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Abstract

Objective: Bipolar I disorder patients often experience relapse once and even more with no limit on number of relapses. The time to relapses of these patients are rarely studied particularly considering heterogeneity across individuals. The aim of this study was to identify some risk factors of time to recurrent relapses in bipolar I disorder patients with a recurrent event model in survival analysis.

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Conclusions: Substance abuse, marital status and RF are important risk factors in order to plan for postpone the time to next relapses. More studies are required to clear out the effect of other covariates with this model.

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Introduction

Bipolar affective disorder a common and chronic, severe and recurrent, mood and brain disorder that causes unusual shifts in mood, energy, activity levels and ability to carry out day-to-day tasks, is characterized by recurrent episodes of mania and depression [1-4]. Studies have estimated the prevalence of bipolar disorder to be between 1% and 2% and up to 90% of BD patients have at least one relapse in their lifetime [2, 5-9]. Bipolar disorder causes substantial psychosocial morbidity that frequently affects the patient's marriage, children, occupation, and other aspects of the patient's life [10]. Bipolar disorder (BD) remains among the 10 most disabling disorders according to the World Health Organization (WHO) causing a significant amount of disability [11]. One of the important types of bipolar disorder is bipolar I disorder with lifetime prevalence of 0.24% [12]. Although bipolar disorder is often hard to be diagnosed due to its irregular patterns, it can be treated and people with it can lead full and productive life, [1,13]. Bipolar disorder is the sixth leading cause of disability in the United States and symptoms can result in damaged relationships and poor job or school performance, as a consequence, it is one of leading causes of disability which contributes to economic burden of this disorder to society [14, 15]. Several studies have reported that 50% to 75% of patients have a recurrence within 4 to 5 years after the first admission [16]. Patients with long duration of illness and highly recurrent course show great impairment of global functioning and number of episodes has been found consistently associated with poor outcome [4]. An important feature of bipolar I disorder is the repetition of relapses over time [9]. Information about time to relapse and efficacy of some risk factors in preventing relapses will provide a valuable tool for planning and evaluating the health-outcome results of treatment [17]. Risk factors have been shown to influence onset in bipolar I disorder such as family history and substance abuse but few research has focused on effect of risk factors on time to relapses and little is known about the factors that may precipitate relapse [15]. Few studies have assessed time to relapse, remission and recovery of patients with bipolar disorder but most of them failed to account the recurrent feature of relapses and correlation

caused by recurrent events whit-in subjects. These studies used the Kaplan-Meier estimator which serves as an estimator for standard survival data but not for recurrence time data or Cox regression for recurrent events that need proportional hazards assumption over time, an assumption that does not hold in many situations [17-24].

In order to study time to relapses, with respect to recurrent characteristic of bipolar disorder, we need recurrent event analyzing techniques of survival analysis. Survival analysis typically focuses on time to event data and recurrent event is a multivariate survival analysis in which event occurs more than once per subject over follow-up time such as hospital stays or heart attacks. Although statistical approaches based on sound principles exist, the methodological issues surrounding the study of recurrent events have received insufficient attention in the clinical and epidemiological literature [25, 26]. The most important issue in recurrent data is correlation among relapses of each patients. In fact, individuals have varied lifestyles, genetic traits, and experiences which influence the likelihood that they will succumb to disease but either cannot be measured and are unknown. These factors are called latent variable. As a result, some individuals are more prone to experience their next disease recurrence more quickly than other individuals. This introduces heterogeneity across individuals and produces within-subject correlation in the timing of recurrent events within a given subject so, response rates can be homogeneous within individuals producing within-subject correlation in event times [27-28].Correlated event times are common in the study of health and related sciences. So, there is a need for a general and flexible model that simultaneously incorporates the effects of covariates, as well as the effect of latent or unobserved variables [29]. Statistical techniques that consider the recurrent events and the dependency of the observations are necessary to answer research questions. Frailty or random effects models incorporate heterogeneity into the estimator by making assumptions about the frailty distribution and incorporating it into the model estimates [30]. Bipolar I disorder is a recurrent disorder for the vast majority of patients, and hospitalization is normally used to control severe symptoms and the goal of treating bipolar I disorder is prevention of relapses/recurrences. In this study, we

present a semi-parametric frailty model using penalized approach which accounts for time dependent covariates and heterogeneity in repeated relapses of bipolar I disorder.

