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Detection of Progressive Deterioration in Early Onset Schizophrenia with a New Statistical Method

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Detection of Progressive Deterioration in Early Onset Schizophrenia with a New Statistical Method

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Abstract

Much controversy exists over whether the course of schizophrenia, as defined by the lengths of repeated community tenures, is progressively ameliorating or deteriorating. This article employs a new statistical method proposed by Wang and Chen (2000) to analyze the Denmark registry data in Eaton, et al (1992). The new statistical method correctly handles the bias caused by induced informative censoring, which is an interaction of the heterogeneity of schizophrenia patients and long-term follow-up. The analysis shows a progressive deterioration pattern in terms of community tenures for the full registry cohort, rather than a progressive amelioration pattern as reported for a selected sub-cohort in Eaton, et al (1992). When adjusted for the long-term chronicity of calendar time, no significant progressive pattern was found for the full cohort.

1. Introduction

An analysis of data on long-term rates of hospitalization from cohorts in two psychiatric case registers concluded that the course of hospitalization became slightly more benign as it progressed, consistent with the concept of "progressive amelioration" (Eaton et al. 1992). The discussion to that paper expressed concern that there was no adequate control for a viable alternative explanation, and that the appearance of amelioration had been artifactually produced by gradual changes in the administrative structure of the hospitals in the register area. In this analysis we apply a new statistical method (Wang and Chen 2000) which allows adjustment for calendar year of admission, stratification into subgroups, and corrects for other deficiencies in that method (described further below), using data from the same time period and national population, that is, the psychiatric case register of Denmark.

The question of deterioration in course has been central to the study of schizophrenia since the syndrome was first defined. Kraepelin (Kraepelin 1919) seemed to imply that the course of schizophrenia was progressively deteriorating; others have concluded that the course might be better characterized with a term like "progressive amelioration" (Bleuler 1924; Harding, et al. 1987; McGlashan 1988). Recently, Mason, et al (Mason, et al. 1996) studied 67 patients with ICD-9 schizophrenia in a 13-year follow-up study. Their data analysis does not support either progressive deterioration or progressive amelioration and hence concludes that the course of schizophrenia should be relatively stable. With data on the course of hospitalizations, the statistical problem is to assess the trend in the episodes of community tenures, which can be measured by the lengths of two consecutive hospitalizations: are they becoming shorter and shorter (deteriorating course), or longer and longer (improvement in course)? In addition, data

from psychiatric case registers have important limitations in addressing this question, because the time between hospitalizations itself does not always reflect the ebb and flow of the clinical course. Even if the notion that hospitalizations are produced by the new emergence of psychotic symptoms is accepted, it is possible that changes in the threshold of hospitalization over time could produce apparent changes in the length of community tenure over time. In this situation, the statistical problem is to adjust the assessment of trend, for the calendar year in which any given hospitalization occurs.

The symptomatology of schizophrenia may reflect more than one disease process, and an important possibility is that schizophrenia may be heterogeneous in its course (Carpenter and Kirkpatrick 1988). Some subgroups of schizophrenia may have a deteriorating course, and others a more benign course. Candidate variables for subdividing schizophrenia into subtypes include important factors that define risk, such as age of onset, family history and obstetric complications. The most common attempt has been to delineate subtypes based on age of onset, perhaps due to success in parallel endeavors with other diseases. Early onset is thought to reflect a more severe form of the disease. There is speculation, with some supportive data, that schizophrenics with early onset have a higher genetic loading for the disorder (DeLisi 1992); but the evidence is far from conclusive. Obstetric complications, on the other hand, are consistently and strongly associated with early age of onset (Verdoux et al. 1997). In 11 studies of age of onset and obstetric complications, the age thresholds used to define "early" had an average of 22 years. The statistical problem here is to test for the presence of an interaction of age of onset with the adjusted trend in community tenure episodes over the long-term course of the disorder.

