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Predictability of rehospitalization for schizophrenia

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Abstract This analysis examines the predictability of the course of schizophrenia using long-term follow-up data on hospital episodes in a cohort of patients from a psychiatric case register in Denmark. We focus on whether clinical and sociodemographic data collected during the first episode are related to the number of hospitalizations during follow-up and the association of patients' course of hospitalizations with the risk of being rehospitalized. A Poisson regression model and a proportional hazards model were used to address these questions. Age of onset and time to the first rehospitalization were strong early predictors of chronicity of course, as measured by the number of psychiatric hospitalizations for each schizophrenic patient. The results also show that the risk of rehospitalization depends on the previous tenures in the community.

Key words Age · Epidemiology · Hospitalization
Patient readmission · Statistics and numerical data
Schizophrenia

Introduction

Kraepelin's initiative to differentiate chronic mental illness depending on outcome greatly helped to clarify the classification of mental disorders. Dementia praecox was considered to be a disorder with a deteriorating course. However, numerous studies show that schizophrenia may not have a unique and deteriorating course [5, 6, 8, 9, 17, 18, 25, 30]. The natural history of schizophrenia seems to be heterogeneous, ranging from patients who only have one episode during their lifetime and from which they recover completely to patients who are severely impaired in their social, family, and personal life.

The search for prognostic factors of the course of schizophrenia has important implications for the clinician and investigator. Patients and families are eager to know from the clinician the outlook of the disorder and the finding of determining factors gives clues for etiology. Many clinical studies have addressed this question, with multiple findings (for a review of long-term follow-up studies see Refs. 4 and 24). Women seem to have a better course [3, 13, 16, 32, 36], which may be attributed to differences in the illness per se, social roles, or illness behavior [3, 14, 32]. Early or insidious onset has been associated with a higher risk of rehospitalization and a worse outcome [24, 33, 36] that has been related to a poorer premorbid adjustment and/or lower educational achievement [2, 24, 28]. Other prognostic factors also relevant for the present study are the better outcome of married patients and of patients with a shorter duration of illness [24, 30, 33, 34].

In the study of the course of mental disorders psychiatric case-register data possess some advantages that complement the findings of clinic-based studies. Firstly, the number of patients and follow-up periods tracked by registers are usually much greater and longer than in clinical studies. Secondly, attrition of the study population due to losses through follow-up may be minimized if the register includes all facilities in the community and if the catchment area is sufficiently large. Finally, registers provide continuous time data. This allows the use of survival-analysis methods and the better control of biases resulting from the collection of information at fixed points in time.

In recent years new developments in the computerized analysis of longitudinal data have provided methods to control for biases that had affected previous studies in the study of prognostic factors in schizophrenia. The widely

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employed multivariate survival-analysis methods (e.g., proportional hazards model [10]) adjust for biases arising from different follow-up times and from the competing effect of several covariates. The analysis of rehospitalization data is also subject to biases originating from the correlation between different observations for the same patient: Each patient's characteristics determine his/her proneness to rehospitalization, and these unknown factors are common to all the hospitalizations for a given patient. An analysis that does not consider these effects may yield biased results, because the variances of the estimates and the statistical tests will usually be smaller than the ones resulting when taking it into account [21, 37].

In other published works the authors have employed this methodology to study the factors that influence first rehospitalization [12], the decrease of the readmission risk with the passage of time [11], and the changing patterns of predictors with increasing numbers of readmissions [26]. The present analysis with a smaller subsample includes some of the previous findings, but its main innovation is the study of the length of tenure in the community as a predictor of course and the first use of a Poisson regression model to predict number of episodes.

In this study we tried to estimate the course of schizophrenia using hospitalization data from the Danish psychiatric case register. Number of hospitalizations or, conversely, length of stay in the community, were used as proxy measures for chronicity of schizophrenia. We have posed two questions: Firstly, can we estimate the chronicity of schizophrenia from sociodemographic data collected during the first episode? In order to answer this question we have related the number of future admissions for each patient to the characteristics of his/her first hospitalization using a Poisson regression model. Secondly, is the patient's hospitalization history related to his/her future course? To address this issue we used a proportional hazards model to correlate the risk of rehospitalization with the length of previous stays in the community.