Method:

Participants and Procedure

In a retrospective longitudinal study data of 526 bipolar I patients with at least one relapse, who were hospitalized at Razi Psychiatric hospital in Tehran between 1993 and 2011, were collected from their medical records. The onset of bipolar I disorder was considered as the time of their follow up, and they were followed in terms of their relapses. Relapse was defined as observing bipolar I disorder symptoms in the first re-hospitalization after discharge and following re-hospitalizations. Patients who had been admitted to another hospital or have relapsed inside the house after first admission removed from study because we suppose hospitalization was immediately after relapses. The time to recurrent relapses were considered in months. We use the gap time timescale that is most often used timescale in survival analysis: after an event, the subject starts again at time 0 and the time to the next event corresponds to the number of month that it takes to experience the next event [31].We assessed number of month patients remained to be re-hospitalized as time to event. Right censoring occurs when a subject leaves the study before an event occurs, or the study ends before the event has occurred [32]. Available data fields included: gender, marital status, family history of bipolar disorder (FH), substance abusing, Regular fluctuation (RF), negative life events (NLE) and types of episode. Patients with abusing any kind of drugs other than cigarettes have the positive substance abuse. Patients who divorce or married during the study have removed from study so their marital status unchanged during the study. There were cases of clients in some patients during the study that an individual has the mood fluctuations of bipolar disorder but the symptoms do not meet the criteria for any of the other subtypes or the mood changes are abrupt and irregular[33]. RF factor (Regular Fluctuation) was created for this situations. If a patient in one of clients, was cyclothymia, NOS or schizoaffective then RF is negative. NLE and types of episodes defined according to the Diagnostic and

Statistical Manual of Mental Disorders book (DSM4). NLE include stressful life events that often require sweeping readjustments in a person's life such as; death of a loved one, job loss, major illness or injury. There are 3 types of episode in bipolar I disorder (mania, depression, mix) which could vary in each recurrence of episodes, so we should recognize it as a time varying covariate [34].

Statistical Analysis

In many epidemiological and medical studies, the outcome variable of interest is a recurrent event [17]. In these studies each subject is at risk of experiencing repeated events and investigators are interested in evaluating the effects of covariates on the recurrent event times and predicting the developments of future events [35]. An important issue in recurrent events approach is to consider dependency of observations per subjects, called frailty or latent random variable, which is unobservable but influence the model with the meaning that all sampled individuals into the study are not subject in principle under the same risk of death or disease recurrence [36]. A useful approach to accommodate dependency of the recurrent event times within the same subject is to incorporate a random effect or frailty [37]. Frailty model has many uses in survival analysis. The notion of frailty provides a convenient way to introduce random effects, association and unobserved heterogeneity into models. Frailty models are extensions of well-known Cox (1972) proportional hazards model and are used when proportional assumption holds not true [38]. A very common situation in survival analysis is clustered or repeated data. Clustered data are for instance data where individuals are divided in groups likes family or study centers or repeated measures within individuals. The dependence usually arises because individuals in the same group are related to each other or because of the recurrence of an event for the same individual. The aim of the frailty is to take into account the presence of the correlation between the multivariate survival times [39].In statistical terms, for cluster data a frailty model is a random effect model for time-to-event data where has a multiplicative effect on the baseline hazard function and individuals in a cluster are assumed to share the same frailty which is why this model is called shared frailty

model [40]. In most studies there are time-dependent covariates, e.g. HIV status in addition to time-independent covariates, e.g. race and gender. The statistical analysis is complicated by presence of frailty and time-varying coefficient so using the EM algorithm as an estimation tool is not suitable because it is slow and implementation is not available widely in packages. Penalized models provide an alternative estimation approach in which the frailty terms are treated as additional regression coefficients and are constrained by a penalty function added to the log-likelihood. [38]. Semi-parametric penalized frailty model is a recurrent frailty model that is suitable when there are time-varying covariates or we need to consider too many covariates in model. The advantage of this model is that it can easily evaluate frailty parameter and time varying covariates. R3.2.0 software was used to analyze data. In this software with default packages, results could evaluate without problem. Usually, it is assumed that the frailty follows a gamma distribution with mean 1 and unknown variance θ. The value $\theta = 0$ corresponded to independence and a high value of θ should preferably correspond to a high correlation between the survival times [41].

Results:

In studied sample 64.8% (341) of patients were males, 60.4% (318) were single and 58.2%% (306) with-out family history of bipolar disorder. 56.4% (297) of patients did not experience negative life events, 52.4% (276) have substance abuse and 60.0% (316) have not RF (Table 1). Entirely 2889 relapses were registered for 526 patients. 2519 of these were for BP I and 391were for NOS or cyclothymia or schizoaffective. Maximum number of recurrence was 24 but 98.01% of relapses happened up to 9^{th} recurrenc.77.25% of relapses were in mania phase, 3.65% were mixed and 19.09% were depressed (table2).In survival analysis model with considering correlation between recurrence of relapses by frailty, variance of frailty parameter (θ=0.287) is highly significant ($p<0.001$), suggesting present of heterogeneity among data. Among risk factors, substance abuse (p=0.041), RF (p=0.002) and marital status (0.009) were significant (table2). Shape of shared gamma

frailty distribution is shown and quartiles are 0.609, 0.906 and 1.287 respectively (chart1). Overall hazard function show that hazard increased by time generally (chart2).