2. Methods

2.1 Data

Systematic registration of patients admitted to mental hospitals in Denmark was started in 1938. The associated hospital data was computerized in 1970 to include all cases from 86 psychiatric institutions in Denmark. The catchment area for the registry is the entire nation of Denmark. The anonymous data file recorded recurrences of hospitalizations and other associated information from 8,811 patients (5,493 males and 3,318 females) who were admitted to the hospital with the diagnosis of schizophrenia for the first time in their lives during the period April 1, 1970, through March 25, 1988. The recurrence and censoring times are measured in days.

2.2 Statistical Analysis: Previous Approaches

Preliminary data analysis was conducted and presented in Eaton, et al. (Eaton, et al. 1992). To study schizophrenia progression over time, two conceptualizations were adapted: one was to study the occurrence rate of the episodes of hospitalization over time in equal intervals over the entire followup period, noting that episodes tended to cluster in earlier time periods; another method was to study the hazard rate of hospitalizations adjusting for risk factors such as gender, age of onset, and total number of hospitalizations during followup, by pooling all episodes within individual participants. The adjustment for total number of hospitalizations estimated the tendency of any given individual to have many or few episodes – in effect, an indicator of severity, which measures pre-existing heterogeneity in the sample as to natural course. After that variable was adjusted, the time to the next hospitalization was predicted by the

total number already experienced. The parameter for the hazard rate for the nth hospitalization was small but negative, suggesting that hospitalizations later in the course were more spread out temporally than those earlier in the course: progressive amelioration.

The latter conceptualization provides a more appropriate analytical strategy for the analysis of trend/pattern of hospitalization over time. Using a variant of the Cox Proportional Hazards model (Prentice, Williams and Peterson, 1981), a parameter was estimated for the trend in periods between hospitalizations. However, the procedure used an inappropriate indicator of heterogeneity: it did not correct for induced informative censoring, as described below, and it did not have the important ability to adjust for calendar year in which the hospitalization occurred. Heterogeneity is observed as different distributional patterns of the recurrent hospitalizations for different individuals. Part of the heterogeneity can be explained by the observed independent variables, such as gender, and age of onset. However, some of the heterogeneity can be caused by unobservable or immeasurable variables, such as participants' exposure to unknown environmental risk factors, or participants' genotypes. Therefore, even after adjusting for the observed independent variables, there may still be unexplained heterogeneity left among participants, with the result that the recurrent hospitalizations are not independent. How to account for the dependence structure in studying the trend is statistically challenging.

2.3 Statistical Analysis: New Approach

A participant's followup is called "censored" if the recurrences of hospitalizations are not completely observed. Censoring occurs in most longitudinal followup studies when the full course for survival outcomes is not observed. There are a number of possible reasons why the

outcomes are not fully observed. In the situation to be studied, the two prominent causes of censoring are mortality prior to the end of the followup, and the fact that the followup ended before individuals in the sample had finished their course of hospitalizations. The proportional hazards model (Cox, 1972, Eaton, et al. 1992) requires the assumption that censoring is independent. However, the heterogeneity of recurrences in hospitalizations produces a serious complication. To illustrate the problem, consider two specific episodes of community tenures between hospitalizations, that is, the time from the first hospitalization to the second hospitalization (first community tenure), and the time from the second to the third hospitalization (second community tenure). Although the censoring time of the first community tenure can be assumed independent of the first recurrence time, the censoring time of the second community tenure is no longer independent because the second community tenure is more or less likely to be censored depending on whether it is longer or shorter. This phenomenon is called as "induced informative censoring," which arises as a result of the unadjustable heterogeneity of the recurrent hospitalizations. If the induced informative censoring occurs, as seen in the data to be analyzed, a naïve application of the proportional hazards model to analyze the second and later hospitalizations leads to bias (Wang and Chang 1999).

Wang and Chen (Wang and Chen 2000) introduced the concept of comparability to overcome the problem of induced informative censoring. A pair of uncensored recurrent times of hospitalization for one participant is said to be "comparable" when both of them are not longer than half of their respective censoring time. Based on the comparability concept, hypothesis testing and the stratified regression models are developed to study the long-term progression of schizophrenia measured by participants' hospitalizations.

