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Original Article

Recurrent Events Model Application in Determining the Risk Factors of Bipolar Disorder Recurrence

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Abstract

Objective: Recurrent events data is one of the most important types of survival data whose main feature is correlation between individual's observations. The aim of this study was to analyze the time to bipolar disorder (BD) relapse and determine the related factors using recurrent events models.
Method: In this retrospective study, records of 104 BD patients with at least one relapse who were admitted for the first time (2001-2015) in Farabi hospital of Kermanshah were gathered to identify the factors influencing the time intervals between the recurrent survivals data using the Cox model with and without frailty (shared frailty), once with frailty gamma distribution and once with log-normal distribution frailty. All calculations were performed using R and SPSS software, versions 3.0.2 and 16 and the level of significance was considered at 0.05.
Results: Among the employed models, Cox model with lognormal shared frailty showed better fit for BD recurrent survival data. According to results of Cox model with lognormal frailty, 2 factors (marital status and history of veteran) were identified to affect the time intervals between relapses.
Conclusion: Because of the better fit of the models with the frailty effect on data, the correlation between the recurrent time intervals of each subject's relapse of BD was confirmed. Also, since the risk of subsequent relapses was less in married and veteran patients, marriage and emotional care supports can be considered as effective factors in reducing the risk of subsequent relapses of this disease.

Key words: *Bipolar Disorder; Cox Frailty Model; Recurrence; Survival Analysis*

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Bipolar Disorder (BD) is a chronic mental disease, initiates with a period of depression and after one or more periods of depression, a manic period appears (1). Among the symptoms of mania, restlessness, extreme sense of happiness, grandiose, inability to concentrate, and needing less sleep can be mentioned (2). The prevalence of this disorder in the entire lifetime is between 2% to 5% (3). According to disability-adjusted life year (DALY), this disease is the sixth cause of disability worldwide (4). It disrupts social relations and the affected individual's performance in the workplace and home. In most cases, to prevent patients from harming themselves and others, they have to be hospitalized (5).

More than 60% of patients have a history of drug use and 15%-19% die due to suicide (6, 7). During the course of treatment, especially at the beginning, severity of the disease gradually decreases and the patient returns to the preexisting condition. That is why many patients and their families feel that the whole course of the disease has passed and continuation of treatment is not necessary, and thus they give up treatment. However, early cessation of treatment increases the risk of subsequent relapses. This results in the disease recurrence within a few months (8). Therefore, has frequent relapses and usually 90% of patients experience relapse. The risk of recurrence in 2 and 5 years is about 60% and 75%, respectively (9-11).

Due to frequent relapses and residual symptoms between episodes, recurrence rate is high and stabilizing the patients' mood is a difficult task (12). To treat chronic phases of the disease, relapses and initiation of next periods of the disease must be prevented. In many medical studies, sometimes a person may experience an event, such as recurrent tumors in different parts of the body several times. Such events that are within the scope of survival analysis are called recurrent events (13). Considering that in recurrent events, each person will experience recurring events, it makes sense that a correlation may exist among events occurring to a person. Because of this correlation, conventional survival models cannot be used for recurring data modeling. Therefore, frailty models are recommended (14). For the recurrent events analysis, recurrent survival models were used in this study to identify the critical risk factors influencing the disease recurrence, which are important both for physicians and patients. Other models usually consider only the first recurrence and may lead to incorrect assessment of the effects of risk factors. Because they do not reflect the complete patients' record, they may result in loss of valuable information (15, 16). Therefore, use of recurrent events of survival models will be necessary. The present study aimed at analysis of time to BD relapse and determining the related factors using recurrent events models and penalized likelihood nonparametric method to estimate risk functions.

