PREDICTORS OF TIME TO RELAPSES AMONG SCHIZOPHRENIC PATIENTS IN ST.AMANUEL MENTAL SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

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Abstract: Schizophrenia is a chronic psychiatric disorder with a modest treatment outcome. In addition, relapses are usual. The time among relapses are rarely considered in studies. The aim of this study was to investigate the associated factors that affect time to relapses in schizophrenic patients at ST. Amanuel mental specialized hospital with recurrent events model in survival analysis. Medical records of 332 individuals with schizophrenia were examined covering a two year period. The distributions of number of relapses were 162. The median survival time of schizophrenic patients was 665 days. The parametric frailty models were used to determine the correlation between discharge times and relapse and to identify risk factors. The unobserved heterogeneity in individual and correlation between relapses as estimated by the Weibull-gamma frailty model was (p-value=0.000) and Kendall's Tau (Γ) =0.498. This indicated that there was heterogeneity among the participants and correlation between relapses. The final model showed that the effect of comorbidity (HR= 6.522, p-value=0.000), employment status (HR= 5.334, p-value =0.001), history of suicide attempt (HR= 2.167, p-value=0.003) and history of traditional treatment (HR= 1.973262, p-value=0.021) were significant on the hazard time to relapses. Age of onset of schizophrenia and drug adherence was not predictive. Data indicate that, Subsequent relapses are likely dependent on the first and previous relapses. Comorbidity, employment status, history of suicide attempt and history of traditional treatment are important risk factors influencing hazard of time to relapse, which is increase the risk of relapse. Clinicians should be given special attention to patients with comorbidity condition.

Keywords: Schizophrenia; Relapse; Recurrent Events; PH models, Frailty models

INTRODUCTION

A mental disorder or psychiatric disorder is a behavioral or mental pattern that causes significant distress or impairment of personal functioning (Bolton, 2008). Such features may be persistent, relapsing and remitting, or occur as a single episode.

Schizophrenia is a severe and disabling chronic mental disorder characterized by deficits in the thought process, perception of reality, and emotional responsiveness (James Sadock, 2015). This mental disorder affects a person's, feelings, behaviors, and social interactions. It is among the most disabling and economically catastrophic medical disorders, ranked by the World Health Organization as one of the top ten illnesses contributing to the global burden of disease (Ayano, 2016).

Symptoms of schizophrenia includes hallucinations which may be visual or auditory (seeing things that aren't there, hearing voices), delusions (fixed false beliefs), cognitive impairment manifesting as an unusual way of thinking or disorganized speech, and difficulty in social relationships and result in problems in social and occupational functioning, and self-care (McGrath et al., 2008; Rahmati et al., 2015).

The lifetime prevalence of schizophrenia has generally been estimated to be approximately 1% worldwide (Balhara and Verma, 2012). However, a systematic review by Saha et al of 188 studies drawn from 46 countries found a lifetime risk of 4.0 per 1000 population; prevalence estimates from countries considered least developed were significantly lower than those from countries classed as emerging or developed (Koeda et al., 2012). The incidence or annual number of new cases of schizophrenia is estimated to be 1.5 per 10,000 people (Epidemiol Reviews, 2008).

Schizophrenic patients often experience relapses once and even more with no limit on number of relapses (Rahmati et al., 2015). Preventing relapse and thereby reducing the risk of unplanned acute readmissions is a very important goal in the treatment of patients with schizophrenia after discharge from hospital (Kroken et al., 2012). Age of onset, sex, marital status and family history are documented to be important risk factors influencing hazard of time to relapses (Rahmati et al., 2015). Relapse hazard ratio increased with a history of suicide attempts, and a gradual compared to a sudden onset of disease (Davarinejad, Mohammadi Majd et al. 2021).

