the patients previously diagnosed with psychiatric disorders by the research team, consisting of two psychiatrists. The patients who met the study criteria came for follow-up examination and treatment at the Psychiatry Outpatient Department. After providing informed consent, participants were interviewed by one of the three researchers, which were two trained psychiatric internists, or a psychiatrist not involved in the patient's treatment. Researchers also collected

data from patient medical records. The clinical characteristics studied included gender, age, age of illness onset, psychiatric family history, drug treatment resistance, atypical depression features, number of depressive episodes, frequency of self-harm or suicide attempts, history of antidepressant-induced symptoms of mania or hypomania.

Definition

Atypical depression is defined as a depressive episode characterized by increased appetite, weight gain, and excessive sleep, occurring within the past or current depressive episodes[6,10,24].

Treatment-resistant depression referred to patients experiencing depressive symptoms that do not respond to treatment with at least two different antidepressants over a minimum period of four weeks[25].

Statistical analysis

The present research study employed Stata Statistical Software, version 17 (StataCorp LLC, College Station, TX, USA) to analyze all data. The data analysis was conducted as follows:

First, the basic information of the patients in the case and control groups was analyzed using frequency and percentage when the clinical characteristics variables were categorical variables. Mean and standard deviation statistics were employed when the clinical characteristics variables were numerical variables. The data between the two groups were then compared using Fisher's exact probability test when the clinical characteristics variables were categorical variables and t-test when they were numerical variables. Statistical significance was determined at a p-value less than 0.05, and each factor was evaluated to differentiate diseases using univariable logistic regression, presenting the results with the area under the receiver operating characteristic (AuROC) curve and 95% confidence interval (CI).

The researchers pre-selected five clinically important predictive factors, such as age at illness onset, the number of self-harm or suicide attempts, atypical depression, treatment resistant to at least two types of antidepressants, and a history of antidepressant-induced symptoms of mania or hypomania before analyzing the data. Additional predictive factors were added to create a prediction model if they were found to be statistically significant.

Continuous predictive factors, including age at illness onset, the number of self-harm or suicide attempts, and the number of depressive episodes, were categorized into categorical variables to calculate the odds ratio. Before categorization, these factors underwent analysis to ensure a linear association, utilizing the locally weighted scatterplot smoothing (LOWESS) graph.

Once the predictive factors were made as categorical predictors, they were calculated to find the Odds ratio under multivariable logistic regression. The regression coefficients in each group of predictive factors were then multiplied by the lowest coefficients and converted them to the nearest 0.0 or 0.5 to create clinical risk scores for each predictive factor. The scores were then summed up to get a total score. The total score was then calculated for the discriminative performance of the prediction model, shown as the AuROC curve, and performed a calibration of the prediction model to see the agreement between the predicting risk and the observed risk values. The results were then presented with a calibration plot graph. After that, the internal validation was performed by using bootstrapping of 500 replications.

The patients' total scores were divided into three levels, low-risk, moderate-risk, and high-risk groups. The predictive ability of each score was expressed as the likelihood ratio of positive (LHR+) and 95% CI by determining the confidence in the statistical test at a level of less than 0.05.

The present research study was registered with the Thai Clinical Trials Registry, identification number TCTR20230629004 (https://www.thaiclinicaltrials.org/show/TCTR20230629004). The authors asserted that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. All procedures involving human patients were approved by the Naresuan University Institutional Review Board, Phitsanulok, Thailand, under approval number P3-0034-2566. All participants provided written informed consent before participating in the study. To provide clarity and aid comprehension, refer to the study flow diagram in Figure 1, which illustrates the sequential steps involved in the research process.

Results

The present study included 81 participants, categorized into two groups, 13 with bipolar disorder as five with Bipolar I and eight with Bipolar II, and 68 with depressive disorder (Figure 1). When comparing the two groups, the general characteristics