Materials and Methods

In this retrospective study, statistical society included all BD patients who were admitted at least once in Farabi hospital of Kermanshah due to recurrence of the disease. Statistical sample also included all BD patients with at least one relapse between early 2001 and December 14, 2015, who were admitted for the first time to this hospital because of the same problem. Records of this period were collected as the hospital registration system was more accurate since 2001. A total of 220 patients were selected by convenience sampling method. However, 116 patients with incomplete information were excluded due to incomplete information (hospitalization dates, clearance, and personal information). The collected information included admission and discharge dates (year/month/day), age of the patient, age at onset of disease, gender, marital status, mental problems history in the family, how the disease began, history of head trauma, veteran, physical problems history, alcohol use, smoking, drug abuse, and imprisonment, residence, education level, and occupation. History of mental problems in patients' family included mental health problems, such as history of drug addiction in the family and BD itself, and other mental illnesses. Also, history of the patients' physical problems included physical problems associated with physical illness, accident, surgery, or congenital physical problems, such as impairment and all kinds of disabilities. All information about patients was kept confidential. This study was approved by the ethics committee of Kermanshah University of Medical Sciences (KUMS.REC.1395.74).

The response variable in the study referred to time interval on daily basis between the successive relapse of the disease for each patient. The last time may be censored for all the patients. As there was no record after the last discharge, right censoring was used, which was considered to be independent of the event process. Considering that a number of unknown factors may affect the time of subsequent relapses, in this study, correlations were expected among survival times (ie, admission time) of each patient. Hence, using Cox proportional hazards model with (shared frailty) and without frailty, once with frailty gamma distribution and once with log-normal distribution frailty, intervals between frequent relapses of patients with BD were modeled after comparing the results of the 3 models with each other. The correlation between intervals of frequent relapses was also measured. Data were analyzed using R and SPSS software versions 3.0.2 and 16, respectively. To use the Cox model with and without fragility, once with the fragility of the gamma distribution and once with the fragility of the log-normal distribution, the Lickleigh validation method and Likelihood cross-validation (LCV) criterion, from frailtypack were used. Frailtypack is an R package for the analysis of correlated survival data with frailty models using penalized

likelihood estimation or parametrical estimation. In this study the level of significance was set at 0.05.

Results

104 BD patients were enrolled in this study. Patients' age ranged from 18 to 83 years, with the mean and standard deviation of 38.3±14.3. Also, the mean and standard deviations of age at onset of BD in men and women were 27.9±14.5 and 29.1±13.8, respectively (Table 1). During the follow-up, 365 relapses were recorded for 104 studied patients. The average rate of relapses was 3.51±3.3 and the obtained relapse mode was 2 (Table 2).

In this study, with regards to LCV criteria, models with frailty effect showed better fit to data than model without frailty effect. Of the 2 models with frailty effect (lognormal and gamma), models with lognormal frailty effect showed the lowest value for LCV criteria. Thus, Cox model with lognormal frailty was selected as the best model which fitted to recurrent survival data obtained from relapses of BD. Summary results of Cox model with lognormal frailty effect fit to recurrent events data obtained from relapses of BD with penalized likelihood estimation method showed that using this model, marital status and veterans had significant effects on time intervals between recurrences of the disease. For marital status variable, risk of subsequent relapses in unmarried patients was different and more than married ones. In case of veteran, as a variable in this model, risk of subsequent relapses in nonveteran patients was more than veteran patients (Table 3). When the final model was considered with only 2 variables (marital status and veteran), the latter was still significant but the former was not that significant. In the model fitted to recurrent events data obtained from the relapses of BD, frailty effect variance was 0.095 (P = 0.0002). Thus, there was a significant correlation between time intervals of recurrences of BD for each person. Also, significant effect of frailty showed non-observable and non-measurable factors that created individual differences in the study. That is, in Cox model without frailty, gender, marital status, veteran, and history of smoking had significant effects on time intervals between relapses of BD, but in Cox model with lognormal frailty, gender and history of smoking were not significant. However, in the current study, the estimated variance for lognormal frailty effect (0.095) was more than the estimated variance for gamma frailty effect (0.066). Therefore, lognormal distribution could better explain the unknown factors.

