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Predictive Factors of Bipolar Disorder in Hospitalized Patients with Major Depressive Disorder

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Abstract

Introduction: Bipolar Mood Disorder (BMD) is a debilitating psychiatric illness with features of mania, hypomania, and depressive episodes. The correlation between some features of major depressive episodes and change of diagnosis to BMI has been investigated in previous studies. Thus, this study aimed to evaluate predictive factors of BMD in hospitalized patients with Major Depressive Disorder (MDD).

Materials and methods: In this retrospective descriptive study, medical files of all patients admitted to Ibn-e-Sina Hospital in Bandar Abbas with an MDD diagnosis between 2011 and 2015 were evaluated. Inclusion criteria were at least one readmission, at least a 3-month interval between 1st and 2nd admissions and at least a 3-year follow-up in patients without change of diagnosis. Patients' information including age at first admission, gender, marital status, education, drug abuse, family history of mood disorders, suicidal thoughts, psychotic symptoms, atypical depressive symptoms during depressive episodes, age at the change of diagnosis to BMD, time to change of diagnosis, the total number of admissions, admissions with MDD and an average number of admissions per year were recorded in a checklist. The acquired data were then entered into the SPSS software for statistical analysis and appropriate statistical tests such as chi-square and Fisher's exact test were used to analyze the data.

Results: In general, the medical files of 183 patients with MDD were evaluated. Among them, 101 (55.2%) were male and 82 (44.8%) were female. The mean age at first admission was 35.39 ± 1.56 years. Change of diagnosis occurred in 51 patients (27.9%). The average total number of admissions, the average age at the change of diagnosis, and the mean time to change of diagnosis were 37.04 ± 12.26 years, 3.93 ± 3.85, and 40.82 ± 65.4 months (3.4 ± 5.45 years), respectively. A significant reverse relationship was found between drug abuse and change of diagnosis to BMD (P=0.033). In addition, there was a significant correlation between atypical and psychotic symptoms with the change of diagnosis (P<0.001 and P=0.004, respectively). Number of admissions with MDD was also significantly higher in those with a change of diagnosis (P=0.006). However, in logistic regression, only atypical sympotms were significantly correlated with a change of diagnosis to BMD (OR=35.45, 95% CI, 9.53-131.84, P<0.001).

Conclusion: A typical and psychotic symptoms during depressive episodes, lack of drug abuse, and higher hospital admissions with MDD can predict the change of diagnosis to BMD in patients with MDD.

Keywords: Major depressive disorder • Bipolar mood disorder • Change of diagnosis • Predictive factors

Introduction

Bipolar disorder (BMD, Bipolar Mood Disorder) is a debilitating and chronic psychological disease with an estimated prevalence of 0.1 to 7.5%. This disorder is characterized by episodes of mania and hypomania and episodes of depression [1]. In the long term, bipolar disorder is associated with a high risk of recurrence and relapse, and depressive episodes in affected patients are longer than mania episodes [2]. During a depressive episode, patients experience symptoms such as helplessness, decreased energy, and feelings of disgust. While in the mania phase, they feel great, increase energy, decrease sleep and feel superior. The neural mechanism of both is clearly defined [3]. In some studies, the prevalence of this disorder is reported to be 2 to 5% of the world's population, and it is associated with suicide-related deaths [3]. In a systematic study in Iran, the prevalence of suicide was 9.4 per 100,000 people. Bipolar disorder is one of the most important psychiatric disorders related to suicide so 29% of these patients commit suicide [4].

A large group of patients with bipolar disorder have experienced one or more major depressive episodes before the onset of a manic episode. The question of who progresses to mania with unipolar depression is difficult to answer. Many studies have shown that patients with bipolar disorder are often misdiagnosed as major depressive disorder [5,6]; And it takes almost a decade from the patient's first visit to receiving a diagnosis of bipolar disorder [7,8]. In general, in the studies that have been conducted, a series of characteristics have indicated a higher risk for the conversion of unipolar depression to bipolar disorder, which are: more number of depressive episodes, early onset of symptoms, greater severity of depression, psychotic symptoms and positive family history of bipolar disorder [9]. The occurrence of mania and hypomania in people receiving antidepressant treatment is considered a side effect. Among these drugs, tricyclic antidepressants (TCA, Tricyclic Agents) and venlafaxine are more related to this issue. However, this issue is not completely clear so it is not clear whether these antidepressants are the cause of acute mania or hypomania or a predisposing factor for experiencing bipolar disorder [10].

Many people with bipolar disorder experience one or more major depressive episodes before their first manic episode. The ability to recognize people with unipolar depression who are at a higher risk of manic episodes and thus turning into bipolar disorder can be useful in interventions, observing symptoms and designing studies to prevent bipolar disorder [11]. Therefore, this study was designed to investigate the frequency of changing

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the diagnosis of Major Depressive Disorder (MDD) to Bipolar Disorder and its related factors. In this way, we are trying to find more possible risk factors in addition to the proven cases related to changing the diagnosis of patients with unipolar depression to bipolar disorder. Knowing these risk factors will be a great help in planning the prevention and treatment of the bipolar disorder [12-14].

Material and Methods

Participants and design

The research population includes all patients who were admitted to Ibn Sina Hospital with a diagnosis of major depressive disorder in the years 2011-2015 and had a history of re-hospitalization at least once. Inclusion criteria: A) All patients admitted to Ibn Sina Hospital between 2011 and 2015 were diagnosed with major depressive disorder. B) At least one history of re-hospitalization with an interval of at least three months. C) At least 3 years of follow-up in patients whose diagnosis did not change? Exclusion criteria: A) Changing the diagnosis in the final hospitalization to schizophrenia or other psychotic disorders. B) Having mood disorders caused by substances and medical causes.