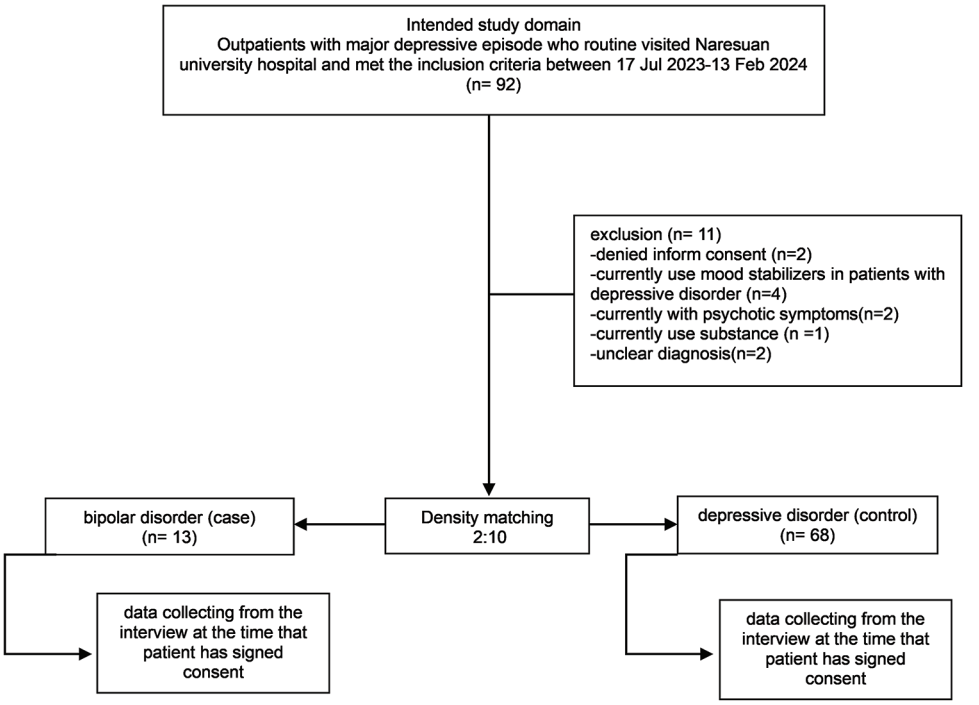

Figure 1. Study flow diagram.

Table 1. General characteristics of the patients

Characteristics	Bipolar disorder 13 (16.0)	Depressive disorder 68 (84.0)	p-value	AuROC (95% CI)
Male (%)	3 (23.1)	12 (17.7)	0.700	0.53 (0.40 to 0.65)
Age (year); mean±SD	27.5±8.0	30.1±11.3	0.423	0.56 (0.40 to 0.72)
Age of illness onset (year); mean±SD	20.3± 6.0	26.3±10.9	0.057	0.69 (0.52 to 0.85)
Family history of psychiatric diseases; n (%)				
Bipolar disorder	1 (7.7)	1 (1.5)	0.297	0.53 (0.45 to 0.61)
Psychotic disorders	2 (15.4)	2 (2.9)	0.119	0.56 (0.46 to 0.67)
Depressive disorder	4 (30.8)	1 (1.5)	0.002	0.65 (0.52 to 0.78)
Attention deficit hyperactivity disorder; n (%)	1 (7.7)	3 (4.4)	0.511	0.52 (0.44 to 0.60)
Number of self-harm or suicide attempts; mean±SD	4±3.9	2.5±3.9	0.217	0.66 (0.51 to 0.81)
Number of depressive episodes; mean±SD	6.6± 4.9	1.6±1.7	<0.001	0.88 (0.76 to 0.99)
Treatment resistance to at least 2 types of antidepressants; n (%)	3 (23.1)	6 (8.8)	0.153	0.57 (0.45 to 0.70)
Atypical depression; n (%)	8 (61.5)	28 (41.2)	0.228	0.60 (0.45 to 0.75)
History of antidepressant-induced symptoms of mania or hypomania; n (%)	10 (76.9)	3 (4.4)	<0.001	0.86 (0.74 to 0.98)

AuROC=area under the receiver operating characteristic curve; CI=confidence interval; SD=standard deviation
Clinical characteristics of the case group vs. the control group, evidence of a difference (p-value).

of the patients, including age and gender, were not significantly different. Among the five pre-selected clinically important predictive variables, only one variable showed significance, a history of antidepressant-induced symptoms of mania or hypomania. It was significantly higher in the case group than in the control group at 76.9% versus 4.4% (p<0.001). Other predictive factors, including the age of illness onset, a history of the number of self-harm or suicide attempts, treatment resistance to at least two types of antidepressants, and atypical depression, did not show significant differences between the case and control groups. Additionally, a history of depression in the family was significantly higher in the case group at 30.8% versus 1.5% (p=0.002), as was the number of depressive episodes at 6.6±4.9

