

Factors influencing relapse in schizophrenia: A longitudinal study in China.

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Abstract

Identifying predictors of relapse in Schizophrenia (SZ) has been a hot issue since relapse is associated with worse clinical outcome. In this study, relapse rates of SZ patients after hospital discharge and their possible factors were investigated annually over 3 years to differentiate short-term and long-term predictors for relapse in SZ in China. According to the sequence of discharge date, 420 SZ patients were recruited. The severity of disease, compliance with medication use, social functions, and relapse rate were assessed at the time points of 1-, 2- and 3-year after hospital discharge. After each assessment, only the not-relapsed participants remained in the study for the next assessment. The factors influencing relapse in SZ were analysed by a logistic regression. Our results indicated that the relapse rate at 1-, 2- and 3-year after hospital discharge was 33.0%, 29.8%, and 16.4%, respectively. Compliance with medication use, communication skills, and work/study functioning were associated with relapse in SZ, with differential long-term and short-term effects. Especially, the compliance with medication use in the relapsed participants were significantly worse than that in the not-relapsed participants in three assessments over 3 years ($P<0.001$). Logistic regression analyses also revealed that SZ patients with worse compliance with medication use, communication skills, and work/study functioning showed higher risk of relapse. Importantly, worse compliance with medication use was associated with a 6.369-, 13.889-, and 8.850- fold increase in relapse at 1-, 2- and 3-year after hospital discharge, respectively ($P<0.001$). To our knowledge, this is the first longitudinal study to investigate factors influencing relapse in SZ in China. Our results demonstrated that good compliance with medication use, communication skills, and work/study functioning may reduce the risk of relapse in SZ. The findings of this study suggested that good compliance with medication use is critical to prevention of SZ relapse.

Keywords: Schizophrenia, Relapse rate, Compliance with medication use, Social functions, Influencing factors.

Accepted on February 6, 2017

Introduction

Schizophrenia (SZ) is a chronic mental disorder characterized with high rates of relapse and disability. The relapse of SZ is the characteristics of disease aggravation, leading to overall hypofunction, decreasing the working or learning ability [1] and increasing social and economic burden [2]. Over 50% of SZ patients present with repeated episode [3,4]. For patients with the first episode, the 1-year relapse rate is 28% on average, 43% for 1 to 1.5 years and 54% for 3 years [5]. Approximately 20% to 56% of patients have relatively poor compliance [6]. High relapse rate of SZ is a challenge for physicians. Poor compliance is the highest risk factor of SZ relapse [7]. Most previous studies are cross-sectional studies and only investigate severity of disease, compliance, and relapse rate at 1 year after hospital discharge; these studies show a large difference in relapse rates of SZ [5,7,8]. To identify the relationship between the relapse rate of SZ patients and influencing factors, a longitudinal study is necessary and of grate interest.

In this study, the severity of disease, compliance with medication use, social functions, and relapse rate were assessed at the time points of 1-, 2- and 3-year after hospital discharge. The relationships between relapse rates and influencing factors were analysed by logistic regression analyses. The findings of this study may provide evidences whether effective prevention is helpful to reduce the risk of relapse in SZ.

Subjects and Methods

Subjects

According to the sequence of hospital discharge date, 420 patients diagnosed with SZ admitted to the Affiliated Brain Hospital of Guangzhou Medical University between September 2011 and August 2012 were recruited in this study. Written informed consents were signed by all patients or their relatives. The study procedures were in accordance with the Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University.

Inclusion criteria

1) In accordance with the diagnostic criteria of SZ in ICD-10 (International Classification of Diseases 10th Revision); 2) patients obtained "recovery" upon hospital discharge; 3) aged 18-65 years; 4) informed consents were signed by patients or their relatives.

Exclusion criteria

1) Patients with residual core symptoms upon hospital discharge; 2) those with unknown clinical efficacy upon hospital discharge; 3) those rejected to participate in this study; 4) those failed to attend follow-up by telephone.

Criteria of loss to follow-up

1) No telephone answering ≥ 3 times on different days; 2) those rejected to participate in this study after 3 times of explanation and persuasion at different time points; 3) wrong contact information.

Finally, we included 370, 218, 128 SZ patients in the 1-, 2-, and 3-year assessment, respectively (Figure 1).