After approving the research and receiving the code of ethics from the ethics committee of the Hormozgan Faculty of Medical Sciences, first, by referring to the medical records office of Ibn Sina Hospital, the files of all patients with the mentioned criteria were obtained. The person's first hospitalization should have been with a diagnosis of major depressive disorder (the diagnosis was based on the final diagnosis recorded in the patient's file by a psychiatrist). In patients whose diagnosis did not change, the interval between the first hospitalization and the last hospitalization of the individual should be at least 3 years (that is, the minimum follow-up period is 3 years and the patients were followed up until the end of 2018). The patient's hospitalization episodes were analyzed from the first hospitalization episode with the diagnosis of major depression to the first hospitalization episode due to bipolar disorder or the last hospitalization in a patient who did not change the diagnosis. The primary factor evaluated was the change of diagnosis to bipolar disorder, based on which the patients were divided into two groups: 1. Patients in whom the change of diagnosis occurred 2. Patients in whom the change of diagnosis did not occur.

Measurements

To evaluate the variables related to the change of diagnosis, a checklist was prepared and the required items (as described in the research tool) were recorded for each patient. Based on the goals of the project, a checklist was designed that included: gender, marital status, education, age of the first hospitalization with a diagnosis of major depressive disorder, age of change of diagnosis to bipolar disorder, total number of hospitalizations, number of hospitalizations with major depressive disorder, the average number of hospitalizations per year, time interval until the change of diagnosis (in months), drug abuse (and type of drug consumed), family history of mood disorders, suicidal thoughts in a depressive episode, presence of psychotic symptoms in depressive episode and presence symptoms of atypical depression.

Ethical considerations

Consent for publication was obtained from all participants. Hormozgan University of Medical Sciences Ethical Committee approved the study under the ethical code IR.HUMS.REC.1398.155.

Sampling and statistical analysis

The present study is a retrospective descriptive-analytical type, and after collecting the desired data, it was entered into SPSS version 25 software and then analyzed using descriptive statistics. Appropriate statistical tests such as chi-square and Fisher's exact test were used to analyze the data, and a P-value less than or equal to 0.05 was considered a significant level. Sampling in this research was by census method so that all the patients who were admitted to Ibn Sina Hospital with a diagnosis of major depressive disorder between 2011 and 2015 were examined. In this way, 338 cases registered in the mentioned years were evaluated; out of which, 183 cases having all the required information, were entered into the study and analyzed.

Results

The average age of the patients at the first hospitalization was 35.39 ± 12.56 years. Among the examined people, 101 people (55.2%) were men and 82 people (44.8%) were women. The diagnosis was changed to bipolar disorder in 51 people (27.9%).

The mean and Standard Deviation (SD) of the age when the diagnosis was changed and the interval, until the diagnosis was changed (in months and years), are reported in Table 1 for these people.

The average number of hospitalizations in the participants of this study was 3.93 ± 3.85 times (minimum 2 and maximum 40 times). In addition, the average number of hospitalizations of people with MDD was 2.95 ± 3.25 times (minimum 1 and maximum 37 times) and the average number of hospitalizations per year was 1.21 ± 0.79 times (minimum 0.2 and maximum 5 times). On the other hand, in the people who finally changed the diagnosis to bipolar disorder, the average age at the time of diagnosis change was 37.04 ± 12.26 years (minimum 17 and maximum 62 years) the average distance to the change of diagnosis was 82.65 ± 4.4 months. 40 months (minimum 1 and maximum 360 months) and 3.4 ± 5.45 years (minimum 0.08 and maximum 30 years) were obtained (Table 1).

Table 1. Mean and standard deviation of quantitative variables examined in the study using descriptive statistics.

Variable	Average	SD	Minimum	Maximum
Age on the first hospitalization	35.39	12.56	14	65
Numbers of Hospitalization	3.93	3.85	2	40
Total times of hospitalization with depression	2.95	3.25	1	37
The average number of hospitalization in the year	1.21	0.79	0.2	5
Age of change in diagnosis (Years)	37.04	12.26	17	62
Time interval to diagnosis change (Months)	40.82	65.4	1	360
Time interval to diagnosis change (Years)	3.4	5.45	0.08	30

In terms of marital status, most of the people in this study were married (63.9%), single (31.7%), divorced and widowed (2.2% each). They were in the next ranks. In terms of education level, most of the people had middle school education (26.2%), and people with diploma education level (20.2%), elementary school (18.6%), illiterate (18%), high school (8.7%), associate graduate (4.9%) and bachelor's degree (3.3%) were in the next ranks in terms of frequency. Drug abuse, family history of mood disorders, suicidal thoughts, psychotic symptoms, and atypical symptoms were observed in 39.9, 26.2, 61.7, 45.9, and 53% of people, respectively. As previously stated, 27.9% of people were diagnosed with bipolar disorder, and in 72.1% of people, the final diagnosis was MDD (Table 2).

Table 2. Frequency of qualitative variables examined in the study using descriptive statistics.