Table 1. Number and Rate of Enrolled Patients Based on Given Risk Factors of Bipolar Disorder Recurrence

Row	Variable	Variables' subscales	No.	%	Row	Variable	Variables' subscales	No.	%
1	Age (year)	0-29	33	31.7	9	Marital status	Married	43	41.3
		30-49	49	47.1			Single, divorced, widowed	61	58.7
		50≤	22	21.2					
2	Age at onset of disease (year)	0-29	70	67.3	10	History of mental problems in the family	No	55	52.9
		30-49	24	23.1			Yes	49	47.1
		50≤	10	9.6					
3	Gender	Female	45	43.3	11	History of other physical problems	No	56	53.8
		Male	59	56.7			Yes	48	46.2
4	How the disease began	Sudden	60	57.7	12	History of just smoking	No	59	56.7
		Gradual	44	42.3			Yes	45	43.3
5	History of head trauma	No	100	96.2	13	History of drug abuse	No	74	71.2
		Yes	4	3.8			Yes	30	28.8
6	Veteran	No	100	96.2	14	History of imprisonment	No	88	84.6
		Yes	4	3.8			Yes	16	15.4
7	History of alcohol use	No	92	88.5	15	place of residence	Rural	25	24
		Yes	12	11.5			Urban	79	76

		Housewife	32	30.8			Illiterate	18	17.3
		Employee	8	7.7			Primary	22	21.2
8	occupation	Worker	16	15.4	16	Education	High school	21	20.2
		Self employed	13	12.5			Diploma	27	26
		Other*	35	33.7			College	16	15.4

* Other includes students, college students, and unemployed.

Table 2. Distribution of Relapses in Patients with BD Based on Given Risk Factors of Bipolar Disorder Recurrence

Variables	Variables' subscales	No.(%)						Total
		One	Two	Three	Four	Five	More	
Age (year)	0-29	4 12.12	14 42.42	7 21.21	3 9.09	2 6.06	3 9.09	33 100
	30-49	9 18.36	12 24.5	5 10.2	6 12.24	5 10.2	12 24.5	49 100
	50≤	6 27.27	11 50	3 13.63	0 0	2 9.09	0 0	22 100
Age at onset of disease (year)	0-29	10 14.3	23 32.85	11 15.71	7 10	7 10	12 17.14	70 100
	30-49	8 33.33	8 33.33	2 8.33	2 8.33	1 4.16	3 12.5	24 100
	50≤	1 10	6 60	2 20	0 0	1 10	0 0	10 100
Gender	Female	10 22.22	16 35.56	7 15.56	5 11.11	4 8.88	3 6.67	45 100
	Male	9 15.25	21 35.6	8 13.56	4 6.78	5 8.47	12 20.34	59 100
Marital status	Married	7 16.3	18 41.9	3 7	4 9.3	5 11.6	6 13.9	43 100
	Single, divorced, widowed	12 19.67	19 31.14	12 19.67	5 8.2	4 6.56	9 14.75	61 100
History of mental problems in the family	No	12 21.82	24 43.64	4 7.27	4 7.27	3 5.45	8 14.55	55 100
	Yes	7 14.28	13 26.53	11 22.45	5 10.20	6 12.24	7 14.28	49 100
History of other physical problems	No	11 19.64	21 37.5	8 14.29	6 10.71	5 8.93	5 8.93	56 100
	Yes	8 16.67	16 33.33	7 14.59	3 6.25	4 8.33	10 20.83	48 100
How the disease began	Sudden	8 13.33	28 46.67	10 16.67	1 1.67	5 8.33	8 13.33	60 100
	Gradual	11 25	9 20.45	5 11.36	8 18.18	4 9.09	7 15.9	44 100
History of head trauma	No	19 19	35 35	15 15	9 9	8 8	14 14	100 100