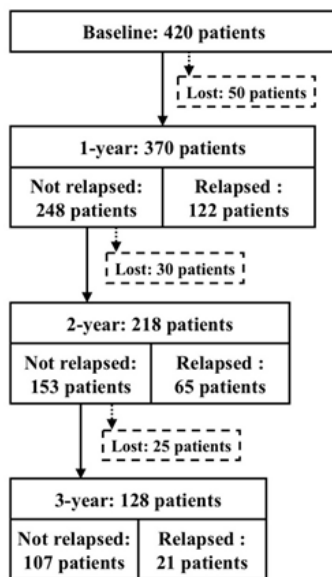


Figure 1. Subjects included in a longitudinal study.

Methods

According to the clinical treatment, the questionnaire survey was self-invented and divided into the medical record and telephone investigations. The severity of disease, compliance with medication use, and social functions were obtained at the time points of 1-, 2- and 3-year after hospital discharge. After each assessment, only the not-relapsed participants remained in the study for the next assessment. According to the methods by Weiden et al. [9], compliance with medication use was classified into complete compliance and non-compliance (partial or non-compliance).

Questionnaire survey

1) Demographic data (e.g., gender, age, marriage status, residence place, educational background) and medical history of mental disorders (e.g., course of diseases, age of onset, frequency of hospitalization, days of hospital stay, family history) were obtained from medical record investigations; 2) telephone investigations included questions, such as frequency of re-examinations, current medication use, adverse drug reaction, compliance with medication use, possible reasons of non-compliance, attitudes of family members to medication use, relapse and possible factors, self-care ability of daily living, communication skills, work/study functioning, drinking, smoking.

Assessment of compliance with medication use

1) **Complete compliance:** Patients taking the medication strictly according to the doctor's advice or the time of non-compliance with the medication intake according to the doctor's advice < 1 week; 2) **partial compliance:** in the recent 1 year, the time of non-compliance with the medication intake according to the doctor's advice ranging from 1 week to 6 month; the time of medication termination < 1 week; 3) **non-compliance:** those opposed to medication or terminated the medication voluntarily ≥ 1 week, or the time of non-compliance with the medication intake according to the doctor's advice ≥ 6 months.

Diagnostic criteria for SZ relapse

Referring to the diagnostic criteria for SZ relapse [10], one of the following conditions should be met: 1) those requiring increasing dose or type of antipsychotics due to the fluctuation of patient's conditions; 2) those requiring higher frequency of out-patient or hospitalization due to unstable patient's conditions; 3) those requiring strengthened nursing care to avert the incidence of accident or danger due to the fluctuation of patient's conditions.

Investigators

All investigation procedures were accomplished by professional clinicians receiving training courses from the Department of Neurology. Both medical record and telephone investigations were completed by one single physician.

Statistical analysis

All statistical analyses were performed by SPSS 18.0. Group comparisons between the relapsed and not-relapsed participants were analysed by using independent sample t-test, non-parametric rank-sum test, and chi-square test. The relationships between relapse rates and influencing factors were analysed by logistic regression analyses. A P-value of less than 0.05 (two-side) was considered as statistical significance.

Results

Baseline data

The demographic data and mental illness history of all subjects at baseline were shown in Table 1. Briefly, a total of 420 SZ

patients were eligible for this study including 202 males (48.1%) and 218 females (51.9%), aged (36.6 ± 11.9) years on average; the age of onset was (26.5 ± 9.6) years; the mean length of hospital stay was (59.4 ± 1.9); the course of diseases was 7 years on average (3 to 15 years).

Table 1. Comparison of clinical parameters between the relapsed and not-relapsed patients at 1 year after hospital discharge.

	Not-relapsed N=248	Relapsed N=122	t/χ ² /z	P
Demographic data and mental illness history				
Gender (male)	117 (47.2%)	61 (50.0%)	0.261	0.658
Age (years)	35.5 ± 11.7	38.1 ± 12.7	-1.936	0.054
Marriage status (married)	115 (46.4%)	65 (53.3%)	1.562	0.225
Residence place (city)	146 (58.9%)	63 (51.6%)	1.74	0.187
Educational background (technical college above)	60 (24.2%)	15 (12.3%)	8.931	0.2
Course of diseases (year)	7 (3, 13)	8.5 (2.8, 20)	-1.757	0.079
Age of onset (year)	26.5 ± 10.0	26.34 ± 9.0	0.154	0.878
Frequency of hospitalization				
(≥ 4 times)	52 (21.0%)	46 (37.7%)	11.765	0.001**
Days of hospital stay	60.5 ± 1.92	57.24 ± 1.9	0.755	0.451
Family history (Yes)	70 (28.2%)	27 (22.1%)	1.57	0.258
At 1 year after hospital discharge				
Compliance with medication use (good)	197 (79.4%)	62 (50.8%)	31.886	<0.001**
Communication skills (good)	152 (61.3%)	39 (31.9%)	28.154	<0.001**
Work/ study functioning (Yes)	180 (72.6%)	77 (63.1%)	3.454	0.063