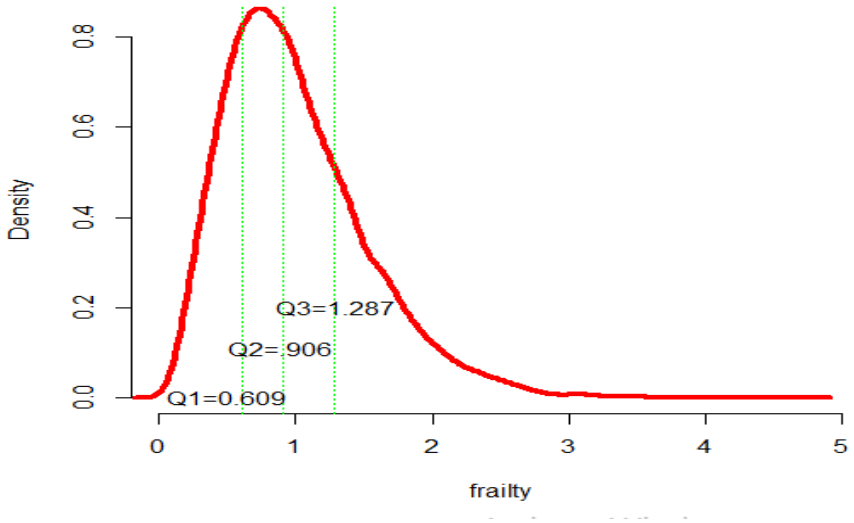

Chart1: Distribution of frailty

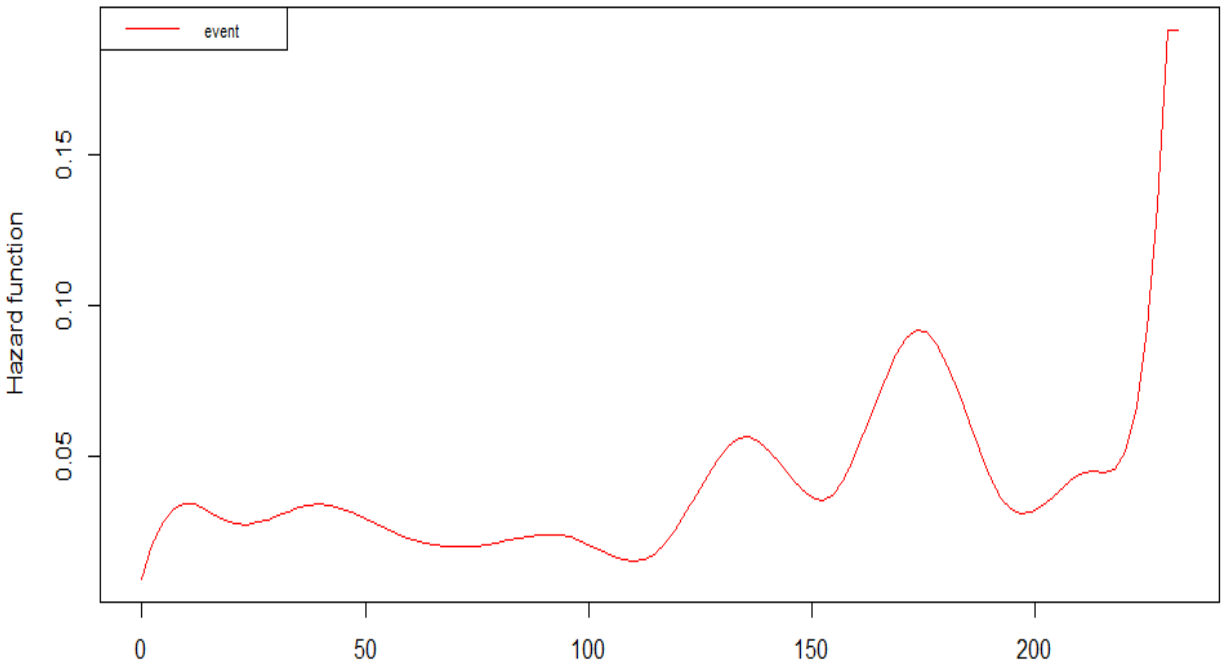

Chart2: Overall hazard function over time

Table1: Frequency of risk factors in patients with bipolar I disorder

covariates	**categories**	Count (n%)
sex	Male	341(64.9)
	Female	185(35.1)
family history	No	306(58.2)
	yes	220(41.8)
substance abuse	No	250(47.6)
	yes	276(52.4)
Negative life event	No	297(56.4)
	Yes	229(43.6)
Marital status	Single	318(60.4)
	married	208(39.6)
RF	No	316(60.0)
	yes	210(40.0)

