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Original Article

Effective Factors on the Recurrence of Bipolar Mood Disorder I in an Iranian Population Sample Using the Frailty Model with Bayesian Approach

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Abstract

Objective: Bipolar I disorder is one of the most frequent mental disorders characterized by manic or mixed +/- depressive episodes. Drug treatment has been proved to diminish next episodes, but many other factors are important for exacerbating the conditions. This study aimed to investigate the effective factors on the time and number of episodes in these patients by applying the shared frailty model.
Method: In this retrospective longitudinal study, the information of 606 patients with bipolar I disorder, admitted for the first time in Ibn-e-Sina psychiatric hospital in Mashhad from the beginning of 2007 until the end of 2009 were used. These patients were followed up until the end of 2018 for readmission. The Cox model with gamma frailty and Bayesian approach were used to determine the effective factors of frequent recurrences.
Results: History of head trauma, substance abuse, and legal conflict had a positive impact on recurrences, while age had a negative effect on recurrences and the risk of recurrence was higher in younger people ($P < 0.05$). The variance estimation of frailty effect was 0.97 that indicates a correlation between the recurrence intervals of bipolar I patients, owing to a heterogeneity among patients.
Conclusion: Based on the results, a higher risk of recurrence of bipolar I disorder was found in younger patients and those with a history of head trauma, substance abuse, and legal conflicts. Further investigations are required to account for the genetic factor and psychosocial exposure during critical periods applying this model.

Key words: *Bayesian Analysis; Bipolar Disorder; Recurrence*

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Mood disorder is one of the most prevalent psychiatric disorders and it is considered as a major precluding factor worldwide (1). Bipolar disorder is classified as a mood disorder and it is identified by episodic changes in the mood (2). The studies related to the cost burden of different disorders indicated that the financial burden of bipolar disorder is more than the other behavioral disorders (3). Bipolar disorder types I (BD-I) may be characterized by recurrent episodes of mania, mixed or/and depression (4).

Based on the Iranian mental health survey, the prevalence of BP-I is reported as 1% (5). Despite the genetic risks in pathogenesis of this disease (6), it seems that different factors can influence the course, symptoms, severity, respond to treatment, harmful outcomes and recurrence of bipolar disorder (7-13). In regard to the chronic nature of this illness, it can have an impact on all aspects of patient's life and despite the various medical and psychological interventions (14-17), it leads to dysfunction in different dimensions (18). Also, the recurrence of this disorder is common. Based on a study, recurrence occurs during 2 years among approximately 50% of patients receiving medical treatments (19). The repetitive recurrences included higher patients' disability, harm effects, dysfunction, and cost burden (20). Therefore, the factors related to recurrence should be identified for better management and control of the treatment process. Based on the previous studies, different factors were suggested as risk factors for recurrence, such as type of disorder, time after first episode, gender, age, family history, nonadherence to treatment, psychiatric comorbidities, educational level, marital status, life events, and alcohol or substance abuse (20-28). Since there is no study concerning the importance of individual characteristics as risk factors for the recurrence of bipolar disorder in Iran, this study aimed to assess the effective factors on the recurrence of bipolar mood disorder I in an Iranian population using a frailty model with the Bayesian approach. This study was approved by the ethics committee of Mashhad University of Medical Sciences in Iran with the ethics code of MUMS.REC.1395.101.

Materials and Methods

This retrospective longitudinal study was conducted on 606 hospitalized BD-I patients with at least 1 history of readmission due to recurrence from the beginning of 2007 to the end of 2009 in Ibn-e-Sina psychiatric hospital (one of the greatest psychiatric hospitals in Iran) of Mashhad (Northeast of Iran). The patients were followed up for recurrence until the end of 2018. Data were collected using the medical records. Recurrence is defined by having a new manic, mixed or major depressive episode that needs hospitalization and a minimum 2-month's interepisode time. All patients had experienced at least an acute manic or mixed episode and the diagnosis was based on a semistructured interview of 2 psychiatrists based on the DSM-IV-TR criteria. The variables including gender, age at onset of illness, the obvious stress (individual, business, family), marital status, family history, severe head trauma, substance abuse, and legal conflicts were recorded and analyzed in this study.