In Ethiopia the study conducted by (Kebede et al., 2003) has shown that the prevalence of schizophrenia is 0.47%. Over half of the people with this disabling and chronic mental disorder experience continuous or episodic illness over a 10-year period (Shibre et al., 2015) with limited service coverage and financial protection for people. In regards to the situation in Ethiopia, analysis of time to relapse is important in the assessment of treatment outcome. Different studies have been done about schizophrenia. However, the time among relapses are rarely considered in studies. none of them tried to account for the correlations caused by recurrent events and event dependence which are key features of studies in schizophrenia. Therefore, this study was proposed to model time to relapse among schizophrenic patients and to explore factors that have strongly association on time to relapse in ST. Amanuel Mental Specialized Hospital, Addis Ababa, Ethiopia.

Objective

The objective of this study was to investigate the associated factors that affect time to relapses of schizophrenic patients in ST. Amanuel Mental Specialized Hospital, Addis Ababa, Ethiopia.

Methods

Description of Data

This study used data obtained from a retrospective cohort follow up study from schizophrenic patients who under follow up from January, 2019 to December 2020 in ST. Amanuel Mental Specialized Hospital, Addis Ababa, Ethiopia. The onset of schizophrenia was considered as the time of their follow up, and they were followed in terms of their relapses. Relapse was defined as observing schizophrenia symptoms in the first re-hospitalization after discharge and following re-hospitalizations. The charts of all hospitalized patients were retrieved using the medical record number obtained from the psychosis registry. Finally, the socio-demographic characteristics and all the required information were extracted from 332 patient medical records and included in the analyses.

Statistical Analysis

Time to relapses in schizophrenic patients can be studied with suitable failure time models. Frailty models extend Cox proportional hazards model by introducing unobserved “frail- ties” to the model. In this case, the hazard rate will not be just a function of covariates, but also a function of frailties (Abdulkarimova, 2013). Normally, in most clinical applications, survival analysis implicitly assumes a homogenous population to be studied. This means that all individuals sampled into that study are subject in principle under the same risk (e.g., risk of death, risk of disease recurrence). However, in many applications, the study population cannot be assumed to be homogeneous but must be considered as a heterogeneous sample, i.e. a mixture of individuals with different hazards. The frailty approach is a statistical modeling concept which aims to account for heterogeneity, caused by unmeasured covariates. In statistical terms, a frailty model is a random effect model for time-to-event data, where the random effect (the frailty) has a multiplicative effect on the baseline hazard function (Wienke, 2014).

Parametric Frailty Models

Frailty models have been used frequently to model the multivariate dependence in time of an interest event (Gutierrez, 2002). Usually dependency is generated because subjects from the same group are either related or because multiple recurrent events occur in the same subject. In this case the traditional proportional hazard model could not be applied. One possible solution to this problem is to use the conditional proportional hazard model taking into account frailty terms event (Raıces et al., 2018). In this model the variability has two different sources: the natural variability, included in the baseline hazard function and the other which is given by a frailty term that represents the unobserved variability from the covariates (Wienke, 2010).

In this model is assumed that a given frailty term, the risk of each survival time follows a proportional hazard model, where the frailty term has a multiplicative effect on the baseline hazard function and also the covariates. For that reason we have to specify the assumed distribution for baseline hazard function and frailty term. Recently frailty models have been more used, because they allow considering the individual heterogeneity from each subject or grouping either from a disease or interest event. Frailty is an unobserved quantity modeled as a random variable over the population of individuals, with a high (low) value of the frailty term associated with a large (small) risk of acquiring the disease or the occurrence of an interest event (Raıces et al., 2018).

The frailty model is defined in terms of the conditional hazard:

$$h_j(t/z) = h_0(t)zexp^{(x^T{}_j\beta)} \tag{1}$$

With $j \in J = \{1, \dots\dots, n\}$ $h_0(.)$ is the baseline hazard function, z the frailty term , x_j the vector of covariates for subject j , and β the vector of regression coefficients.