table2: frequency of recurrences in 3 types of episodes

	Number of episodes									
Types of episode	First(%)	Second(%)	Third(%)	4^{th}(%)	5^{th}(%)	6^{th}(%)	7^{th}(%)	8^{th}(%)	9^{th}(%)	10^{th} and more
Mania	403(15.9)	401(15.9)	387(15.3)	316(12.5)	223(8.8)	94(3.73)	49(1.9)	26(1.0)	17(0.67)	30(1.19)
mixed	16(0.63)	21(0.83)	13(0.51)	7(0.27)	12(0.47)	0(0)	6(0.23)	5(0.19)	5(0.19)	7(0.27)
Depression	107(4.24)	98(3.89)	86(3.41)	68(2.69)	41(1.62)	39(1.54)	17(0.67)	7(0.27)	5(0.19)	13(0.51)

Table3: Parameter estimation in semi-parametric penalized frailty model

Covariates		**Reference category**	$\hat{\beta}$(p-value)	**SE**	**HR**
Gender	Female	Male	0.075 (0.559)	0.128	1.078
Family history	Yes	No	0.073 (0.541)	0.128	1.076
Marital status	Single	Married	0.320(0.009)	0.123	1.377
Substance abuse	Yes	No	0.795 (0.041)	0.125	1.344
Negative life events	Yes	No	0.085 (0.453)	0.113	1.089
Type of episodes	Mania Depression	Mix	0.006 (0.979) -13.416 (0.365)	0.262 10.283	1.007 1.491
RF	Negative	Positive	0.372(0.002)	0.125	1.451

θ=0.287 (p<0.001) , SE=0.066 , LCV=2.949

Discussion:

About 77.25% of episodes were manic, 19.09% depressed and 3.65% mixed (table2) these results are near preview study reported that 74% of index episodes were mania, 21% were depressed, and 5% were mixed [42]. Clearly, unobserved patients characteristics have a very substantial effect on survival so the result will be bias whit out considering individuals heterogeneity. Heterogeneity is considered in terms of frailty and variance of frailty (theta) measures the variability of frailties. If θ differs from zero indicating the presence of unobserved heterogeneity [43], so in the significant level of .05 the frailty should be considered in the model. From the shape of frailty distribution (Q1/Q2=.672 and Q3/Q2=1/420) we see that patients with frailty at Q1 have 33% lower risk, and patients with frailty at Q3 have 42% higher risk, than patients with median frailty. However the interpretation of the hazard ratios in the frailty model is slightly different from the other models and the hazard ratios are compared in the given same value of frailty [44]. In semi-parametric penalized frailty model substance abuse have significant effect on hazard rate of relapses and patients with equal frailty who use substance have 0.34 times more chance to have next relapse. Substance abuse may prolong bipolar symptoms, and the behavioral control problems associated with mania can result in a person drinking too much [1] this results support the suggestion that individuals with bipolar affective disorder complicated by substance abuse may have more hospitalizations [45]. Marital status is another effective factor. Single patients have 0.37 times more chance to have next relapse compared to married patients at the same level of frailty although in other studies with cox models, which needs initial assumption that always not hold, marital status was not significant [46]. RF factor is also significant. Patients have not RF have 0.45 times more chance to experience next relapse than who have RF. It implies that there should

be more attention in treatment procedure and diagnostic criteria in confront of patients with irregular pattern. We found that type of episodes and marital status have no influence on time to relapses in bipolar I disorder patients. Recent study with using Cox regression model in the 12-month follow-up period study, has reported no significant differences in recovery from hospitalization between patients with mania compared with mixed bipolar disorder and another study found that bipolar women experienced an equal greater risk of recurrence than men [47,48]. Negative life event has not significant effect on outcome although most studies with-out considering frailty have found that negative life events precede episodes of bipolar individuals [49]. It shows that when we consider individuals heterogeneity in model this factor lose its efficiency. It seems negative life events have not direct effect on hazard of next relapse but it depends on each individual to how handle it. Family history has not significant effect on time to relapse although have effect on incident of disorder and children with a parent or sibling who has bipolar disorder are much more likely to develop the illness, compared with children who do not have a family history of bipolar disorder [1].

Conclusion: substance abuse, RF and marital status are important risk factors influencing hazard of time to relapses. Having a kind spouse and Withdrawal of addiction could help to postpone the next relapses. Significance of RF factor suggesting further studies around borderlines and treatments of types of bipolar disorder. The course of bipolar I disorder seems to be progressive in nature irrespective of gender, type of disorder, FH and NLE.More studies are required to clear out the effect of other covariates such as place of residence (urban vs. rural), education level, economic status of patients on time to relapses with this model.

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