Statistical analysis:

The most common method for survival data analysis is Cox proportional hazards model (29).

The requirement of this model is survival time independence. There is a correlation between survival times for each person in the cases of diseases with recurrence and return probability. This correlation due to individual and hereditary characteristics that differ from person to person, cannot be measured and incorporated into the model. Ignoring this correlation leads to an underestimation of the parameters' estimation (29). To eliminate the effect of these factors, they are multiplied as random variables by the hazard function that is called shared frailty model. $\lambda(t \mid \mathrm{x}, \mathrm{u}) = \lambda_0(t) u \exp(Bx)$, where is the indicator of known variables vector and is the indicator of unknown variables vector with a gamma distribution and λ_0 as a piecewise constant baseline hazard function. In this current study, the model is specified as :

$$\lambda_i(t) = \lambda_0(t) \times u_i \times \exp[\beta\, Age_i + \beta\, Headtrauma + \beta \times Stress + \beta_4 \times Sex + \beta \times maritalstatus + \beta \times Familyhistory + \beta_7 \times subs\tan ceAbuse + \beta_8 \times Legalconfilct]$$

In this study, the time from each discharge from the hospital until the next episode and readmission was considered as survival time. It means the first survival time is the time from the first discharge until the second admission and the second survival time is the time from the second discharge until the third admission and so on. The Bayesian approach was applied to estimate the parameters of the model. The advantage of this approach is that it combines experimental and prior or external information via the Bayes theorem for producing the posterior distribution that is used to make all inferences about the estimate of interest.

$p(d \mid data) \sim p(data \mid d) \times p(d)$, where is the parameter of interest. Posterior distribution ~ data likelihood prior distribution. In cases where selecting a prior distribution is difficult, a prior distribution can be selected in which the dominant information in the posterior distribution provided by the data, such priors, are known as noninformative prior (30). The software employed in this analysis was Win BUGS.

Results

A total of 606 patients with BD-I participated in this study, of whom 380 patients (62.7%) were male and 226 (37.3%) were female. The mean age was 13.25 ± 38.92 years. A total of 331 patients (54.9%) were married and 165 (27.2%) had a history of head trauma, 313 (51.8 %)

a history of stress. A total of 181 participants (29.9 %) had a history of substance abuse and 163 (26.9%) had a history of legal conflict. Of these, 115 patients with BD-I (34.8%) had experienced more than 2 episodes with admissions (Table 1).

In the frailty model, history of head trauma ((95% CI: [0.95, 0.98]), history of substance abuse ((95% CI: [0.14, 0.68]), history of legal conflict ((95% CI: [0.25, 0.77]), age ((95% CI: [-0.019, -0.005]), and the frequent recurrences of bipolar disorder were significant through Bayesian credible intervals, which did not include zero. Also, the mean posterior frailty variance was estimated to be 0.97 with ((95% CI: [0.79, 1.23]), indicating that there was heterogeneity among participants, which was significant according to their credible intervals (Table 2).

Table 1. The Frequency and Times of Recurrence among Bipolar I Patients

Recurrence number	Frequency	Percent
Once	140	42.1
Twice	77	23.1
Three times	54	16.26
Four times	20	6.02
Five times and more	41	12.52

Table 2. Statistical Summary of the Cox Proportional Hazard Shared Gamma Frailty Model among Bipolar I Patients

Variable	Reference Category	Mean	SE	CI 95%
Age		-0.0156	0.0053	(-0.019, -0.005)
Head trauma	Doesn't have	0.7418	0.1216	(0.495, 0.980)
Stress	Doesn't have	0.1941	0.137	(-0.378, 0.1186)
Sex	Male	-0.039	0.1012	(-0.2038, 0.086)
Marital status	Single	-0.0123	0.137	(-0.378, 0.1186)
Family history	Doesn't have	0.517	0.1202	(-0.183, 0.270)
Substance abuse	Doesn't have	0.383	0.13	(0.14, 0.68)
Legal conflict	Doesn't have	0.4935	0.133	(0.257, 0.777)
Fragility variance		0.97	0.148	(0.76, 1.23)

Mean: mean posterior distribution; SE: standard deviation; CI 95%: credible interval 95%.