Note: *denotes P<0.05, **denotes P<0.01.

Comparison of SZ relapse and influencing factors

The relapse rate at 1-, 2- and 3-year after hospital discharge was 33.0%, 29.8%, and 16.4%, respectively. The overall rate relapse of 3 years was 58.0%.

In the assessment of 1-year after hospital discharge, 50 patients were lost to follow-up and 370 completed the follow-up. Compared with the relapsed participants, the non-relapsed participants showed better compliance with medication use (χ²=31.886, P<0.001) and better communication skills (χ²=28.154, P<0.001), as shown in Table 1.

In the assessment of 2-year after hospital discharge, 30 patients were lost to follow-up and 218 completed the follow-up. Compared with the relapsed participants, the non-relapsed participants showed better compliance with medication use (χ²=62.668, P<0.001), better communication skills (χ²=22.388, P<0.001), and better work/ study functioning (χ²=10.472, P=0.001). However, no significance was found in these factors between two groups in the assessment of 1-year after hospital discharge, as shown in Table 2.

Table 2. Comparison of clinical parameters between the relapsed and not-relapsed patients at 2 year after hospital discharge.

	Not-relapsed N=153	Relapsed N=65	t/χ ² /z	P
Demographic data and mental illness history				
Gender (male)	73 (47.7%)	29 (44.6%)	0.176	0.675
Age (years)	36 ± 11.1	34.8 ± 11.8	0.713	0.477
Marriage status (married)	71 (46.1%)	30 (46.2%)	0.001	0.973

Residence place (city)	93 (60.8%)	36 (55.4%)	0.551	0.485
Educational background (technical college above)	38 (24.8%)	13 (20.0%)	3.078	0.745
Course of diseases (year)	8 (3, 13)	6 (3, 14.5)	-0.267	0.782
Age of onset (year)	26.6 ± 9.8	25.5 ± 10.3	0.724	0.47
Frequency of hospitalization				
(≥4 times)	36 (23.5%)	13 (20.0%)	-0.479	0.632
Days of hospital stay	59.5 ± 1.8	65.4 ± 1.9	-1.019	0.309
Family history (Yes)	40 (26.1%)	20 (30.8%)	0.489	0.484
At 2 year after hospital discharge				
Compliance with medication use (good)	197 (79.4%)	62 (50.8%)	31.886	<0.001**
Communication skills (good)	152 (61.3%)	39 (31.9%)	28.154	<0.001**
Work/ study functioning (Yes)	180 (72.6%)	77 (63.1%)	3.454	0.063
Note: *denotes P<0.05, **denotes P<0.01.				

In the assessment of 3-year after hospital discharge, 25 patients were lost to follow-up and 128 completed the follow-up. Compared with the relapsed participants, the non-relapsed participants showed better compliance with medication use ($\chi^2=20.713$, $P<0.001$), better communication skills ($\chi^2=7.149$,

$P=0.008$), and better work/ study functioning ($\chi^2=12.339$, $P<0.001$). However, no significance was found in these factors between two groups in the assessment of 2-year after hospital discharge, as shown in Table 3.

Table 3. Comparison of clinical parameters between the relapsed and not-relapsed patients at 3 year after hospital discharge.