Baseline Hazard Function

As in the proportional hazards model, parametric or non-parametric forms of baseline hazard can be assumed in frailty models. If non-parametric form is assumed for, $h_0(t)$ then semiparametric proportional hazards model is considered and the estimates are usually obtained by using Expectation-Maximization (EM) algorithm. If parametric form for $h_0(t)$ is assumed, then maximum likelihood estimates can be obtained by maximizing the likelihood function. The parametric baseline hazards are Weibull, exponential and Gompertz (Abdulkarimova, 2013). Using parametric baseline hazards not only makes the estimation easier, but it can also describe explicitly the effect of the frailty on hazard ratios over time. Under the parametric approach, the baseline hazard is defined as a parametric function and the vector of its parameters, say ψ, is estimated together with the regression coefficients and the frailty parameter(s).

Statistical Distributions for Frailty

The frailty denoted by z_i is an unobservable realization of a random variable Z with probability density function $f(.)$, the frailty distribution. Since z_i multiplies the hazard function, Z has to be non-negative. The choice of the frailty distribution is very important in the area of frailty models. Any distribution with a positive random variable can be used to model frailty. One-parameter gamma distribution is the most widely used frailty distribution proposed by (Clayton, 1978), since it is very tractable. (Hougaard, 1986) suggested the gamma, and the inverse-Gaussian distributions on the positive stable family of distributions for the frailty model. (Oakes, 1989) suggested the inverse Gaussian model for the distribution of the frailty.

Estimation of Parametric Frailty Model

In the parametric setting, estimation is based on the marginal likelihood in which the frailties have been integrated out by averaging the conditional likelihood with respect to the frailty distribution. Under assumptions of non-informative right-censoring and of independence between the censoring time and the survival time random variables, given information, the marginal log-likelihood of the observed data $Z = \{z_j;\ j \in J\}$ can be written as (Van den Berg and Drepper, 2016).

$$\ell_{marg}(\psi, \beta, \xi;\ z|\tau) = \sum_{i=1}^{G} \left\{ \left[\sum_{j=1}^{n_i} \delta_{ij} \left(log\left(h_0(y_{ij}) \right) + x^T{}_{ij}\, \beta \right) \right] + log\left[(-1)^{d_i} \mathcal{L}^{(d_i)} \left(\sum_{j=1}^{n_i} H_0(y_{ij})\, exp^{(x^T{}_{ij}\, \beta)} \right) \right] - \log\left[\mathcal{L}\left(\sum_{j=1}^{n_i} H_0(\tau_{ij})\, exp^{(x^T{}_{ij}\, \beta)} \right) \right] \right\} \quad (2)$$

With $d_i = \sum_{j=1}^{n_i} \delta_{ij}$ the number of events in the i^{th}individual, and $\mathcal{L}^{(q)}(.)$ the q^{th} derivative of the Laplace transformation of the frailty distribution define as

$$\mathcal{L}(s) = E\left[exp^{(-zs)}\right] = \int_0^\infty exp^{(-z_i s)} f(z_i) dz_i \quad (3)$$

Results

In this study 332 schizophrenic patients were included. From the participants for the studied sample were 198 (59.64%) males and 134 (40.36%) females. As Table1, distribution of the number of relapses in schizophrenic patients shows that the total numbers of relapse in schizophrenic patients were 162, among these 95(58.6%) relapses were observed in males, and 67(41.4%) relapses in females during the study period. A total 86(69.9%) of patients had experienced one (1) relapses, 35 (28.5%) of patients had experienced two relapse and 2(1.6%) of patients had experienced three relapse during the study period from the patients who had history of relapses. From 86 patients who had experienced one relapse 46(53.5%) of patients were male and 40(46.5%) of patients were female. Out of 35 patients who had experienced two relapse 23(67.7%) of patients were males and 12(34.3%) of patients were females. Likewise, on view of 2 patients who had experienced three relapse 1(50%) of patients were male and 1(50%) of patients were female.