Variable		Frequency	Percentage
Gender	Male	101	55.2
	Female	82	44.8

Marital Status	Single	58	31.7
	Married	117	63.9
	Divorced	4	2.2
	Widowed	4	2.2
Educational Status	Illiterate	33	18
	Elementary School	34	18.6
	Middle School	48	26.2
	High School	16	8.7
	Diploma	37	20.2
	Associate Degree	9	4.9
	Bachelor's Degree	6	3.3
Drug Abuse	Yes	73	39.9
	No	110	60.1
Family History of mood disorder	Yes	48	26.2
	No	135	73.8
Suicidal thoughts during a depression episode	Yes	113	61.7
	No	70	38.3
Psychotic symptoms in a depression episode	Yes	84	45.9
	No	99	54.1
Atypic symptoms in a depression episode	Yes	97	53
	No	86	47
Changed diagnosis to bipolar disorder	Yes	51	27.9
	No	132	72.1

In 73 people who had a history of drug abuse, the most common substance used was opium (54.8%), followed by opium and hashish (12.3%), Opium and alcohol (11%) alcohol (9.6%), opium and amphetamine (6.8%), hashish (4.1%), and amphetamine and hashish (1.4%).

The normality of the distribution of the quantitative data of the study was checked by the Kolmogorov-Smirnov test, and according to this, the distribution of none of these variables (age of the first hospitalization, total number of hospitalizations, number of hospitalizations with MDD and average number of hospitalizations per year) was not normal. To compare these variables between people with diagnosis change to BMD and without diagnosis change, Mann-Whitney non-parametric test was used and for ease of analysis, central index, mean and SD were reported (Table 3).

Table 3. Type of drugs used in people with a history of drug abuse.

Variable		Frequency	Percentage
Type of Drug Use	Opium	40	54.8
	Hashish	3	4.1
	Alcohol	7	9.6
	Opium and Alcohol	8	11
	Opium and hashish	9	12.3
	Opium and amphetamine	5	6.8
	Amphetamine and hashish	1	1.4

Among the 73 people whose diagnosis was changed to bipolar disorder, 27 were women and 24 were men. In 23.8% of men and 32.9% of women, the diagnosis was changed to bipolar disorder, and despite the higher percentage of women with a change of diagnosis, the chi-square test showed that the difference between the two is not statistically significant (P=0.169). Therefore, there is no significant relationship between gender and changing the diagnosis of major depressive disorder to bipolar disorder (Table 4).

Table 4. Type of drugs used in people with a history of drug abuse.

Variable		Sex		P-value
		Frequency (Percentage)		
		Female	Male	
The diagnosis changed to bipolar disorder	Yes	27 (39.9)	24 (23.8)	0.169
	No	55 (67.1)	77 (76.2)	

Although the average age of the first hospitalization in people with a change of diagnosis to bipolar disorder (32.86 ± 11.45 years) is lower than the average age of the first hospitalization in people without a change of diagnosis to bipolar disorder (36.37 ± 12.87 years), the difference between these two is not statistically significant (P=0.790). Therefore, there is no significant relationship between the age of the first hospitalization and the change of diagnosis from major depressive disorder to bipolar disorder (Table 5).

Table 5. The relationship between the age of the first hospitalization and the change of the diagnosis of major depressive disorder to bipolar disorder.

Variable		Age on first hospitalization (Year) (Mean ± SD)	P-value
The diagnosis changed to bipolar disorder	Yes	32.86 ± 11.45	0.79
	No	36.37 ± 12.87	

The change of diagnosis to bipolar disorder did not occur in any of the divorced and widowed people. On the other hand, in 29.3% of single people and 29.1% of married people, the diagnosis of major depressive disorder was changed to bipolar disorder. However, according to Fisher's exact test, the difference between different groups of marital status in terms of changing the diagnosis to bipolar disorder is not significant (P=0.558). Therefore, there is no significant relationship between marital status and changing the diagnosis of major depressive disorder to bipolar disorder (Table 6).

Table 6. The relationship between marital status and changing the diagnosis of major depressive disorder to bipolar disorder.

Variable		Marital Status (Percentage)				P-value
		Single	Married	Divorced	Widowed	
The diagnosis changed to bipolar disorder	Yes	29.3 (17)	34 (29.1)	0 (0)	0 (0)	0.558
	No	41 (70.7)	83 (70.9)	4 (100)	4 (100)	

The change of diagnosis to bipolar disorder is mostly in people with middle school education level (35.4%), followed by people with elementary school education level (32.4%), high school (31.3%), illiterate (30.3%), bachelor's degree (33.3%), postgraduate diploma (22.2%) and diploma (10.8%). Fisher's exact test showed that the difference between these groups is not statistically significant (P=0.199). Therefore, there is no significant relationship between educational attainment and change in the diagnosis of major depressive disorder to bipolar disorder (Table 7).

Table 7. The relationship between education level and the change in the diagnosis of major depressive disorder to bipolar disorder.

Variable		Educational Level Frequency (Percentage)							P-value
		Illiterate	Elementary School	Middle School	High School	Diploma	Associate Degree	Bachelor's Degree	
The diagnosis changed to bipolar disorder	Yes	10 (30.3)	11 (32.4)	17 (35.4)	5 (31.3)	4 (10.8)	2 (22.2)	2 (33.3)	0.199
	No	23 (69.7)	23 (67.6)	31 (64.6)	11 (68.8)	33 (89.2)	7 (77.8)	4 (66.7)	

Based on the chi-square test, the rate of change of diagnosis to bipolar disorder in people without a history of drug abuse (33.6%) is significantly more than in people with a history of drug abuse (P=0.033). Therefore, there is a significant inverse relationship between drug abuse and the change of major depressive disorder to bipolar disorder, at the presence of drug abuse reduces the probability of changing the diagnosis to bipolar disorder, and in fact, the probability of changing the diagnosis to bipolar disorder is less in people with drug abuse (Table 8).