Suppose that T_{ij} is the jth community tenure of the ith participant. The following test statistic will be used to test the direction and significance of schizophrenia progression:

$$TS = \frac{\sum_{i=1}^{n} U_i}{\sqrt{\sum_{i=1}^{n} U_{i=1}^2}},$$

where $U_i = \sum_{j<k} \delta_{i,jk} \operatorname{sgn}\left\{\left(T_{ik} - T_{ij}\right)\left(Z_{ik} - Z_{ij}\right)\right\}$, $\delta_{i,jk}$ is the comparability indicator of T_{ij} and T_{ik}, and Z_{ij} and Z_{ik} are the trend measures of the jth and kth community tenures. The null hypothesis of H_0 of this test is the equality of distributions of all community tenures $F_{i1} = F_{i2} = \ldots$ against *a prior* alternative of $F_{i1} \le F_{i2} \le \ldots$ or $F_{i1} \ge F_{i2} \ge \ldots$, for $i = 1, 2, \ldots, n$.

For the regression analysis, a class of accelerated failure time models with random effects is used to estimate the magnitude of the progression:

$$\log T_{ij} = \alpha_i + \beta j + \gamma z_{ij} + e_{ij},$$

where α_i, β, γ are parameters and e_{ij} is random error. Here e^{β} is the Multiplicative Progression Constant (MPC) of consecutive recurrent hospitalization times or community tenures, γ is the effect for any possible confounding factors and α_i are subject-specific effect which represents the possible unadjustable heterogeneity. It is noted that the parameter of β is of the most interest in characterizing the progression over time. For example, if $\beta = \log 2$, then the MPC of community tenures is 2, which indicates progressive amelioration because the hospitalization tends to be longer and longer by doubling; if $\beta = -\log 2$, then the MPC of community tenures is ½, which indicates progressive deterioration because the inter hospitalization times tend to be shorter and shorter by halving; if $\beta = 0$, then it means there is no

progression tendency whatsoever.

To better understand the MPC, we introduce an equivalent concept, termed "Doubling-Halving Constant" (DH Constant). The DH Constant is the number of community tenures after which the length of community tenure is doubled (if progressive amelioration) or halved (if progressive deterioration). It is defined as

$$DH = \left\lfloor \frac{\log 2}{|\beta|} \right\rceil,$$

where $\left\lfloor \frac{\log 2}{|\beta|} \right\rceil$ is the closest integer to $\frac{\log 2}{|\beta|}$. For example, if $\beta = 0.1$, then the MPC is $e^{0.1} = 1.105$ and DH=6. This means the second community tenure is 10.5% longer than the first community tenure for two consecutive pairs. Or equivalently, after 6 consecutive community tenures, the 7th community tenure will be doubled. If $\beta = -0.1$, then the MPC is $e^{-0.1} = 0.905$ and DH=6. This means the second community tenure is 9.5% shorter than the first community tenure for two consecutive pairs. Or equivalently, after 6 consecutive community tenures, the 7th community tenure will be halved.

3. Results

For the Danish data described in the above section, we first perform statistical testings to explore whether or not there is a progressive tendency of recurrent community tenures, and detect the potential direction of such tendency. Test statistics are computed and displayed in Table 1. For the test statistics shown in the table, associated *p*-values are calculated based on the standard normal distribution. In general, a *p*-value that is less than 0.05 implies a "significant"

progression trend over time. The sign of the test statistic represents the direction of the progression – a positive sign means overtime increase in length of community tenures, that is, "progressive amelioration," while a negative sign means "progressive deterioration." As shown in Table 1, for all the 8,811 registrants in the data set, the test statistic for the progression is –5.5165 with a *p*-value much less than 0.05, which means that the entire study cohort has a general pattern of significant progressive deterioration if the induced informative censoring is accounted for, that is, the community tenures tend to be shorter and shorter. If the entire study cohort is divided into male and female groups, then both gender groups show significant tendency of progressive deterioration. If it is divided into four groups according to the participants' onset ages (no older than 20, 21-30, 31-44 and no younger than 45), then the participants with early schizophrenia onset show strong tendency of progressive deterioration, as manifested by the significant test statistics of the groups of onset ages no older than 20, 21-30 and 31-44. Although the test statistic is also negative for the participants with their first schizophrenia symptoms after age 45, it does not show a significant tendency of either progressive amelioration or deterioration. Furthermore, if the entire study cohort is cross-classified by gender and onset age groups, for both males and females, participants with earlier onset ages consistently show significant tendency of progressive deterioration (males no older than 20, 21-30, 31-44 and females no older than 20, 21-30), while those with later onset ages do not show any significant pattern.