	Yes	0 0	2 50	0 0	0 0	1 25	1 25	4 100
Veteran	No	18 18	35 35	15 15	9 9	8 8	15 15	100 100
	Yes	1 25	2 50	0 0	0 0	1 25	0 0	4 100
History of alcohol use	No	17 18.48	37 40.21	11 11.95	7 7.6	8 8.7	12 13.04	92 100
	Yes	2 16.67	0 0	4 33.33	2 16.67	1 8.33	3 25	12 100
occupation	Housewife	7 21.87	11 34.37	6 18.75	3 9.37	4 12.5	1 3.12	32 100
	Employee	1 12.5	2 25	1 12.5	1 12.5	1 12.5	2 25	8 100
	Worker	1 6.25	5 31.25	2 12.5	3 18.75	1 6.25	4 25	16 100
	Self employed	1 7.69	4 30.77	1 7.69	1 7.69	2 15.38	4 30.77	13 100
	Other*	9 25.71	15 42.86	5 4.28	1 2.86	1 2.86	4 11.42	35 100
History of just smoking	No	14 23.73	23 38.98	10 16.95	5 8.47	2 3.39	5 8.47	59 100
	Yes	5 11.11	14 31.11	5 11.11	4 8.88	7 15.56	10 22.22	45 100
History of drug abuse	No	16 21.62	33 44.6	9 12.16	5 6.75	3 4.05	8 10.81	74 100
	Yes	3 10	4 13.33	6 20	4 13.33	6 20	7 23.33	30 100
History of imprisonment	No	15 17.04	34 38.64	12 13.64	8 9.09	8 9.09	11 12.5	88 100
	Yes	4 25	3 18.75	3 18.75	1 6.25	1 6.25	4 25	16 100
place of residence	Rural	4 16	10 40	3 12	2 8	1 4	5 20	25 100
	Urban	15 18.99	27 34.17	12 15.18	7 8.86	8 10.12	10 12.65	79 100
Education	Illiterate	3 16.67	8 44.44	3 16.67	0 0	2 11.11	2 11.11	18 100
	Primary	3 13.64	12 54.55	2 9.09	1 4.54	1 4.54	3 13.64	22 100
	High school	5 23.81	4 19.05	4 19.05	1 4.76	2 9.52	5 23.81	21 100
	Diploma	6 22.22	7 25.92	3 11.11	4 14.81	3 11.11	4 14.81	27 100
	College	2 12.5	6 37.5	3 18.75	3 18.75	1 6.25	1 6.25	16 100

Table 3. Results of Cox Proportional Hazard Model with Lognormal Frailty Effect of the Risk Factors of Bipolar Disorder Recurrence

Variables	β coefficient	SD	Hazard Ration (HR)	Confidence Interval 95% (HR)	P-Value
Age	-0.3	0.28	0.74	(0.43 - 1.29)	0.295
Age at onset of disease	0.13	0.15	1.14	(0.85 - 1.54)	0.384
Gender	0.28	0.19	1.32	(0.91 - 1.93)	0.146
* Marital status	0.36	0.15	1.43	(1.06 - 1.93)	0.02
History of mental problems in the famil	0.03	0.14	1.04	(0.78 - 1.37)	0.809
How the disease began	0.08	0.14	1.09	(0.83 - 1.43)	0.555
History of head trauma	0.42	0.35	1.53	(0.76 - 3.06)	0.235
* Veteran	-1.1	0.47	0.33	(0.13 - 0.84)	0.02
History of the patient's physical problems	-0.04	0.14	0.96	(0.72 - 1.27)	0.777
History of alcohol use	0.08	0.21	1.08	(0.71 - 1.64)	0.714
History of just smoking	0.25	0.17	1.29	(0.93 – 1.79)	0.124
History of drug abuse	-0.04	0.17	0.96	(0.68- 1.34)	0.793
History of imprisonment	-0.005	0.21	0.99	(0.66 – 1.5)	0.978
Place of residence	0.11	0.16	1.12	(0.81 – 1.54)	0.494
Education level	-0.04	0.06	0.96	(0.86 – 1.08)	0.527
Occupation	-0.05	0.05	0.95	(0.85 – 1.05)	0.329