Table 8. The relationship between drug abuse and changing the diagnosis of major depressive disorder to bipolar disorder.

Variable		Drug Abuse Frequency (Percentage)		P-value
		Yes	No	
The diagnosis changed to bipolar disorder	Yes	14 (19.2)	37 (33.6)	0.033
	No	59 (80.8)	73 (66.4)	

In 33.3% of people with a family history of mood disorders and 25.9% of people without a family history of mood disorders, the diagnosis was changed to bipolar disorder based on the chi-square test. The difference between these two is not statistically significant (P=0.326). Therefore, there is no significant relationship between the family history of mood disorders and the change of diagnosis from major depressive disorder to bipolar disorder (Table 9).

Table 9. Relationship between family history of mood disorders and change of diagnosis of major depressive disorder to bipolar disorder.

Variable		Family history of mood disorder Frequency		P-value
		Yes	No	
The diagnosis changed to bipolar disorder	Yes	16 (33.3)	35 (25.9)	0.326
	No	32 (66.7)	100 (74.1)	

Based on the chi-square test, the rate of change in diagnosis to bipolar disorder in people with atypical depressive symptoms in depressive episodes (49.5%) is significantly higher than in people without atypical depressive symptoms in depressive episodes (3.5%) (P<0.001). Therefore, there is a significant relationship between the presence of atypical depressive symptoms in depressive episodes and the change of diagnosis from major depressive disorder to bipolar disorder; In other words, the possibility of changing the diagnosis to bipolar disorder increases significantly in people with atypical depressive symptoms during depressive episodes (Table 10).

Table 10. The relationship between the presence of atypical depressive symptoms in depressive episodes and the change of diagnosis to bipolar disorder.

Variable		Atypic depression symptoms in depressive episodes		P-value
		Yes	No	
The diagnosis changed to bipolar disorder	Yes	48 (49.5)	3(3.5)	<0.001
	No	49 (50.5)	83(96.5)	

In 30.1% of people with suicidal thoughts during depressive episodes and 24.3% of people without suicidal thoughts during depressive episodes, the diagnosis changed to bipolar disorder, which the chi-square test shows. The difference between these two is not statistically significant (P=0.395). Therefore, there is no significant relationship between the presence of suicidal thoughts in depressive episodes and changing the diagnosis of major depressive disorder to bipolar disorder (Table 11).

Table 11. The relationship between the presence of suicidal thoughts in depressive episodes and the change of diagnosis to bipolar disorder.

Variable		Suicidal thoughts in depressive episodes		P-value
		Yes	No	
The diagnosis changed to bipolar disorder	Yes	34 (30.1)	17 (24.3)	0.395
	No	79 (69.9)	53 (75.7)	

Based on the chi-square test, the rate of change in diagnosis to bipolar disorder in people with psychotic symptoms in depressive episodes (38.1%) is significantly higher than in people without atypical depressive symptoms in depressive episodes. (19.2%) (P=0.004). Therefore, there is a significant relationship between the presence of psychotic symptoms in depressive episodes and the change of diagnosis from major depressive disorder to bipolar disorder; In other words, the possibility of changing the diagnosis to bipolar disorder increases significantly in people with psychotic symptoms during depressive episodes (Table 12).

Table 12. The relationship between the presence of psychotic symptoms in depressive episodes and the change of diagnosis to bipolar disorder.

Variable		Psychotic symptoms in depressive episodes		P-value
		Yes	No	
The diagnosis changed to bipolar disorder	Yes	32 (38.1)	19 (19.2)	0.004
	No	53 (61.9)	80 (80.8)	

According to the Mann-Whitney test, the average number of depressive episodes in people with a diagnosis changed to bipolar disorder (3.31 ± 5.55 times) is significantly higher than the average number of depressive episodes in people without changing the diagnosis to bipolar disorder (2.80 ± 1.69) (P=0.006). Therefore, there is a significant relationship between the number of depressive episodes and changing the diagnosis of major depressive disorder to bipolar disorder; with the increase in the number of depressive episodes, the possibility of changing the diagnosis to bipolar disorder increases (Table 13).

Table 13. The relationship between the number of hospitalizations for depression and the change in the diagnosis of major depressive disorder to bipolar disorder.

Variable		Number of hospitalizations with depression (Mean ± SD)	P-value
The diagnosis changed to bipolar disorder	Yes	3.33 ± 5.55	0.006
	No	2.80 ± 1.69	

Even though the average number of hospitalizations per year is lower in people with a change of diagnosis to bipolar disorder (1.30 ± 0.82) compared to people without a change of diagnosis to bipolar disorder (78 1.78 ± 0.01), according to the Mann-Whitney test, the difference between these two is not statistically significant (P=0.281). Therefore, there is no significant relationship between the average number of hospitalizations per year and the change of diagnosis from major depressive disorder to bipolar disorder (Table 14).

Table 14. The relationship between the average number of hospitalizations per year and the change in the diagnosis of major depressive disorder to bipolar disorder.

Variable	The average number of hospitalizations per year		P-value
The diagnosis changed to bipolar disorder	Yes	1.30 ± 0.82	0.281
	No	1.78 ± 0.78	

As mentioned before, out of 183 patients with major depressive disorder investigated in this study, 51 people changed their diagnosis to bipolar disorder, so the overall incidence of bipolar disorder among patients with major depressive disorder is 278.7 people out of every thousand people. According to the total time interval from the first change of diagnosis to the last one (29.92 years), the incidence rate of bipolar disorder among those suffering from depression is calculated to be 3.9 out of every thousand people per year.