	Not-relapsed N=107	Relapsed N=21	t/ χ^2 /z	P
Demographic data and mental illness history				
Gender (male)	51 (47.7%)	10 (47.6%)	0	0.997
Age (years)	36.9 ± 10.9	31.9 ± 11.2	1.893	0.061
Marriage status (married)	51 (47.7%)	9 (42.90%)	0.163	0.687
Residence place (city)	61 (57.0%)	13 (61.9%)	0.172	0.678
Educational background (technical college above)	30 (28%)	2 (9.6%)	11.831	0.014*
Course of diseases (year)	8 (4, 14)	8 (3, 12.5)	-0.444	0.657
Age of onset (year)	26.6 ± 9.6	23.7 ± 9.0	1.314	0.191
Frequency of hospitalization				
(≥ 4 times)	27 (25.2%)	7 (33.3%)	-0.623	0.533
Days of hospital stay	59.8 ± 1.9	53.0 ± 2.0	0.717	0.474
Family history (Yes)	32 (29.9%)	3 (14.3)	2.156	0.142
At 2 year after hospital discharge				
Compliance with medication use (good)	89 (83.2%)	18 (85.7%)	0.082	0.774
Communication skills (good)	91 (85%)	16 (76.2%)	1.004	0.316
Work/study functioning (Yes)	86 (80.4%)	15 (71.4%)	0.884	0.358
At 3 year after hospital discharge				
Compliance with medication use (good)	87 (81.3%)	14 (66.7%)	20.713	<0.001**

Communication skills (good)	89 (83.2%)	12 (57.1%)	7.149	0.008**
Work/ study functioning (Yes)	74 (69.2%)	6 (28.6%)	12.339	<0.001**

Logistic regression analyses

In the assessment of 1-year after hospital discharge, the relapse of SZ was used as a dependent variable; the frequency of hospitalization, compliance with medication use, communication skills, and work/study functioning were

regarded as the independent variables for the logistic regression analysis. Participants with better compliance with medication use (OR=6.369, P<0.001) or better communication skills (OR=2.653, P<0.001) had a lower risk of SZ relapse, as shown in Table 4.

Table 4. Logistic regression analysis of factors influencing relapse in schizophrenia at 1 year after hospital discharge.

Dependent variable	Independent variable	B	S.E.	Wald	P	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
1-year schizophrenia relapse	Poor compliance (vs. good compliance) ^a	1.851	0.307	36.334	<0.001	6.369	3.484	11.628
	Poor communication skills (vs. good communication skills) ^a	0.976	0.252	14.961	<0.001	2.653	1.618	4.348

Note: ^aRepresents follow-up status at 1 year after hospital discharge.

In the assessment of 2-year after hospital discharge, the relapse of SZ at 2-year was used as a dependent variable; the frequency of hospitalization at 1-year assessment, compliance with medication use, communication skills, and work/study functioning at both 1-year and 2-year assessments were regarded as the independent variables for the logistic

regression analysis. Participants with better compliance with medication use (OR=13.889, P<0.001), or better communication skills (OR=3.413, P=0.002), or work/study functioning (OR=2.611, P=0.019) had a lower risk of SZ relapse, as shown in Table 5.

Table 5. Logistic regression analysis of factors influencing relapse in schizophrenia at 2 year after hospital discharge.

Dependent variable	Independent variable	B	S.E.	Wald	P	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
2-year schizophrenia relapse	Poor compliance (vs. good compliance) ^a	2.633	0.386	46.582	<0.001	13.889	6.536	29.412
	Poor communication skills (vs. good communication skills) ^a	1.228	0.395	9.678	0.002	3.413	1.575	7.407
	No work/study (vs. work/ study) ^b	0.96	0.409	5.501	0.019	2.611	1.171	5.814

Note: ^aRepresents follow-up status at 1 year after hospital discharge; ^bRepresents follow-up status at 2 years after hospital discharge.

In the assessment of 3-year after hospital discharge, the relapse of SZ at 3-year was used as a dependent variable; the frequency of hospitalization at 1-year, compliance with medication use, communication skills, and work/study functioning at both 2-year and 3-year assessments were

regarded as the independent variables for the logistic regression analysis. Participants with better compliance with medication use (OR=8.850, P<0.001) or work/study functioning (OR=5.714, P=0.002) had a lower risk of SZ relapse, as shown in Table 6.

Table 6. Logistic regression analysis of factors influencing relapse in schizophrenia at 3 year after hospital discharge.

Dependent variable	Independent variable	B	S.E.	Wald	P	Exp(B)	95% CI for EXP(B)	
							Lower	Upper
3-year schizophrenia relapse	Poor compliance (vs. good compliance) ^a	2.179	0.561	15.081	<0.001	8.85	2.941	26.315
	Poor communication skills (vs. good communication skills) ^a	1.742	0.575	9.172	0.002	5.714	1.848	17.513

Note: ^aRepresents follow-up status at 3 year after hospital discharge.