From distribution of the number of relapses in schizophrenic patients 37(64.9%) of males and 24(72.7%) of females who have a comorbidity condition, 24(82.8%) of females who have a history of suicide attempt, 26(72.2%) of males who have a history of traditional treatment, 36(76.6%) of females who were unemployed and 39(76.5%) of females who were adherence to medication perfectly had experienced one (1) relapse during the study period.

Table 1: Frequency of Relapses in Schizophrenic Patients due to their Sex and different covariates

Covariates	Categories	Male			Female		
		Numbers of relapses					
		One	Two	Three	One	Two	Three
Comorbidity	No	9(69.2%)	4(30.8%)	0	16(80%)	4(20%)	0
	Yes	37(64.9%)	19(33.3%)	1(1.8%)	24(72.7%)	8(24.2%)	1(3.03%)
History of suicide attempt	No	25(75.6%)	8(24.2%)	0	16(66.7%)	7(29.2%)	1(4.2%)
	Yes	21(56.6%)	15(40.5%)	1(2.7%)	24(82.8%)	5(17.2%)	0
History of traditional treatment	No	20(58.8%)	13(38.2%)	1(2.9%)	16(94.1%)	1(5.9%)	0
	Yes	26(72.2%)	10(27.8%)	0	24(66.7%)	11(30.6%)	1(2.7%)
Employment status	Employee	10(90.9%)	1(9.1%)	0	4(66.7%)	2(33.3%)	0
	Unemployed	36(61%)	22(37.3%)	1(1.7%)	36(76.6%)	10(21.3%)	1(2.1%)
Drug adherence	No	13(59.1%)	9(40.9%)	0	1(50%)	1(50%)	0
	Yes	33(68.8%)	14(29.2%)	1(2.0%)	39(76.5%)	11(21.6%)	1(1.9%)

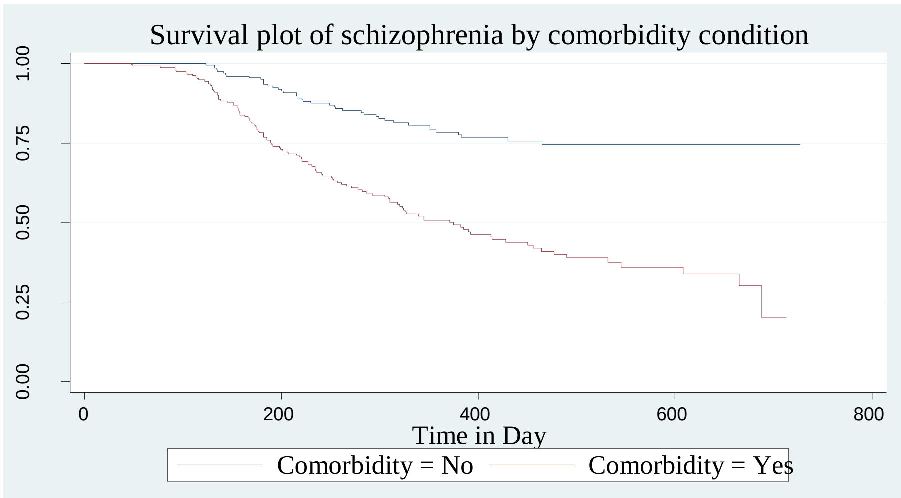

Figure 1: K-M survival Plot of Schizophrenia Data set by Comorbidity Condition

The survival of the patients those without comorbidity condition is greater as compared to the survival of the patients those with comorbidity condition. That is, the probability of delaying relapse time at a given time for patients without comorbidity condition is greater as compared to those with comorbidity condition shown in (1).

