Original Article

JHSMR Journal of Health Science and Medical Research

Analysis of Time to Relapse among Schizophrenia Patients in St. Amanuel Mental Specialized Hospital, Addis Ababa, Ethiopia

Gebremedhin Desta Belihu M.Sc.[1], Wudneh Ketema Moges M.Sc.[1], Asamin Kasiye Yimer, M.Sc.[2]

[1]Department of Statistics, College of Natural Science, Debre Berhan University, Debre Berhan, Ethiopia.
[2]Department of Statistics, College of Natural Science, Kebir Dehar University, Kebir Dehar, Ethiopia.

Received 18 March 2023 ● Revised 28 November 2023 ● Accepted 29 November ● Published online 27 March 2024

Abstract:

Objective: To investigate the associated factors that affect time to relapse in patients with schizophrenia at St. Amanuel Mental Specialized Hospital, with recurrent events model.

Material and Methods: A hospital-based retrospective review of the medical records of 332 patient with schizophrenia, covering a two-year period, were examined. Parametric frailty models were used to determine the correlation between discharge times and relapse, and to identify risk factors using R-software.

Results: The distribution number of relapses was 162, and the median survival time of patients with schizophrenia was 665 days. The unobserved heterogeneity in patients and correlation between relapses, as estimated by the Weibull-gamma frailty model, was p-value≤0.001 and Kendall's Tau (Γ)=0.498. This indicated that there was heterogeneity among participants and a correlation between relapses. The final model showed that the effect of psychiatric comorbidity (hazard ratio (HR)=6.522, p-value≤0.001), 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) had a significant effect on the hazard time to relapse. Onset Age of schizophrenia and drug adherence were not predictive. Subsequent relapses are likely dependent on both the first and previous relapses.

Conclusion: Comorbidity, employment status, history of suicide attempt and history of traditional treatment are imperative risk factors influencing the hazard of time to relapse, which increases the risk of relapse.

Keywords: frailty models, proportional hazard model, recurrent events, relapse, schizophrenia patients

Contact: Gebremedhin Desta Belihu, M.Sc.
Department of Statistics, College of Natural Science, Debre Berhan University, Debre Berhan, Ethiopia.
E-mail: gmd202@gmail.com

J Health Sci Med Res .....
doi: 10.31584/jhsmr.20241049
www.jhsmr.org

Introduction

A mental disorder or psychiatric disorder is a behavioral or mental pattern that causes significant distress or impairment of personal functioning[1]. 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[2]. This mental disorder affects a person's, feelings, behaviors, and social interactions. It is among the most disabling and economically catastrophic medical disorders, and is ranked by the World Health Organization (WHO) as one of the top ten illnesses contributing to the global burden of disease[3]. Symptoms of schizophrenia include hallucinations that may be visual or auditory, delusions, cognitive impairment; manifesting as an unusual way of thinking or disorganized speech, and difficulty in social relationships, resulting in problems in social and occupational functioning and self-care[4,5].

The lifetime prevalence of schizophrenia has generally been estimated to be approximately 1% worldwide[6]. However, a systematic review[4] of 188 studies drawn from 46 countries found a lifetime risk of 4.0 per 1,000 population. Additionally, prevalence estimates from countries considered as least developed were significantly lower than those from countries classed as emerging or developed[7]. The incidence of an annual number of new cases of schizophrenia is estimated to be 1.5 per 10,000 people[4].

Patients with schizophrenia often experience relapses once or more, with no limit on the number of relapses[5]. 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 the hospital[8]. Age of onset, gender, marital status and family history are documented to be important risk factors influencing the hazard of time to relapses[5]. Relapse hazard ratio increases with a history of suicide attempts, and is gradual compared to a sudden onset of disease[9].

In Ethiopia, the study conducted by Kebede has shown that the prevalence of schizophrenia is 0.47%[10]. Over half of the people with this disabling and chronic mental disorder experience continuous or episodic illness over a 10-year period, with limited service coverage and financial protection for people[11]. In regards to the situation in Ethiopia, analysis of time to relapse is important in the assessment of treatment outcomes. Although different studies have been conducted in regards to schizophrenia, the time among relapses is rarely considered in studies. None of them tried to account for the correlations caused by recurrent events and event dependence, which are key features in studies of schizophrenia. Therefore, this study was proposed to model the time to relapse among patients with schizophrenia and to explore factors that have a strong association with time to relapse in St. Amanuel Mental Specialized Hospital, Addis Ababa; Ethiopia.