Materials and methods

The Danish psychiatric case register was computerized in 1969 and covers all psychiatric hospitals in the country (5.1 million inhabitants). No private psychiatric hospitals or departments exist in Denmark and hospital treatment is free. The data set we analyzed included 9250 patients with a diagnosis of schizophrenia (ICD-8: 295) who were first hospitalized between April 1, 1970 and March 25, 1988, with a total number of 85,778 hospitalizations. The patients included received a diagnosis of schizophrenia during at least one hospitalization, the first of which was considered the index admission.

For our analyses we selected a cohort of patients who had been followed for at least 16 years following the first discharge with a diagnosis of schizophrenia. This constraint allowed us to avoid a number of biases arising from the inclusion of patients with a short follow-up period who might have had more hospitalizations if they had been followed for a longer period. To further control for time biases and to make all patients comparable regardless of when they were first hospitalized, episodes that occurred after the 16-year follow-up for each patient were not included. Because the proportional hazards model we use is sensitive to outlier values, and in order to remain consistent with previous analyses [11], the strata of number of episodes which had fewer than five patients were omitted. This resulted in the elimination of 23 individuals with more than 21 episodes. The characteristics of the register, the editing of the data, and the selection of the cohort have been described in more detail elsewhere [11, 12].

The number of hospitalizations in each patient's follow-up period was linked to the sociodemographic and clinical variables of the first admission (age, gender, marital status, number of previous psychiatric hospitalizations, and tenure in the community after first discharge). We used a Poisson regression model, which is appropriate when the dependent variable is a count, as in the case of number of hospitalizations [23]. This model can be expressed as:
Log (number of episodes) = $a + b_1 * x_1 + b_2 * x_2 + \ldots + b_n * x_n$
where a = intercept, $b_1 \ldots b_n$ = regression coefficients, and $x_1 \ldots x_n$ = corresponding explanatory variables.

The antilogarithm of the regression coefficients is an estimate of the ratio of the number of episodes the patient with that characteristic will have compared to the reference category. In the case that all patients are followed for the same amount of time (i.e., 16 years), this amount is a rate ratio. In our study this is only approximately true, because deaths or losses through follow-up (i.e., emigration) were not considered in this part of the analysis.

Because people with a longer stay in the community after first discharge – people who are rehospitalized later – will have less time to develop new episodes during the 16-year follow-up, the effect in the model of the variable 'stay in the community after first discharge' may be biased. In order to control this bias we repeated the analysis with another cohort of patients selected from the original data of 9250 individuals. This cohort included patients who had been followed for 12 years after the second discharge.The length of follow-up for these patients is the same regardless of the time between the first and second episodes. This new cohort will be named cohort B, and the 16-year follow-up cohort will be identified as cohort A.

In order to study the effect of the duration of previous interepisode times in the course, we used the proportional hazards model [37]. This statistical technique assesses the effects of predictor variables on the time to an event. The event under study is rehospitalization. Thus, this model will determine the effect of the predictor variables on the time to rehospitalization. If a lengthy previous tenure in the community is an indicator of a relatively stable protective factor or signals improvement in prognosis, length of community tenure will decrease the hazard of rehospitalization. The logarithm transformation of tenure in the community was used because the original data had a skewed distribution. Other covariates included in the model allowed us to control for the effects of initial heterogeneity concerning chronicity (measured by the total number of episodes in the follow-up) and of the diminishing risk of rehospitalization over time. This was necessary because hospital admissions for schizophrenia tend to cluster at the beginning of the course [11].

A final problem arises from the fact that hospitalizations are not independent of each other, because each individual can generate more than one hospitalization. If this effect is not taken into account as in most of the statistical packages, the estimate of the coefficients will still be correct, but their variance will be biased. In order to estimate this variance we used an algorithm that takes into account the correlation between multiple observations in each person and that is based in semi-non-parametric methods [37].

Results

A total of 600 patients were included in the cohort (cohort A). The mean age at first admission was 27.3 years and the proportion of females was 36.2%. The mean number of episodes in the follow-up period was 5.3.