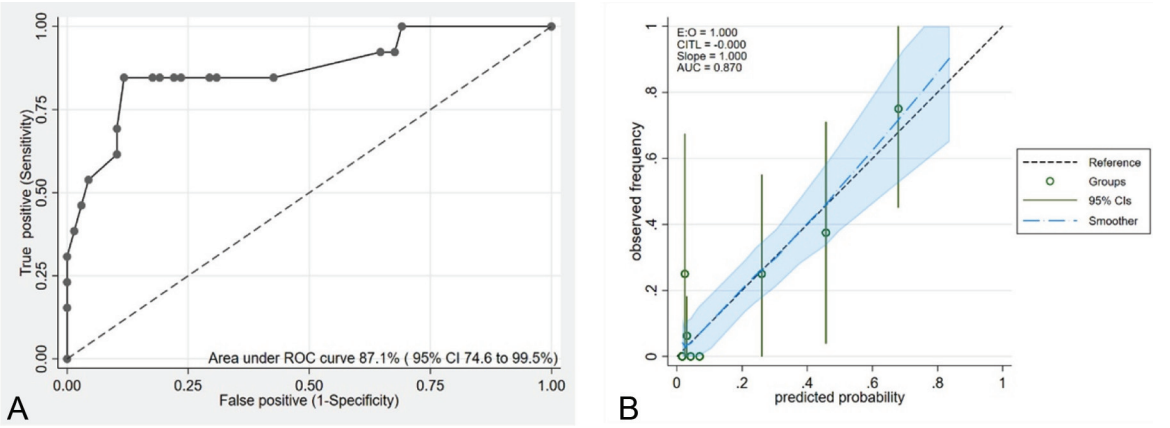

Figure 2. (A) Area under receiver operating characteristic curve of clinical risk score and 95% confidence interval (CI) in predicting a diagnosis of bipolar disorder. (B) Calibration plot; compare between the predicted probabilities to the observe frequency.

versus 1.6±1.7 (p<0.001). Among all predictive factors, the variable with the highest predictive ability, estimated from the AuROC curve, was the number of depressive episodes, as shown in Table 1.

Since the patients in the case group, the bipolar disorder, had a history of taking antidepressants and then developed symptoms of mania or hypomania, this resulted in a diagnosis of bipolar disorder. Therefore, the research team decided to exclude this factor from the predictive factors. In addition, the predictive factor depressive disorder in the family, although there was a statistically significant difference between the case and the control groups, this data was obtained from patient interviews, which indicated the emotional symptom of most family members was depression. This may cause incorrect data. The research team, therefore, did not include this factor in the prediction model. As a result, there were five predictive factors that were used to create a bipolar disorder diagnosis prediction model, of which four were pre-selected as age of illness onset, the number of self-harm or suicide attempts, atypical depressive characteristics, treatment resistance to at least two antidepressants, and the number of depressive episodes selected based on statistical significance.

Continuous predictors were categorized to facilitate item score calculation by transforming their logistic regression coefficients. The sum of clinical risk scores is derived from adding up each item score, as shown in Table 2.

The clinical risk score ranged from 0 to 17.5. The discriminative ability of the clinical risk score, as indicated by the AuROC curve, was 87.1% (95% CI 74.6 to 99.5), with the Hosmer-Lemeshow goodness of fit showing a p-value of 0.092 (Figure 2A). Furthermore, it was noted that as the predictive probability increased, it closely approximated the actual value, from the observed proportion, with a slope of 1.00 (95% CI 0.51 to 1.50) and a calibration in the large (CITL) of –0.00 (95% CI –0.75 to 0.75) (Figure 2B). In the process of internal validation utilizing the bootstrapping method with 500 replications, the AuROC curve maintained a proximity to the original at 87.1% (95% CI 76.8 to 101.0), exhibiting bootstrap shrinkage of 1.025, a slope of 1.025 (95% CI 0.43 to 1.73), and a CITL of 0.07 (95% CI –0.84 to 1.19).