The objective of this study was to investigate the associated factors that affect time to relapse of patients with schizophrenia in St. Amanuel Mental Specialized Hospital, Addis Ababa, Ethiopia.

Material and Methods

Description of data

This study data was obtained from a retrospective cohort follow-up study from patients with schizophrenia that were 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 numbers 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 patients with schizophrenia can be studied with suitable failure time models. Frailty models extended the 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[12]. Normally, in most clinical applications, survival analysis implicitly assumes a homogenous population to be studied. This means that all individuals sampled in the said study are subject in principle to the same risk. 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 that 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, wherein the random effect (the frailty) has a multiplicative effect on the baseline hazard function[13].

Parametric frailty models

Frailty models have been used frequently to model the multivariate dependence in time of an interest event[14]. 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 term events[15]. 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[16].

In this model, it is assumed that a given frailty term, the risk of each survival time, follows a proportional hazard model wherein the frailty term has a multiplicative effect on the baseline hazard function also in addition to the covariates. For this reason, one has to specify the assumed distribution for baseline hazard function and frailty term. Recently frailty models have been used more because they allow for the consideration of 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[15].

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

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

With $j \in J = \{1, \ldots\ldots, n\}$ $h_0(.)$ 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 the non-parametric form is assumed for, $h_0(t)$ then the semiparametric proportional hazards model is considered, and the estimates are usually obtained by using an Expectation-Maximization (EM) algorithm. If the parametric form $h_0(t)$ is assumed, then the maximum likelihood estimates can be obtained by maximizing the likelihood function. The parametric baseline hazards are Weibull, exponential and Gompertz[13]. Using parametric baseline hazards not only makes the estimation easier but 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 frailty distribution is very important in the area of frailty models. As any distribution with a positive random variable can be used to model frailty. The one-parameter gamma distribution is the most widely used frailty distribution, as proposed by Clayton[17], since it is very tractable. Whereas Hougaard suggested the gamma and the inverse-Gaussian distributions on the positive stable family of distributions for the frailty model, whilst Oakes suggested an inverse Gaussian model for the distribution of the frailty[18,19].

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, $Z=\{z_j;\ j \in J\}$ which can be written as follows[20].

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

With $d_i=\sum_{j=1}^{n_i}\delta_{ij}$ being 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 defined 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 patients with schizophrenia were included. The participants for the studied sample were 198 (59.64%) males and 134 (40.36%) females. As in Table 1, the distribution of the number of relapses in patients with schizophrenia shows that the total number of relapses in patients with schizophrenia was 162; among these, 95 (58.6%) relapses were observed in males, and 67 (41.4%) relapses in females over the study period. A total of 86 (69.9%) patients had experienced one relapse, 35 (28.5%) had experienced two relapses and 2 (1.6%) had experienced three relapses during the study period from the patients who had a history of relapses. From the 86 patients having experienced one relapse, 46 (53.5%) patients were male and 40 (46.5%) were female. Out of the 35 patients having experienced two relapses 23 (67.7%) were males and 12 (34.3%) were females. Likewise, in view of the 2 patients having experienced three relapses 1 (50%) was male and 1 (50%) was female.

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

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

The result of the Weibull-gamma frailty model is shown in Table 2. From this result, the frailty variance, which measures the degree of heterogeneity among subjects

and the correlation among relapse 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 θ=0 would indicate that the frailty component does not contribute to the model. A likelihood ratio test for the hypothesis θ=0 as shown in Table 2, indicates a chi-square value of 10.31, with one degree of freedom resulting in a highly significant p-value of 0.001. This implies the model does not consider the frailty of patients and is not an appropriate model. Additionally, a model comparison was performed using Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and log- likelihood as selection criteria. The best model is the one with the lowest value of AIC and BIC, and with the largest value of log-likelihood. The AIC and BIC values of Weibull were the smallest (680.392 and 713.614) and had the largest value of log-likelihood (-332.196) implying that the Weibull parametric proportional hazard model was the best model to describe the schizophrenia data. The estimated value of shape parameter in this selected model was (2.502). This value is greater than unity indicating the shape of hazard functions increases up as time increases.

Discussion

Chronic diseases such as the schizophrenia are, roughly speaking, lifelong transitions between the states of relapse and recovery. Long-term patterns of recurrent times-to-relapse can be investigated with routine register data on hospital admissions. Herein, the Weibull-Gamma Frailty Model was used to estimate these parameters. In the model, the effects of comorbidity condition, employment status, reported suicide attempts and history of traditional treatment were significant, which means these factors were most likely to increase the risk of relapse in patients with schizophrenia, and all predicted a higher relapse ratio. This may be due to traditional treatment affecting, either directly or indirectly, patients.