Table 1, cohort A presents the results from the Poisson regression model that links total number of episodes of hospitalization over the 16-year follow-up to sociodemo-

Table 1 Poisson regression model of the total number of episodes during the study period. Numbers shown are ratios of number of episodes

	Danish psychiatric case register (1970–1988)	
	Cohort A[a] Ratio (95% CI)	Cohort B[b] Ratio (95% CI)
Age at first hospitalization for schizophrenia (years)		
10–19	1.00	1.00
20–29	1.08 (0.99, 1.17)	0.90 (0.85, 0.93)
30–39	0.76 (0.67, 0.87)	0.66 (0.61, 0.70)
40–49	0.51 (0.43, 0.61)	0.41 (0.37, 0.46)
50–59	0.50 (0.41, 0.60)	0.36 (0.31, 0.42)
60+	0.33 (0.26, 0.41)	0.26 (0.20, 0.33)
Gender		
Male	1.00	1.00
Female	1.05 (0.97, 1.14)	0.91 (0.88, 0.95)
Prior hospitalizations before diagnosis of schizophrenia		
None	1.00	1.00
Any	1.11 (1.02, 1.21)	1.27 (1.22, 1.31)
Stay in the community after first discharge		
1–30 days	1.00	1.00
1 month–5.99 months	0.97 (0.87, 1.07)	0.93 (0.89, 0.97)
6 months–11.99 months	0.82 (0.72, 0.93)	0.79 (0.74, 0.84)
1–1.99 years	0.81 (0.72, 0.90)	0.74 (0.69, 0.79)
2–2.99 years	0.82 (0.70, 0.95)	0.58 (0.52, 0.66)
3–3.99 years	0.76 (0.63, 0.91)	0.70 (0.61, 0.83)
4–5.99 years	0.55 (0.44, 0.69)	0.41 (0.28, 0.62)
6–7.99 years	0.73 (0.59, 0.90)	–
8–9.99 years	0.40 (0.26, 0.60)	–
10–11.99 years	0.43 (0.30, 0.62)	–
12–13.99 years	0.37 (0.26, 0.52)	–
14–15.99 years	0.15 (0.13, 0.18)	–
Number of patients	600	1323

[a] Includes patients with 16 years of follow-up after first hospital discharge with a diagnosis of schizophrenia

[b] Includes all patients with 12 years of follow-up after the second hospital discharge, selected from the initial cohort

graphic variables at first episode. The first category of each variable represents the reference category. Patients with an earlier onset will have a greater number of episodes of the disorder. For example, patients with a first hospitalization during the fifth decade of life will have, in the 16-year follow-up, roughly half of the hospitalizations than patients with onset in the second decade. The model predicts that patients with a first hospitalization in their twenties will have approximately the same number of hospitalizations as the patients who are first hospitalized in their teens. Gender was not found to have any significant impact on the number of episodes patients develop in the follow-up period once an adjustment is made for age of onset. Marital status, dichotomized as never married vs married, divorced, or widowed, was not included because it did not add any significant explanatory value to the model, therefore, it did not have any significant influence in the number of hospitalizations.

An important predictive factor for the number of episodes is the tenure in the community following the first episode: The longer the tenure in the community, the better the prognosis. For example, patients who are rehospitalized between 6 and 12 months after first discharge will have 0.82 times the episodes of patients rehospitalized within 30 days.

In order to control for the bias arising from the fact that patients who are rehospitalized later have less opportunities to experience new hospitalizations in the 16-year follow-up, the analysis was repeated with cohort B, which included individuals followed for 12 years after the second discharge (Table 1, cohort B). The total number of patients in this cohort was 1323. The mean age at first admission was 25.2 years and the proportion of females was 32.3%. Because only people with two or more episodes were included, this cohort contained more severe patients (mean number of episodes in follow-up = 9.3). Length of stay in the community after first discharge was again a strong predictor of future course. The direction of the influence of the other variables was the same as before, except in the case of gender. The effect of gender became significant in this cohort, but it was of small magnitude and may not be considered clinically significant.