[Table 1. about here]

As measured by the test statistics in Table 1 and accounted for the induced informative censoring, the participants subject to early schizophrenia onset show a significant pattern of

shorter and shorter community tenures, which implies progressive deterioration. The question now is, what is the magnitude of such gradual deterioration tendency? We use the proposed regression model to measure the magnitude in terms of the MPC's or DH Constants. Estimates of regression coefficient of β are displayed in Table 2 for the entire study cohort and its subgroups. Similar to the signs of the test statistics in Table 1, a positive (negative) estimate of β implies progressive amelioration (deterioration), respectively. The magnitude of e^{β} is the MPC. For the entire cohort, the MPC is $e^{-0.0138} = 0.986$ with 95% confidence interval (0.983,0.989), which means on average each following community tenure is 1.4% significantly shorter than its preceding one. Or equivalently, DH Constant = 50, i.e., it takes the entire study cohort 50 more community tenures after the first one to halve the community tenure. Although statistically significant, this effect is small in clinical or administrative terms.

For males and females, the MPC's are 98.6% and 98.9%, corresponding to the DH Constants of 48 and 62, respectively. For different onset age groups, the group with schizophrenia onset during age 21 to 30 has the fastest deterioration rate of 1.5% decrement per community tenure (DH Constant = 46), while the latest onset age group has the slowest deterioration rate of 0.7% (DH Constant = 94), which is in fact no longer significant and may imply that the late schizophrenia onset would have relatively stable disease progression. If compared across gender and onset age subgroups, the group with onset ages less than 21 has the largest MPC for the females (MPC = 97.4%, DH Constant = 26) and that with onset age between 31 and 40 for the males (MPC = 97.9%, DH Constant = 33). All gender and onset age subgroups except males with onset ages of 45 or higher show progressive deterioration, although the males

with onset ages less than 21, the females with onset ages between 31 and 44 and 45 or higher do not show significant pattern. However, comparing to other subgroups, we may need more data to increase the sample sizes for further justification.

[Table 2. about here]

Although the progressive pattern of schizophrenia is modeled and identified by comparing two consecutive community tenures, the community tenure itself may be determined by not only the trend measure of what episode it belongs to, but also at what calendar time it starts. This is because many factors that could influence community tenure would vary over time. For example, the changes in the threshold of hospitalization over time could affect the trend. It is necessary to estimate the adjusted progressive pattern, as if every community tenure starts at the same date, as displayed in Table 3. Controlling for the calendar time at which the community tenure starts, the adjusted trend of community tenure for the entire cohort is stable (adjusted MPC = 99.99% with *p*-value of 0.87), suggesting neither progressive amelioration nor deterioration. In terms of the DH Constant, it would take 6,931 more episodes to halve the community tenure, controlling for initiation timing of community tenure. Even though the overall adjusted MPC is not significant, the female group shows significant progressive deterioration with adjusted MPC of 99.47%. All subgroups of different onset ages demonstrate negative adjusted progression patterns, among which the subgroup with the youngest onset ages has significant adjusted MPC of 98.69%.

In summary, if the induced informative censoring is accounted for, the entire study cohort supports the notion of progressive deterioration, although the pattern becomes non-significant if adjusted for the initiation timing of community tenures.

[Table 3. about here]

4. Discussion

The new statistical methodology presented in this article is different from that used in Eaton, et al. (Eaton, et al. 1992). The new method directly models the length of community tenure for every episode, instead of studying the hazard rates of the community tenures. Compared with the methods in Eaton, et al. (Eaton, et al. 1992), the new method has some distinct advantages: (1) the progressive pattern of community pattern is clearly defined in terms of the community tenures themselves, and the defined MPC or DH Constant has explicit clinical interpretation; (2) more importantly, it provides a correct approach dealing with the phenomenon of induced informative censoring caused by the heterogeneity of schizophrenia among individuals.