In the logistic regression, there was a positive and significant relationship between the presence of atypical symptoms in depressive episodes and the change of diagnosis to bipolar disorder (OR=35.45, with a 95% confidence interval in the range of 9.53 to 131/84 and P<0.001). Thus, the probability of changing the diagnosis to bipolar disorder among people with the major depressive disorder who have atypical symptoms in depressive episodes is about 35 times that of those who do not have these symptoms in depressive episodes (Table 15).

Table 15. Evaluation of factors predicting the change of diagnosis to bipolar disorder based on logistic regression.

Variable	B	Odds Ratio	Odds ratio with a 95% confidence interval		P-value
			Minimum	Maximum	
Sex	0.052	1.054	0.405	2.741	0.915
Mariatal Status	-0.723	0.485	0.191	1.233	0.129
Education	-0.191	0.826	0.607	1.125	0.226
Drug Abuse	-0.889	0.411	0.16	1.054	0.064
Family history of mood disorder	0.147	1.159	0.441	3.047	0.765
Suicidal thoughts	0.163	1.177	0.491	2.822	0.715
Psychotic symptoms	0.417	1.517	0.639	3.602	0.345
Atypic Symptoms	3.586	35.449	9.532	131.84	<0.001
Age of the first hospitalization	-0.0039	0.962	0.922	1.004	0.076
Number of hospitalization with depression	0.072	1.075	0.913	1.265	0.385
The average number of hospitalization per year	-0.175	0.84	0.486	1.452	0.532

Discussion

In many cases, the first episode of bipolar disorder may be in the form of depression and the episode of mania or hypomania occurs later, and thus patients are treated as major depressive disorder. In addition, the occurrence of mania and hypomania in people who receive antidepressant treatment is considered a side effect. The relationship between some characteristics of major depressive episodes and the change of diagnosis to bipolar disorder has been investigated in previous studies. Therefore, in this study, we investigated the predictive factors of bipolar disorder in patients with major depression to identify more risk factors if possible.

As seen, the results of the current study indicate that bipolar disorder occurs in 9.3 out of every thousand people with major depressive disorder per year. Also, in this research, inverse and significant relationships were found between drug abuse and the change of diagnosis to bipolar disorder. In addition, there was a significant relationship between the presence of atypical depressive symptoms and psychotic symptoms with the change of diagnosis. The number of hospitalizations with depression was also significantly higher in people with a change in diagnosis to bipolar disorder than in people without a change in diagnosis. However, in logistic regression, only the presence of atypical symptoms in depressive episodes had a significant relationship with changing the diagnosis to bipolar disorder with OR=35.45 (95% confidence interval, 9.53 to 131.84) and P<0.001. In contrast, the average age of the first hospitalization with the diagnosis of major depression, gender, marital status, level of education, family history of mood disorders, the presence of suicidal thoughts in depressive episodes and the average number of hospitalizations per year was not found to be significantly related to the change of the diagnosis of major depressive disorder to bipolar disorder.

In the present study, the diagnosis was changed to bipolar disorder in 27.9% of patients with major depressive disorder. In Akhundpour et al.'s study, 44.8% of patients diagnosed with depression were diagnosed with bipolar spectrum based on the MDQ test [15]. The percentage reported in this study is almost double that of the present study. The reason for the difference between the two studies is probably the diagnosis tool of bipolar spectrum disorders and diseases considered in this spectrum in the study of Akhundpour et al.

Bipolar disorder was diagnosed in 25.4% of patients with MDD in the study of Inoue et al., which is almost in line with the present study [2]. The conversion rate of diagnosis to bipolar disorder in Ratheesh et al.'s review study was 22.5% [16], and conversion to bipolar type I and II in Akiskal et al.'s study was 12.5% [17].

Converting to bipolar disorder within 3 years of follow-up in Gilman et al.'s study was about 1 out of every 20 people who had MDD [6] and undiagnosed bipolar disorder in Abhari et al.'s study in patients with MDD was reported as 53.9% [18].

The change of diagnosis to bipolar disorder in women during pregnancy and after delivery in the study by Sharma et al. was 6.52% [19] and the change of diagnosis to bipolar disorder in patients with MDD resistant to antidepressants in the study of Li et al. was 7.6 to 12.1% [20].

In the current study, the overall incidence of bipolar disorder among patients with the major depressive disorder was 9.3 out of every thousand people per year. And the rate of diagnostic change of bipolar disorder among those suffering from depression was 27.9%. In the study by Ratheesh et al., the incidence rate of bipolar disorder in patients with major depressive disorder within 2 years of follow-up was 4% or 40 people per thousand per year [16]. In another study examined in this review, the incidence rate of bipolar disorder in patients with major depressive disorder in the first 5 years after the depressive episode was reported as 2.5% per year [16].

The percentage of men in Akhundpour et al.'s study was 27.2% [15], in Fela-Thomas et al.'s study it was 30.1% [1], in Inoue et al.'s study it was 47.7% [2], in Gilman's study et al., 27.7% [9], in the study by Abhari et al., 33.9% [18], in the study by Haro et al., 23.9% [21], and in the study by Li

et al., 35.5% [20]. In the study by Sharma et al., according to the study design, all the participants were women [19]. Therefore, it seems that the sex ratio of the participants of Inoue's study is closer to the sex ratio of the participants of the present study than in other studies.