* Significant variable

Discussion

Recurrent events data are very common in medical studies and analysis of their wide range of purposes, including describing the relapse process of an event in people, process distribution from one person to another, and effect of independent variables on time of the event, such as evaluation of treatment effectiveness in delaying relapse and prolonging survival in a patient (17). Researchers often use simpler techniques for data analysis like frequency of events, time to the first event, overall survival time or fit models separately for each events that are inadequate and do not use all available information for accurate estimation. Therefore, finding a suitable method for considering their correlation in a model is important; and frailty models is one of these methods (18). Frailty model which is an extension of Cox model, uses more data information and results in valid inferences. Also, it provides more answers for medical researches than conventional models (19). Nonetheless, it has certain limitations, one of which is that despite solving heterogeneity issue, it ignores chronological order of events, which is another source of correlation between occurrence times for each person (20). Also, since the frailty models are more complicated than other statistical models, they have problems in terms of inference and estimation methods (18). Various methods have already been proposed for estimating purposes. In this study, penalized likelihood estimation method was used for parameter estimation. Since BD is a chronic mental disease in which stabilizing the patients' mood is difficult due to frequent relapses, we decided to identify the factors influencing the frequent relapses of this disease with the help of the shared frailty model. Huang and Liu conducted a research using EM algorithm and Markov chain Monte Carlo (MCMC) methods to study the survival and gap times between recurrent events at the same time. They fitted both Cox model with and without frailty effect to data and concluded that because of the strong correlation between recurrent events, Cox model with frailty effect was more appropriate (21). In this study we also concluded to fit time intervals between recurrent survival data, Cox model with lognormal frailty effect was more appropriate. Weir Gini Rondeau fitted joint frailty model to recurrent events and final event related to follicular lymphoma cancer data using maximum penalized likelihood estimation (22). In our study, the same estimation method was used. In joint frailty model, in addition to a recurrent event, a terminal event (such as death) occurred and both events were considered together. In the present study, only recurrent event (ie, relapse) was present and untill the end of follow-up period, none of them led to a terminal event (such as death) to let us use joint frailty model. In a study to identify risk factors of survival times for recurrent events, Jahangiri Mehr et al. fitted 3 Cox models with and without gamma and log normal shared frailty to determine the interval between relapses using a Bayesian model aproach. Finally, they introduced Cox with gamma frailty as the most suitable model (23). The same 3 models were used in this study. Nonetheless, by employing penalized likelihood estimation method, the researchers concluded that Cox with lognormal frailty effect can be better fitted to time intervals between recurrent events. In most of the researchers on patients with BD, the number of women is usually less than men.

For instance, John Van Zaane et al investigated 375 patients with BD, among whom only 26% were women (24). In this study, also 43.3% of patients were women. Another similarity between the current research and that of John Van Zaane et al is lack of difference between the patients' educational level (24). Nevertheless, these 2 studies have some differences, John Van Zaane et al found no difference between occupational levels of the patients (24). However, 64.5% of patients in this study were housewives, students, or unemployed and did not have any economic capital to spend. Regarding marital status, the research conducted by Mahin Eslami Shahr Babaki et al (25) 58% of 121 patients were single, widowed, or divorced; and 58.7% of the patients in the current research had similar status. In most studies, these patients are almost 40 years old, on average. In a research performed by Chapel et al on 825 patients, the average age range was 41.6±12.1 (26). The average age range in this study was 38.32±14.28. Again, in the research by Chapel et al, the average age range at the onset of the disease was 28.1±11.0 (26), while in this research, it was 28.42±14.2. Chapel et al found considerable number of smokers among their patients (41.5%) (26), which was similar to the current study (43.3%). However, these 2 studies differd in the average number of admissions. In the current study, the average number of admissions (relapse) was 3.51±3.3; the obtained relapse mode was 2. However, the average number of admissions in the research by Chapel et al was 1.1±1.5 (26). McElroy et al found 47% patients with history of drug abuse (27), but in the current study 28.8% patients had history of drug abuse. Here, the lower rate may be due to inaccurate and false statements of patients about their addiction. In a research by Ghoreishi Zade et al, cut and reduced dosage of drug was a factor interfered with BD (28), but in the current research this factor was not considered, as it had not been recorded for all the patients.

Limitation

Limitations may reduce the internal and external validity of the study. Lower sample size and incomplete information in medical records seemed to be most noticeable limitations of this study. Another limitation of this study was that retrospective design could not describe risk factors in details (such as marital statuse), because there were correlations only among variables, which may decrease the internal validity. Therefore, for future studies, it is suggested that the study design be prospective with a larger sample size and patients' medications be examined.

Conclusion

Due to better fit of models with the frailty effect on data, the correlation between the recurrent time intervals of each subject's relapse of BD was confirmed. Also, since the risk of subsequent relapses was less in married and veteran patients, marriage, emotional care, reduced cost of treatment, and enhanced training for the patients and their companions on the necessary cares for patients during treatment can be effective in reducing the risk of subsequent relapses of this disease.

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Conflict of Interest

None.

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