The second part of our analysis was centered on the explanatory value that previous tenures in the community or interepisode times can have on future tenures in the community. Firstly, we looked at the correlation matrix between the rehospitalization or interepisode times of each patient. If past tenures in the community determine the length of future tenures, we would expect a high correlation between them. A positive correlation would mean that longer tenures in the community predict a better outcome. Although from these analyes there seems to be a general positive correlation between the interepisode times across patients, the absolute numbers are in general smaller that 0.25 and there is not a consistent pattern (data not shown).

The simple correlation between interepisode times is an exploratory technique, but its real value is mediated by two main factors: the presence of other covariates (i.e., age, gender, and especially the time-dependent variables) as important predictors of the course and the censoring of interepisode times at the end of the observation period. A proportional hazards model was used to control these possible biases. Table 2 presents the results of a model using days in the community between episodes as the dependent variable. The values shown are the hazard rate ratios of rehospitalization, which are approximately the relative risks of rehospitalization of a patient with that characteristic in relation to the reference category. We included in the model the variables that a priori seemed able to influence the time to rehospitalization (age of onset, gender, and earlier hospitalizations). We also adjusted for the total number of hospitalizations, because those with many hospitalizations will necessarily have a higher risk of rehospitalization at any given time. Because we were interested

Table 2 Proportional hazards model: estimated hazard-rate of rehospitalization (includes all patients with three or more hospital admissions for schizophrenia during the year follow-up)

	Danish psychiatric case register (1970–1988) Relative risk (95% CI)
Age at first hospitalization for schizophrenia (years)	
10–19	1.00
20–29	0.98 (0.76, 1.26)
30–39	0.99 (0.66, 1.46)
40–49	0.71 (0.51, 1.00)
50–59	0.85 (0.56, 1.28)
60+	0.92 (0.56, 1.51)
Gender	
Male	1.00
Female	1.03 (0.82, 1.30)
Prior hospitalizations before diagnosis of schizophrenia	
None	1.00
Any	0.90 (0.70, 1.15)
Total number of hospitalizations for the individual during follow-up	1.12 (1.09, 1.15)
For each additional hospitalization	0.93 (0.93, 0.94)
Logarithm of last interepisode time[a]	0.95 (0.92, 0.97)
Logarithm of next-to-last interepisode time[a]	0.93 (0.90, 0.95)
Total number of hospitalizations	2144
Total number of patients	372

[a] For each unit of the logarithm of the interepisode time the relative risk decreased by the amount shown

in the influence of previous interepisode time on outcome, only third or later episodes from the 16-year follow-up cohort were included. This implies that this cohort included more chronic patients (people with at least three episodes).

As in a previous analysis [11] age of onset, gender, and number of hospitalizations before the diagnosis of schizophrenia did not show a strong effect, and the risk of rehospitalization in the follow-up period decreased as time passed with each additional hospitalization. The effect of previous tenures in the community was included in the model as the logarithm of the two previous interepisode times. The data show that the longer the two previous tenures in the community, the lower the risk of rehospitalization. Although significant, this effect is not very large. A decrease in one unit in the natural logarithm of the interepisode time, i.e., a 2.7 increase in the interepisode time, decreases by 0.95 the risk of rehospitalization. For example, if we compare the risk of hospitalization of one patient who was readmitted 2 months after the previous hospitalization to that of another who remained 2 years in the community, the former's risk of hospitalization is 1.14 times greater than that of the latter.

Similar analyses were performed using additional interepisode times, but interepisode times from farther in the past did not predict future tenures. Thus, the tenure in the community after the third previous hospitalization or earlier tenures do not affect future interepisode times if more recent tenures are taken into account. Equivalent results were obtained for the cohort of patients followed for 12 years (cohort B).

Discussion

In this study we address the question of the predictability of the course of schizophrenia as measured by the number of hospitalizations patients suffer during their lifetime. We have analyzed predictors from the early and late course of the disorder, using recently developed statistical methods. We first employed a Poisson regression model for the study of the long-term course of schizophrenia.