In the current study, even though the percentage of women with a change of diagnosis to bipolar disorder (32.9%) was higher than the percentage of men with a change of diagnosis (23.8%), the difference between the two was not significant, and in fact, there was a significant relationship between gender and a change in diagnosis from major depressive disorder to bipolar disorder was not found. The findings of the study by Akiskal et al., Inoue et al., Abhari et al., Haro et al., and Li et al. are consistent with this study [2,17,18,20,21].

In the review study by Ratheesh et al., in 7 studies with homogeneous gender distribution, the chance of becoming bipolar disorder was non-significantly lower in women than in men, but in one of the reviewed studies, a significant relationship was found between the change of diagnosis and male gender [16]. These findings are contrary to the findings of the present study and the difference between the two studies is probably due to the different gender distribution.

In Akhundpour et al.'s study, 79.6% of the patients were married, 18.8% were single, 1.2% were divorced, and 0.4% were widows [15], which is similar to the present study. Also, comparing the frequency of the bipolar disorder in patients by marital status, there was no significant difference, which is also consistent with our study.

Unlike the present study, in Akiskal et al.'s study, the probability that people with a change of diagnosis were married or had a partner was lower (31.2% vs. 50.9%) compared to people without a change in diagnosis, and the absolute probability or widowhood and singleness of people with a change of diagnosis were more (33.3% vs. 20.9% and 35.4% vs. 28.1%, respectively) and the differences were significant. On the other hand, to control the effect of age in this study, the marital status of people at least 25 years of age was examined, and the risk of changing the diagnosis to bipolar disorder in people with a breakup of marriage (separation or divorce) was 1.7 times that of others [17]. The difference between the two studies may be due to the difference in the distribution of marital status.

In line with the present study, there was no significant difference in terms of marriage history, divorce, spouse's death, presence of a spouse, presence of children, and the presence of a housemate, between people with a change of diagnosis to bipolar disorder and without a change of diagnosis in the study of Inoue et al. [2]. In the study by Sharma et al., the difference between single and married people was not significant in terms of changing the diagnosis to bipolar disorder [19].

However, in Haro et al.'s study, in terms of the percentage of single people, divorced or separated people, and widows, a significant difference was found between the two groups with the start of antidepressant treatment and the change of treatment [21], which due to the different design of this study and the present study. The findings are not comparable.

In Abhari et al.'s study, 66.1% of the participants were married and 33.9% were single, divorced or widowed, which is almost similar to the present study. However, the percentage of married people in patients with a change in diagnosis to bipolar disorder was significantly lower than in people without a change in diagnosis [18].

In the current study, there was no significant relationship between the level of education and the change of diagnosis from major depressive disorder to bipolar disorder. But in the study by Fela-Thomas et al., respectively, 52% of the people had high school education, 19.5% elementary school education, and 19.1% university education, and 7.7% did not have any academic education. Of course, the design of this study was different from the present study and the percentages are not comparable [1]. In the study by Haro et al., with a different design compared to the present study, there was a significant difference in terms of the percentage of people without a degree or with a diploma, education at the elementary school, high school level, non-university degree, and university degree between people who started or changed antiretroviral therapy. Depression was found [21]. Consistent with the present study, in Inoue et al.'s study, the average years of education did not have a significant difference between the two groups with a change in diagnosis to bipolar disorder and without a change in diagnosis [2]. On the other hand, in the study of Gilman et al., a significant relationship was found between educations less than high school level and changing the diagnosis to bipolar disorder [9].

In the current study, the average age when the diagnosis changed from major depressive disorder to bipolar disorder was 37.04 ± 12.26 years (minimum 17 and maximum 62 years). This variable was not reported in the studies reviewed in this research. In the review study conducted by Ratheesh et al., in one study, the most change in diagnosis occurred in the first 4 to 8 years of follow-up. In two other studies, 85% of the changes in diagnoses occurred in the first 3 to 5 years [16]. According to the average of 3.4 years in the present study, the findings are somewhat consistent.

In Inoue et al.'s study, 24.7% of diagnoses changed within 1 year, 11.3% between 1 and 2 years, 11.3% between 2 and 3 years, 6.2% between 3 and 4 years, and 46.4% had occurred within 4 years or more from the first visit of patients with MDD, and the average of this time was 4.6 and the median was 3 years [2]. But, in the present study, the average interval until the change of diagnosis was 40.82 ± 65.4 months (minimum 1 and maximum 360 months) and 3.4 ± 5.45 years (minimum 0.08 and maximum 30 years).

In the study by Li et al., bipolar disorder occurred in 7.6% of the cohort participants within 5 years, in 10.1% of the same cohort within 8 years, and in 12.1% of the 2003 cohort participants within 5 years was diagnosed with major depressive disorder [20].

On the other hand, in most of the studies, the age of the first admission with the major depressive disorder was recorded, the average of which in the present study was 35.39 ± 12.56 years, and it was insignificantly lower in people with a diagnosis change to bipolar disorder than in people without a change in diagnosis (32.86 ± 11.45 versus 36.37 ± 12.87 years, P=0.790).

The average age of onset of depression in the patients of Akhundpour et al.'s study was 30.93 ± 4.99 years [15]. In a review study conducted by Ratheesh et al., in 9 studies, the relationship between the age of onset of MDD and the change of diagnosis to BMD was investigated, except for 2 studies, in other studies, there was a significant relationship between the younger age at the onset of MDD and the increase in the rate of change of diagnosis. It was seen [16]. In terms of the significance of the relationship between the findings of this study, it is contrary to the present study, but in this study, in line with our study, the age of onset of MDD in people with a change in diagnosis is on average 4.8 ± 0.52 years less than in people without a change in diagnosis of bipolar disorder.