As a contrast, testing of trend has also been done for the 600 participants of the Danish cohort originally presented in Eaton, et al. (Eaton, et al. 1992). The cohort in that analysis was chosen, in part, to minimize the effect of informative censoring, which might be a nonrandom sample of the entire cohort. By applying the new statistical methods, no significant progression pattern was shown except for the female group with onset age between 31-44 (test statistic = -2.03 with *p*-value 0.04). However, since there are eight subgroups being tested and the result did not make clinical and theoretical sense, we surmise the finding is not meaningful. In short, the new method of analysis generates the same cohort used in the earlier study, as in the entire sample. But, the new method works better when the sample size is fairly large, because only comparable pairs of community tenures are utilized to construct appropriate testing and

estimation procedures. This may also be why the new method, though correct, does not efficiently detect the progressive pattern in the cohort of 600 participants.

In summary, development of a new statistical procedure allowed a direct and unbiased test of the question of progressive amelioration versus deterioration. There was some evidence for deterioration in unadjusted models, especially in groups with early onset. After adjustment for calendar time, the trend in times between hospitalizations was stable over time – that is, presented no evidence for either progressive amelioration or progressive deterioration.

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Table 1. Hypothesis testing on long-term trend of community tenures

	# of Subjects	Test Statistics	p-value
Entire cohort	8,811	-5.52	<0.005
Classified by age of onset			
-20	1,065	-2.24	0.03
21-30	4,168	-5.34	<0.005
31-44	2,330	-3.31	<0.005
45-	1,248	-0.48	0.63
Classified by gender			
Female	3,318	-3.89	<0.005
Male	5,493	-4.08	<0.005
Cross-classified by gender and age of onset			
Female			
-20	305	-2.87	<0.005
21-30	1,253	-2.43	0.02
31-44	959	-1.24	0.21
45-	801	-0.64	0.52
Male			
-20	760	-1.82	0.07
21-30	2,915	-4.84	<0.005
31-44	1,371	-3.08	<0.005

45-	447	0.54	0.59

Table 2. Magnitude of long-term trend of community tenures

	Beta	SD	p-value	DH
Entire cohort	-0.0138	0.0014	<0.005	50
Classified by age of onset				
-20	-0.0107	0.0042	0.01	65
21-30	-0.0151	0.0020	<0.005	46
31-44	-0.0145	0.0027	<0.005	48
45-	-0.0074	0.0039	0.06	94
Classified by gender				
Female	-0.0112	0.0022	<0.005	62
Male	-0.0145	0.0018	<0.005	48
Cross-classified by gender and age of onset				
Female				
-20	-0.0267	0.0075	<0.005	26
21-30	-0.0085	0.0036	0.02	82
31-44	-0.0050	0.0042	0.23	139
45-	-0.0178	0.0510	0.73	39
Male				
-20	-0.0086	0.0048	0.07	81
21-30	-0.0170	0.0023	<0.005	41
31-44	-0.0213	0.0012	<0.005	33

45-	0.0104	0.0062	0.09	67

Table 3. Adjusted magnitude of long-term trend of community tenures by initiation calendar time

	Beta	SD	p-value	DH
Entire cohort	-0.0001	0.00060	0.87	6,931
Classified by age of onset				
-20	-0.0132	0.00169	<0.005	53
21-30	-0.0001	0.00086	0.91	6,931
31-44	-0.0006	0.00113	0.60	1,155
45-	-0.0010	0.00158	0.53	693
Classified by gender				
Female	-0.0053	0.00096	<0.005	131
Male	-0.0001	0.00076	0.90	6,931
Cross-classified by gender and age of onset				
Female				
-20	-0.0008	0.00321	0.80	866
21-30	0.0002	0.00158	0.90	3,466
31-44	0.0010	0.00182	0.58	693
45-	0.0079	0.00062	<0.005	88
Male				
-20	0.0010	0.00204	0.62	693
21-30	-0.0001	0.00033	0.76	6,931
31-44	-0.0002	0.00150	0.18	3,466

45-	-0.0120	0.00267	<0.005	68