In contrast, onset age of schizophrenia, and drug adherence did not predict the odds of relapses and/or relapse latency. These present results add to the current literature in the way that comorbidity conditions, employment status, reported suicide attempts and history of traditional treatment were important factors in higher relapse rates as well as shorter relapse intervals. However, some studies have suggested onset age of schizophrenia was statistically associated with schizophrenia[5,9].

Table 1 Frequency of relapses in patients with schizophrenia, due to their gender and different covariates

Covariates	Categories	Male			Female		
		Numbers of relapses			Numbers of relapses		
		One (%)	Two (%)	Three(%)	One (%)	Two (%)	Three (%)
Psychiatric comorbidity	No	9(69.2)	4(30.8)	0	16(80.0)	4(20.0)	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(61.0)	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(50.0)	1(50.0)	0
	Yes	33(68.8)	14(29.2)	1(2.0)	39(76.5)	11(21.6)	1(1.9)

Table 2 Results of the Weibull-Gamma frailty model

Covariate	Categories	$\widehat{HR}$	$SE(\widehat{HR})$	Z	p-value	95% CI for $\widehat{HR}$	
Onset age 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-value=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, Ln=natural logarithm of the likelihood function, test of theta=hypothesis test of frailty parameter, CI=confidence interval

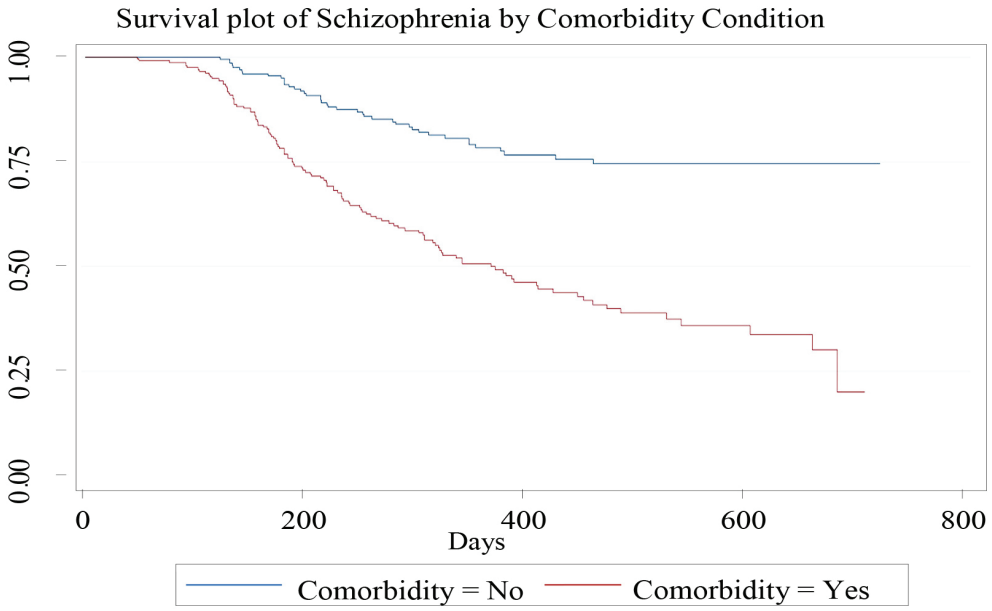

Figure 1 Kaphan-Meier survival plot of Schizophrenia data set by the presence of comorbidity condition

Relapse time significantly differs between the employed and unemployed categories (HR=5.334, 95% confidence interval (CI)=(2.012, 14.138), p-value=0.001). This distinction has significant effects on the conditional hazard function and increases the risk of relapses of schizophrenic patients. In other words, the risk of relapse for patients who were unemployed had a higher risk of relapse as compared to patients being employed. Patients without a job were more likely to have a relapse during the first year after discharge[22].

Comorbidity had significant effects on the conditional hazard function and increased the risk of relapses. This indicated that patients that had comorbidity conditions increased the hazard of relapse as compared to patients that had no comorbidity conditions. This finding aligned with Kazadi, Moosa[21]. Using the Shared Log-Normal Frailty model, a history of suicide attempts had a significant effect on the relapse time of patients with schizophrenia[9].

Finally, the results revealed that the variance of frailty was significant, which is in line with schizophrenia data in frailty models that estimated a frailty variance of 0.206 and 0.08, respectively. This was highly significant, suggesting considerable heterogeneity was present[5,9].