In Akiskal et al.'s study, the age of the first episode of MDD was significantly lower in people with BMD type II diagnosis change than in people without diagnosis change (25.4 ± 10.2 versus 31.3 ± 14.3 years, P =0.006) [17]. In addition, in the logistic regression performed in the study of Inoue et al., younger age at the first episode of depression (less than 25 years) was a significant predictor for changing the diagnosis to bipolar disorder [2]. The findings of Akechi et al.'s study were similar [22].

In the study of Koirala et al., the age of people at the time of the first episode of depression was significantly lower in people with a change in diagnosis than in people without a change in diagnosis [23]. The significant difference between the age of the first episode of depression in people with a change of diagnosis to bipolar disorder and people without a diagnosis (the age of the first episode of depression is lower in people with a change of diagnosis) in most studies and its difference with the findings of the present study (non-significant difference) can be due to the difference In the studied sample size, the role of confounding factors and the fact that in our study, the age of the first hospitalization with major depressive disorder is considered, while the person may have had a major depressive episode before and at a younger age, but not admitted to the hospital.

In the present study, drug abuse was reported in 39.9% of people. Of 73 people who had a history of drug abuse, the most common substance used

was opium (54.8%), followed by opium and hashish (12.3%), opium and alcohol (11%), and alcohol alone. (9.6%), opium and amphetamine (6.8%), hashish (4.1%) and amphetamine and hashish (1.4%). The rate of change of diagnosis to bipolar disorder in people without a history of drug abuse (33.6%) was significantly more than in people with a history of drug abuse. Therefore, there was a significant inverse relationship between drug abuse and the change of major depressive disorder to bipolar disorder, so the presence of drug abuse reduced the probability of changing the diagnosis to bipolar disorder, and in fact, the probability of changing the diagnosis to bipolar disorder was less in people with drug abuse.

Unlike the present study, in the study by Akiskal et al., the history of drug use was associated with a higher probability of converting the diagnosis to bipolar disorder [17]. The difference between the two studies could be due to the difference in the overall prevalence of drug use in the populations or the inaccurate reporting of drug abuse status in the present study.

Drug abuse and its relationship with the change of diagnosis in other studies were not evaluated in the present study because drug abuse was one of the criteria for patients to be excluded from the study in some studies.

In Akhundpour et al.'s study, a family history of depression was reported in 42.8% and a family history of bipolar disorder in 7.6% of the participants [15]. In the same study, unlike the present study, there was a significant difference in comparing the frequency of bipolar spectrum in patients according to the presence of a family history of depression, and people with a positive family history of depression were more likely to have bipolar spectrum. The difference between the two studies could be due to the type of mood disorder considered as family history; If only the family history of depressive disorder was considered in the present study, maybe the difference would be significant.

In Bisharat et al.'s study, unlike the present study, there was a significant difference in terms of family history of bipolar disorder between people with a final diagnosis of bipolar disorder and people with a final diagnosis of major depressive disorder. In this study, only a family history of bipolar disorder among mood disorders was considered [24]. Also, in the study by Sharma et al., a significant relationship was found between the family history of bipolar disorder and the change of diagnosis to bipolar disorder in depressed patients [19]. Similarly, in Abhari et al.'s study, the percentage of people with a family history of bipolar disorder was significantly higher in participants with a change in diagnosis than in participants without a change in diagnosis [18].

In the review study by Ratheesh et al., in 5 studies, a significant relationship was found between a family history of bipolar disorder and conversion of the diagnosis to this disorder in patients with major depressive disorder, and the overall OR in the presence of family history were 2.89. In 4 other studies examined in this review research, a family history of bipolar disorder or depression was considered. In one of these studies, a significant relationship between these records and change of diagnosis was seen, and in the other 3 studies, in line with the present study, there was no relationship between these records and change of diagnosis [16]. In Gilman et al.'s study, in line with the present study, a family history of major depressive disorder had no significant relationship with changing the diagnosis to bipolar disorder [9].

Consistent with the present study, in the review study by Ratheesh et al., suicidal thoughts or attempted suicide were not predictors of changing the diagnosis to bipolar disorder in people with major depressive disorder (16). On the other hand, in Inoue et al.'s study, the history of suicide attempts (and not the existence of suicidal thoughts) had a significant relationship with changing the diagnosis to bipolar disorder [2]. In the study by Haro et al., despite the different design, suicide attempts were significantly higher in people changing antidepressant treatment than in people starting this treatment for the first time [21]. In Abhari et al.'s study, the average number of suicide attempts was significantly higher in people with a change in diagnosis than in people without a change in diagnosis [18]. One of the reasons for the difference between these studies and our study can be due to the consideration of suicide attempts instead of suicidal thoughts (intended in our study).

In the present study, atypical symptoms in depressive episodes were recorded in 45.9% of the participants. The rate of change of diagnosis to bipolar disorder in people with atypical depressive symptoms in depressive episodes (49.5%) was significantly higher than in people without atypical depressive symptoms in depressive episodes (3.5%). Therefore, there was a significant relationship between the presence of atypical depressive symptoms in depressive episodes and the change of diagnosis from major depressive disorder to bipolar disorder; In other words, the probability of changing the diagnosis to bipolar disorder in people with atypical depressive symptoms increased significantly during depressive episodes.