Table 2. Odds ratio, 95% CI, logistic regression coefficient, and item score derivation from selected predictors, from multivariable logistic regression

Predictive factors	OR	95% CI	Coefficient	Score
Age of illness onset (year)				
>18	1.00	Reference	-	0
≤18	1.4	0.27 to 7.8	0.36	1
Number of self-harm or suicide attempts				
≤1	1.00	Reference	-	0
2 to 5	3.7	0.5 to 26.6	1.30	4
≥6	1.4	0.2 to 8.5	0.33	1
Treatment resistance to at least 2 types of antidepressants				
No	1.00	Reference	-	0
Yes	1.5	0.2 to 14.7	0.42	1.5
Atypical depression				
No	1.00	Reference	-	0
Yes	1.8	0.4 to 8.4	0.60	2
Number of depressive episodes ≥2				
No	1.00	Reference	-	0
Yes	19.3	3.2 to 116.3	2.96	9

OR=odds ratio; CI=confidence interval

Table 3. Risk classification of bipolar depressive disorder vs. unipolar depressive disorder (MDD)

Risk categories	Score	Bipolar disorder (%)	MDD (%)	LHR+	95% CI
Low	0 to 2.5	15.38	57.35	0.27	0.03 to 1.29
Moderate	3 to 12	30.77	38.24	0.81	0.18 to 2.93
High	≥12.5	53.85	4.41	12.21	2.32 to 79.41

MDD=major depressive disorder; LHR+=likelihood ratios of positive; CI=confidence interval

The clinical risk scores were categorized into three groups, low risk for a score of 2.5 or below, moderate risk for a scores of 3 to 12, and high risk for a scores of 12.5 or above. To facilitate interpretation and application, the LHR+ was 0.27 (95% CI 0.03 to 1.29) in the low-risk group, 0.81 (95% CI 0.18 to 2.93) in the moderate-risk group, and 12.21 (95% CI 2.32 to 79.41) in the high-risk group (Table 3).

To illustrate the application of the prediction model, considering the case of a 20-year-old female. She had a history of depressive disorder onset at the age of 15 (+1 point), with five suicide attempts (+4 points), treatment resistance to at least two types of antidepressants (+1.5 points), atypical depression (+2 points), and three depressive episodes (+9 points). The total score was 17.5, indicating a high-risk score for diagnosing bipolar disorder.

Discussion

The diagnosis process for bipolar disorder among patients presenting with depressive episodes poses a significant clinical challenge. This difficulty arises from challenges in recalling manic or hypomanic episodes and the absence of a clear family history of bipolar disorder, hindering the practical monitoring of bipolar disorder occurrence in their offspring. This delay in diagnosis impacts patients' long-term quality of life, increasing the risk of suicide[15]. Analysis of the scores obtained from the diagnosis prediction model, created based on the clinical characteristics of patients presenting with depressive episodes, revealed a good ability to differentiate between bipolar disorder and depression (AuROC curve 87.1%, 95% CI 74.6 to 99.5). Internal validation through bootstrapping demonstrated the continued ability of the prediction scores to differentiate diseases (discriminate) accurately and maintain calibration, consistent with prior predictions for bipolar disorder diagnosis or prognosis, with an AuROC curve range of 63% to 85%[10,17,21,26].

The predictive factors in this score-based prediction model were primarily selected from clinically significant factors. These factors were chosen before statistical analysis to avoid bias toward statistically significant factors only. They include a younger age of illness onset, atypical depressive characteristics, treatment-resistant depression, and a more frequent history of self-harm or suicide, all supported by data indicating their association with bipolar disorder[3,6,7,13-15,18,26,27]. Regarding the factor of a history of antidepressant-induced symptoms of mania or hypomania in the case group, it was observed that this factor had a significantly higher prevalence than in the control group. Specifically, most patients in this study were diagnosed with bipolar disorder shortly after experiencing these symptoms. Consequently, while not a diagnostic predictive factor, it is indicative of the diagnosis of mania or hypomania in bipolar disorder[16,28]. Hence, the research team did not include this factor in the prediction model.

Furthermore, the results of univariable analysis indicated that the history of multiple depressive episodes was statistically and significantly different, consistent with previous studies[9,17,29]. Hence, this factor was incorporated into the prediction score-based model as a predictive factor.

Despite the statistical significance of the family history of depressive disorder in univariable analysis, this finding is attributed to patients frequently reporting family psychiatric history as mood disorders, predominantly depression. Hence, due to unclear practical information, the research team opted not to include this factor in the prediction score-based model.