The result of Weibull- gamma frailty model is given below in Table 2. From this result the frailty variance θ, which measures the degree of heterogeneity among subjects and the correlation among relapses times was estimated to be 1.986. This indicated that there was heterogeneity among the participants and a significant correlation between the relapse time of schizophrenia in the disease process (second and subsequent relapses are likely to be influenced by the occurrence of the first) similarly, Γ=0.498, indicates there is a significant correlation between the relapse time of schizophrenia. A variance of zero $\theta = 0$ would indicate that the frailty component does not contribute to the model. A likelihood ratio test for the hypothesis $\theta = 0$ is shown in Table below indicates a chi-square value of 10.31 with one degree of freedom resulting a highly significant p-value of 0.001. This implied the model that does not consider the frailty of patients is not an appropriate model. The estimated value of shape parameter p in this selected model was

(2.502). This value is greater than unity these indicate the shape of hazard functions is increases up as time increase.

Table 2: Results of Weibull- Gamma Frailty Model

Covariate	Categories	$\widehat{HR}$	$SE(\widehat{HR})$	z	P-value	95% CI for $\widehat{HR}$	
Age of onset of schizophrenia		1.019	0.013	1.51	0.132	0.994	1.044
Comorbidity	No(ref)						
	Yes	6.522	2.156	5.67	0.000	3.411	12.467
Employment status	Employee(ref)						
	Unemployed	5.334	2.653	3.37	0.001	2.012	14.138
History of suicide attempt	No(ref)						
	Yes	2.167	0.557	3.01	0.003	1.309	3.586
History of traditional treatment	No(ref)						
	Yes	1.973	0.580	2.31	0.021	1.109	3.510
Drug adherence	No(ref)						
	Yes	0 .555	0.193	-1.70	0.090	0.281	1.096
Ln(p) = 0.917					0.000		
θ = 1.986	LR test of theta=0: chibar2(01) = 10.31				0.001		
p = 2.502		Γ=0.498			AIC= 672.079		

θ= variance of the random effect, Γ = Kendall's tau p =shape parameter, AIC= Akaike Information Criteria, chibar2= Chi-square.

Discussion

Chronic diseases such as schizophrenia are, roughly speaking, lifelong transitions between the states of relapse and recovery. The long-term pattern of recurrent times-to-relapse can be investigated with routine register data on hospital admissions. In this study Weibull- Gamma Frailty Model was used to estimate the parameters. In the model, the effects of comorbidity condition, employment status, reported suicide attempts and history of traditional treatment were significant and all predicted a higher relapse ratio. In contrast, age of onset of schizophrenia, and drug adherence did not predict the odds of relapses and/or relapse latency. The present results add to the current literature in the way in that comorbidity condition, employment status, reported suicide attempts and history of traditional treatment were important factors in higher relapse rates and shorter relapse intervals.

Using multiple logistic regressions, Kazadi, Moosa et al. illustrated that co-morbid depressed mood was the factor most likely to increase the risk of relapse in patients with schizophrenia (Kazadi, Moosa et al. 2008). Schennach et al. suggested that patients without a job were more likely to have a relapse during the year after discharge (Schennach et al., 2012). Using Shared Log-Normal Frailty model, Davarinejad, Mohammadi Majd et al. showed that history of suicide attempt has a significant effect on the relapse time of patients with schizophrenia (Davarinejad, Mohammadi Majd et al. 2021). In this study, the result revealed that the variance of frailty was significant. Rahmati et al. and Davarinejad, Mohammadi Majd et al., analyzed the schizophrenia data in frailty models estimated a frailty variance of 0.206 and 0.08 respectively, which was highly significant, suggesting that considerable heterogeneity was present (Rahmati et al., 2015; Davarinejad, Mohammadi Majd et al. 2021).

Conclusion

In this recurrent failure time model, comorbidity, employment status, history of suicide attempt and history of traditional treatment all predicted higher hospital readmission and a shorter readmission interval after the initial admission. Those, significant predictor variables were important risk factors influencing hazard of time to relapses, that is increase the risk of relapse. On the other hand; age of onset of schizophrenia and drug adherence was not significant predictors for the relapse time of patients with schizophrenia. Given this, counseling should focus on patients distinguished by these risks.

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