The findings of Abhari et al.'s study were consistent with the present study [18], but unlike our study, the presence of atypical symptoms in Gilman et al.'s study had no significant relationship with changing the diagnosis of bipolar disorder [9].

Psychotic symptoms in depressive episodes were found in 53% of the participants of the present study. The rate of change of diagnosis to bipolar disorder in people with psychotic symptoms in depressive episodes (38.1%) was significantly higher than in people without atypical depressive symptoms in depressive episodes (19.2%). Therefore, there was a significant relationship between the presence of psychotic symptoms in depressive episodes and the change of diagnosis from major depressive disorder to bipolar disorder; In other words, the possibility of changing the diagnosis to bipolar disorder was significantly increased in people with psychotic symptoms during depressive episodes.

Consistent with our study, in Akiskal et al.'s study, the presence of psychotic symptoms in depressive episodes had a significant relationship with changing the diagnosis to bipolar disorder [17]. However, in Abhari et al.'s study, even though psychotic symptoms were higher in people with a change in diagnosis to bipolar disorder than in people without a change in diagnosis, the difference was not statistically significant [18]. On the other hand, in the review study by Ratheesh et al., in 5 studies, a significant relationship was found between psychotic symptoms and the later onset of bipolar disorder, and the overall OR for this variable was 4.76 [16].

The average number of hospitalizations of people with MDD in the present study was 2.95 ± 3.25 times (minimum 1 and maximum 37 times). The average number of depressive episodes in people with a change in diagnosis to bipolar disorder (3.31 ± 5.55 times) is significantly higher than the average number of depression episodes in people without a change in diagnosis to bipolar disorder (2.80 ± 1.69). Therefore, there was a significant relationship between the number of depressive episodes and changing the diagnosis of major depressive disorder to bipolar disorder; so with the increase in the number of depressive episodes, the possibility of changing the diagnosis to bipolar disorder increased. Similarly, in Abhari et al.'s study, the average number of hospitalizations with a mood disorder was significantly higher in people with a change in diagnosis than in people without a change in diagnosis [18]. In Haro et al.'s study, the number of previous hospitalizations with depression in people starting treatment was significantly more than in people changing antidepressant treatment [21].

The difference between the average numbers of hospitalizations per year in people with a change of diagnosis to bipolar disorder (1.30 ± 0.82) compared to people without a change of diagnosis to bipolar disorder (1.78 ± 0.78), was not statistically significant. Therefore, there was no significant relationship between the average number of hospitalizations per year and changing the diagnosis of major depressive disorder to bipolar disorder.

In the logistic regression, there was a positive and significant relationship between the presence of atypical symptoms in depressive episodes and the change of diagnosis to bipolar disorder (OR=35.45, with a 95% confidence interval in the range of 9.53 to 131.84 and P<0.001). Thus, the probability of changing the diagnosis to bipolar disorder among people with the major depressive disorder who have atypical symptoms in depressive episodes is about 35 times that of those who do not have these symptoms in depressive episodes.

One of the limitations of this study was that a large number of cases examined in the medical records department of Ibn Sina Hospital, which met the criteria for entering the study, did not contain all the information required for the examination, so in the end, only 183 cases were statistically analyzed. It is possible that several patients were in the hypomania phase and were not hospitalized and since in this study, only the files of patients who were hospitalized were reviewed, these patients were not included in the study.

It is suggested that a similar study be conducted in other centres (in the country) according to the design of this study and the results be compared with the present study. In addition, statistical analysis can be performed on the information obtained from all centres in a pooled form. In this case, as the number of samples increases, the results can be generalized to the entire population.

It is suggested to take measures to consider the variables investigated in this study in the case of patients admitted to Ibn Sina Hospital with a diagnosis of major depression from the beginning and to enter all the related information carefully in the files. Thus, in the coming years, we will be able to conduct a similar study with a higher number of samples in the same hospital.

It is suggested to conduct prospective cohort studies in this field and follow patients in the coming years.

Conclusion

In general, it seems that in patients with major depressive disorder, the presence of atypical depressive symptoms and psychotic symptoms in depressive episodes, the absence of drug abuse, and the higher number of hospitalizations with depression are predictors of changing the diagnosis to bipolar disorder. In contrast, the average age of the first hospitalization with the diagnosis of major depression, gender, marital status, level of education, family history of mood disorders, the presence of suicidal thoughts in depressive episodes and the average number of hospitalizations per year does not seem to significantly predict the change of diagnosis to BMD in patients with MDD.

Ethics Approval and Consent to Participate

Hormozgan University of Medical Sciences Ethical Committee approved the study under the ethical code IR.HUMS.REC.1398.155.

Consent for Publication

Consent for publication was obtained from all participants.

Availability of Data and Materials

The data sets used during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare no conflict of interest.

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Authors' Contributions

FM made a substantial contribution to the design and conception of the study, performed acquisition of data, performed statistical analysis of the data and interpretation of data. SZ made a significant contribution to the design and concept of the study, completed the acquisition of data, and performed statistical analysis of the data and interpretation of data. FH made a substantial contribution design and conception of the study and performed data acquisition. MSA made a considerable contribution in design and conception of the study, performed the data acquisition and wrote the manuscript. AM made a considerable contribution in design and conception of the study, performed the data acquisition and wrote the manuscript. SHS made a considerable contribution in design and conception of the study, performed the data acquisition and wrote the manuscript. ASA made a significant contribution to the design and concept of the research and revisited the manuscript critically. FKM made a substantial contribution to the study's design and conception, reviewing the manuscript critically.

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