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 the hazard of time to relapse, which is an increase in the risk of relapse. On the other hand, the onset age of schizophrenia and drug adherence were not significant covariates for the relapse time of patients with schizophrenia. Given this, counseling should focus on patients who are distinguished by these risks.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Limitations of the study

For some observations, predictors were not registered as base line. Due to these observations with covariates those not registered were ignored in the study.

Ethics statement

The studies involving human participants were reviewed and approved by DBU, College of Natural and Computational Science Research Ethics Review Committee.

Authors contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, gave final approval of the version to be published, agreed to be accountable for all aspects of the work, have read and approved the final manuscript.

Conflict of interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Bolton D. What is mental disorder?: an essay in philosophy, science, and values. International Perspectives in Philosophy & Psychiatry. Oxford: Oxford University Press; 2008.
2. Sadock BJ. Kaplan and Sadocks synopsis of psychiatry. Philadelphia: Lippincott Williams & Wilkins; 2015.
3. Ayano G. Schizophrenia: a concise overview of etiology,

epidemiology diagnosis and management: review of literatures. J Schizophr Res 2016;3:1026.

4. Mcgrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008;30:67–76.
5. Rahmati M, Rahgozar M, Fadaei F, Bakhshi E, Cheraghi L. Identifying some risk factors of time to relapses in schizophrenic patients using Bayesian approach with event-dependent frailty model. Iran J Psychiatry 2015;10:123.
6. Balhara YPS, Verma R. Schizophrenia and suicide. East Asian Arch Psychiatry 2021;2;22:126.
7. Koeda A, Otsuka K, Nakamura H, Yambe T, Fukumoto K, Onuma Y, et al. Characteristics of suicide attempts in patients diagnosed with schizophrenia in comparison with depression: a study of emergency room visit cases in Japan. Schizophr Res 2012;142:31–9.
8. Kroken RA, Mellesdal LS, Wentzel-Larsen T, Jørgensen HA, Johnsen E. Time-dependent effect analysis of antipsychotic treatment in a naturalistic cohort study of patients with schizophrenia. Eur Psychiatry 2012;27:489–95.
9. Davarinejad O, Mohammadi Majd T, Golmohammadi F, Mohammadi P, Radmehr F, Alikhani M, et al. Identification of risk factors to predict the occurrences of relapses in individuals with schizophrenia spectrum disorder in Iran. Int J Environ Res Public Health 2021;18:546.
10. Kebede D, Alem A, Shibre T, Negash A, Fekadu A, Fekadu D, et al. Onset and clinical course of schizophrenia in Butajira-Ethiopia--a community-based study. Soc Psychiatry Psychiatr Epidemiol 2003;38:625–31.
11. Shibre T, Medhin G, Alem A, Kebede D, Teferra S, Jacobsson L, et al. Long-term clinical course and outcome of schizophrenia in rural Ethiopia: 10-year follow-up of a population-based cohort. Schizophr Res 2015;16:414–20.
12. Abdulkarimova U. Frailty Models for Modelling Heterogeneity. 2013 p.1–85.
13. Wienke A. Frailty models. Wiley StatsRef: Statistics Reference Online. Wiley Online Library 2014.
14. Gutierrez RG. Parametric Frailty and shared frailty survival models. Stata J 2002;2:22–44.
15. Raices I, Sistachs V, Liero H, Yera I, Martinez L. Analysis of parametric frailty models to estimate the risk of amputation. Investigación de Operacional 2018;39:33.
16. Wienke A. Frailty models in survival analysis (1st ed.). New York: Chapman and Hall/CRC; 2010.
17. Clayton DG. A model for association in bivariate life tables and its application in epidemiological studies of familial tendency in chronic disease incidence. Biometrika 1978;65:141–51.
18. Hougaard P. Survival models for heterogeneous populations derived from stable distributions. Biometrika 1986;73:387–96.
19. Oakes D. Bivariate survival models induced by frailties. J Am Stat Assoc 1989;84:487–93.
20. Van Den Berg GJ, Drepper B. Inference for shared-frailty survival models with left-truncated data. Econom Rev 2016;35:1075–98.
21. Kazadi N, Moosa M, Jeenah F. Factors associated with relapse in schizophrenia. S Afr J Psychiatry 2008;14:52–62.
22. Schennach R, Obermeier M, Meyer S, Jäger M, Schmauss M, Laux G, et al. Predictors of relapse in the year after hospital discharge among patients with schizophrenia. Psychiatr Serv 2012;63:87–90.