The final diagnostic model incorporated all predictive factors, comprising age of illness onset, atypical depressive characteristics, treatment-resistant depression, number of self-harm or suicide attempts, and number of depressive episodes.

While a previous study may not have definitively determined the age of illness onset or divided cutoff points using statistics[10], the present study categorized age of illness onset into two groups, 18 years or younger and older than 18 years. These categories were based on data distribution in this study and clinical context such as early adolescence, enhancing usability in clinical practice. Likewise, for the number of depressive episodes, data were divided into two groups, the less than two episodes and two or more episodes. This division was based on data distribution and clinical contexts, facilitating clinical application. However, another study used the same cut-off point[9]. The factor of the number of self-harms or suicide

attempts was categorized into three groups, with the one time or less, the two to five times, and the more than six times. This categorization was due to the lack of clear grouping information. Subsequently, the researchers divided the groups based on data distribution and LOWESS graphs, with the highest score in the two to five times group, followed by the more than six times group, and the lowest score in the one time or less group. This adjustment accounted for recall bias resulting from data obtained from patient interviews, especially with multiple instances of self-harm. The present study excluded patients diagnosed with depressive disorder receiving mood stabilizers or antipsychotic drugs to ensure a control group with unipolar depressive disorder, as patients with MDD with mixed features often received these medications, preventing treatment delays[30,31]. Consequently, the research focused solely on unipolar depressive disorder without mania or hypomania symptoms, resulting in selection bias. However, mixed features were present in both bipolar disorder and MDD, with a higher proportion observed in bipolar disorder compared to MDD, where the proportion of mixed features was relatively low[32,33].

A highlight of the present study is the selection of clinically important predictive factors to create a simple score diagnostic prediction model. These factors were derived from detailed patient history interviews conducted as part of routine clinical practice. Moreover, this methodological approach ensured a robust dataset without missing values due to prospective data collection. So, this model can be applied practically, offering valuable insights into diagnostic decision-making processes and improving patient care outcomes.

Risk scores can be categorized into three levels. This may help psychiatrists treat patients, especially those in the high-risk group, by making better decisions about diagnosis and treatment without waiting for a history of mania or hypomania before starting mood stabilizers or antipsychotics. This provides a better treatment option than using antidepressants alone[28,34].

The primary limitation of the present study stemmed from the low prevalence of patients with bipolar disorder within the study setting, leading to acquiring a small sample size. Consequently, a small sample size hindered the verification of other significant factors crucial for accurate diagnosis, thereby compromising overall diagnostic performance of the study. Furthermore, this research did not conduct external validation, limiting the applicability of the prediction model to diagnose bipolar disorder in patients in other contexts, such as different hospitals, locations, or times. Therefore, before deploying this prediction model in diverse contexts, external validation, recalibration, and diagnostic intervention are essential to monitor treatment changes following its use.

Since the family history of bipolar disorder is a key clinical predictor[16,20,21], its absence from the model may reduce predictive accuracy. However, obtaining this information is often challenging because participants may lack knowledge of their family history or may have limited access to relatives. To overcome these limitations, employing a family history screening, especially focused on a history of mania or hypomania, could yield more accurate data and enable its incorporation into future methodological designs, thereby enhancing the model's predictive accuracy.

Conclusion

For the patients with depression who receive treatment from psychiatrists at tertiary care hospitals or university medical schools, psychiatrists can use a diagnostic prediction model based on scoring to determine a diagnosis of bipolar disorder and provide more accurate and expedited treatment for patients in the high-risk group.

What is already known about this topic?

Although numerous predictors for diagnosing bipolar depressive disorder have been well-established, there remains a need for a streamlined prediction model in clinical practice.

What does this study add?

This study presents a diagnostic predictive model and simple scoring system for assessing individual risk levels, based on clinically and statistically validated predictors of bipolar disorder in patients with major depressive episodes. This model could enhance early diagnosis and inform treatment decisions, thereby improving overall patient outcomes.

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Authors' contributions

Conceptualization, AH; methodology, AH and SY; acquisition of data, AH, FA, and MJ; software and analysis, AH; all authors contributed to the interpretation of the results; AH wrote the first draft of the paper; FA, SY, and MJ revised it for important intellectual content; all authors approved the final manuscript prior to publication.

Data availability

The data that support the findings of the present study are available from the corresponding author, upon reasonable request.

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Conflicts of interest

The authors have no potential conflicts of interest to disclose.

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