Discussion

The results of the present study demonstrated that history of head trauma, substance abuse, and legal conflict had a positive impact on recurrences, while age had a negative impact on recurrences. The risk of recurrence was higher in younger people. The variance estimation of the frailty effect indicated a correlation between the recurrence intervals of bipolar I patients, which is due to heterogeneity between individuals. In the absence of careful longtime management and follow-up, many patients with BD-I experience frequent recurrences during their lifetime, which has an influence not only on the mind and functionality but also on the interpersonal and familial status of the patients; and finally, more episodes lead to a worse prognosis (31). According to the study conducted by Ghoreishizadeh et al in Iran, the major factors in the recurrence of bipolar disorder were cessation of medical treatment, a decrease in the dose of medication, insomnia or irregular sleep, lack of knowledge, substance abuse, and lifetime events. The results related to substance abuse and negative lifetime events are in line with the results of the present study (20). Based on the results of Gilman et al study, the age of onset and age of first recurrence of BD-I are assumed as important prognosis predictors, although some studies determined the number of frequent recurrences as a more prominent factor (32), while some studies do not show significant associations (33,34). In this study, the age of onset was proved to be significant, so that young patients who had their first experience of recurrence were more prone to frequent episodes. The negative impact of substance abuse or dependency on the prognosis and recurrences of BD-I was determined in many studies (35). The highest rate for mood disorders (and bipolar disorder) was observed among alcohol and other substance abusers (36). A cross-sectional study on

30 patients with BD-I showed that suicide and lack of medications followed by frequent recurrences were higher in patients with substance abuse (37). These results support the present findings about the effect of age and substance abuse in the recurrence of bipolar disorder. Taheri et al applied the penalized likelihood models for analyzing the time between recurrences for patients with BD-I and determined that age, marital status, and history of substance abuse were significant factors. Moreover, the family history was an effective factor in the onset and recurrences of bipolar disorder (38, 39). However, in some studies there were not any significant relationships between age, family history, and marital status with the rate of recurrence (21). Antypa et al reported a lower age of the disorder onset and the risk of frequent recurrences in BD-I patients with the family history of bipolar disorders (39). A study in London revealed that the first episode in males on average is 3.8 years earlier than in females (40). The prevalence of bipolar disorder in females is higher than in males (41) and females experience more frequent episodes (42). In the study of Kennedy et al, gender differences in different age groups were not significant and the rate of prevalence of BD-I in females, except for the age group (16-25 years), was higher (43). In this study, the frequency of disorder in males was higher compared to females (62.7% vs 37.2%) and sex was not recognized significant in the frequent recurrences of the disorder. In Iran, just like other developing countries, many episodes are often managed in the family environment, so cases with severe aggression and hard to control manic episodes are hospitalized. This issue can suggest why most of readmitted patients are men and the incidence of recurrence is higher in men than in women. Mood disorders are common in those who have the history of brain injury or head trauma, and the risk of mental disorder incidence is significantly higher in the head trauma cases. The rate of bipolar disorder after a traumatic brain injury varied between 1.7% and 17% (44, 45). A literature review study on case control, cohort, cross-sectional and case reports during 1966 to 2003 showed that brain injury after birth is considered as a risk factor for mood disorders (44). In this study, patients with a history of head trauma and brain injury experience significantly more recurrences .

Stress and environmental conditions have a direct intensifying role in mental disorders and patients should reduce the social and psychological stress to prevent more episodes. However, these variables were not considered significant in this study and in the study by Taheri et al (38).

Limitation

The present study had some limitations, such as its retrospective approach, which limited the exact assessment of most factors, such as stressors, medication dose, cessation of medical therapy, and other comorbidities. It is recommended that future studies investigate these factors in addition to variables such as IQ, socioeconomic status, and maintenance therapy methods.

Conclusion

In this paper, we considered the characteristics of Cox risk model with shared frailty effect on the intervals between BD-I recurrences, in which age, head injury, substance abuse, and legal conflicts were significant in the frequent recurrences of the disorder. More studies are required to account for the genetic factor and psychosocial exposure during critical periods using this model.

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Conflict of Interest

None.

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