Interepisode time is a strong predictor of the number of hospitalizations schizophrenic patients experience. Time to first rehospitalization is greatly associated with the total number of hospitalizations a patient will suffer. Longer tenures in the community following the first admission with a diagnosis of schizophrenia are correlated with fewer rehospitalizations and better prognosis. The replication of these results with two differently selected cohorts of patients increases the validity of the findings. This is consistent with the fact pointed out by Anderson et al. [1]: that the risk of relapse is greater during the first year after an episode, and that effort must be put into avoiding relapse during this period. Later in the course, interepisode time loses power in predicting course, although its effect is still significant. The results showed that the longer the two previous interepisode times, the lower the risk of rehospitalization. Although statistically significant, this result is smaller in magnitude than we expected.

Age of onset has also been shown to be an important determinant of number of hospitalizations. After adjustment is made for age of onset, gender and marital status have not been found to be significant predictors of the course of hospitalizations. Whereas our results agree with the widely accepted prognostic value of age of onset [19, 24, 31, 34, 36], several authors have also found that female gender [3, 13, 16, 32, 36] and married status [33] are associated with a better course. Nevertheless, some of these studies do not consider that these effects may be confounded by age of onset: Because females have a later onset than males [15, 20], which is associated with better prognosis, the detected effect of gender could be due to the earlier age of onset in men. The explanation for the supposed effect of marital status could be similar. Other authors have found no relationship between outcome and marital status when gender and age of onset were taken into account [7, 29, 31]. These results complement our previous analysis with registers from four different countries that showed that age of onset, but neither gender nor marital status, is an important risk factor for rehospitalization after first discharge [12]. We also have employed a similar group of patients from the Danish cohort to demonstrate that risk of rehospitalization decreases with time [11] and that there is a subpopulation of schizo-

phrenic patients with frequent relapses [26]. The present work diverges and complements these publications, using a different and innovative statistical approach and focusing on the influence of tenure in the community in the early and late course.

Later in the course of schizophrenia the effect of age of onset loses power in predicting the risk of rehospitalization. For chronic patients the sociodemographic characteristics at onset do not seem to be so important in the determination of the later course of schizophrenia. However, this finding could be due to a statistical bias, because the inclusion of the total number of hospitalizations during follow-up in the proportional hazards model reduces the variability explained by the other variables. In other words, the first part of the analysis has shown that age at first hospitalization influences the total number of hospitalizations during follow-up, and the inclusion of this last variable in the model carries some of the effect of age at first hospitalization. The inclusion of the total number of hospitalizations is, however, necessary to adjust for the different chronicity of patients. The small effect of tenure in the community of interepisode time on risk of rehospitalization in the late course of schizophrenia could also be influenced by this statistical bias.

Because this study is based on hospitalization data from a psychiatric register, our measure of the course of schizophrenia is based on the number of hospitalizations patients experience. This limits the extrapolation of our results to clinically meaningful conclusions. Besides, due to characteristics of our data, important clinical variables such as professional engagement, load factors (i.e., expressed emotion), or neuroleptic compliance could not be considered. However, because a large proportion of schizophrenic patients receive psychiatric treatment and are eventually hospitalized over their lifetime [22, 35], we believe that our study includes a broad representation of schizophrenics. Relapses treated on an outpatient basis may also be assumed to be less disruptive for patients and their social environment, and are thus less severe than relapses that involve an hospitalization.

Biases arising from losses through follow-up bring into question the validity of prospective studies. The two main sources of losses through follow-up in this study were deaths and emigration from Denmark. Although we cannot know the effect of emigration, its effect may be considered small. The effect of deaths during follow-up may be more important. The proportional hazards model takes into account censoring and deaths occurring in Denmark, which were included in the register. That part of the analysis is corrected for the effect of deaths. In the Poisson model patients who die before the end of the 16-year follow-up will have less opportunities to be hospitalized. Because mortality is higher for older patients, the finding that younger patients at first hospitalization tend to have more rehospitalizations than older ones could be partially or completely due to that bias. Nevertheless, Mortensen and Juel [27] found that mortality for schizophrenic patients in the Danish register was very stable for people younger than 50 years, which decreases the relevance of the bias.

Although registers contain continuous-time notification of admissions, large sample sizes, and long follow-up times, their limitations suggest that these findings be explored in clinical studies. We also suggest the replication of these analyses with other data bases in order to compare the results for a variety of clinical and administrative situations.

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