Discussion

To our knowledge, this is the first longitudinal study to investigate factors influencing relapse in SZ in China. Our results indicated that: 1) the risk of SZ relapse was the highest at 1-year after hospital discharge and the relapse rate declined year by year; 2) compliance with medication use, communication skills, and work/study functioning were associated with relapse in SZ, with differential long-term and short-term effects; 3) SZ patients with worse compliance with medication use, communication skills, and work/study functioning showed higher risk of relapse.

A number of previous studies have indicated risk factors of SZ relapse, such as worse compliance with medication use, stressful event, substance abuse and insufficient family and social support [5,11-15]. In this longitudinal study over 3 years, we indicated that the rate of SZ relapse was associated with compliance with medication use, communication skills, and work/study functioning. Importantly, the compliance with medication use in the relapsed participants was significantly worse than that in the not-relapsed participants in three assessments over 3 years. Moreover, worse compliance with medication use was associated with a 6.369-, 13.889-, and 8.850- fold increase in relapse at 1-, 2- and 3-year after hospital discharge, respectively. These findings were consistent with a previous study, in which the percentage of patients with non-compliance with medication use was ranged from 20% to 60.26% [6]. Therefore, we speculated that poor compliance was a major factor influencing relapse in SZ [7,8].

Interestingly, our results showed that the relapse rate was associated with the compliance with medication use in the year, but not with that in the previous year. This finding suggested that the compliance after discharge could predict the short-term effect rather than the long-term effect. Therefore, persistent monitoring is necessary for patients with good compliance with medicine use. Most SZ patients neglect the importance of maintenance of therapy and ignore that compliance of medication use may decline over time [16]. The decline of compliance constantly leads to the relapse in SZ [17]. The relapse in SZ should be highly monitored when the compliance becomes worse. Therefore, the importance of medication use should be delivered to patients during hospitalization and after hospital discharge. After hospital discharge, persistent treatment should be implemented to strengthen the compliance with medication use, which can fundamentally decrease the long-term relapse rate.

In this study, communication skills of relapsed patients significantly differed in three follow-up assessments; work/study functioning also significantly differed in two follow-up assessments. Compared with not-relapsed patients, social functions were severely damaged for relapsed patients. These results were consistent with previous findings regarding the damages of work and communication in SZ patients [18,19]. Negative symptoms were more likely to impact the communication and social skills of the patients [20]. Menendez et al. [21] indicate that psychopathology affected subjective

social functions, whereas the severity of disease and negative symptoms influenced social functions. Improvement of social functions has become an ultimate objective of clinical treatment [22].

Throughout the 3-year follow-up assessments, the factors influencing relapse in SZ significantly varied, suggesting that short-term and long-term influencing factors might differ. During 2- and 3-year after hospital discharge, work/study functioning was an influencing factor of SZ relapse, whereas no statistical significance was observed during the 1st year after discharge, suggesting that work/study functioning mainly affects the long-term relapse rate of schizophrenia. Moreover, patients with higher frequency of hospitalization presented with a higher relapse rate at 1 year after discharge rather than during 2- and 3-year after discharge, suggesting that the frequency of hospitalization is more likely to affect short-term relapse rate. Previous investigations have demonstrated that the frequency of hospitalization is increased and the interval of hospitalization is shortened [11]. Short-term relapse even readmission is probably subject to the influence of the disease itself, especially for lack of self-recognition ability.

There were several limitations in this study. First, the follow-up survey was conducted via telephone and some of the relatives failed to completely answer the questions in details. Second, the patient's condition was not evaluated by an objective evaluation scale, which reduced the accuracy to certain extent. Third, the confounding factors of influencing factors of SZ relapse were not excluded. In future studies, we'll explore a more detailed questionnaire, include the evaluation scale and conduct laboratory examination to further identify the influencing factors of SZ relapse and provide evidence for clinical diagnosis and treatment of SZ for clinicians.

In conclusion, our results demonstrated that good compliance with medication use, communication skills, and work/study functioning may reduce the risk of relapse in SZ. The relapse rate was not affected by the compliance or social functions in the previous year. Persistent treatment after hospital discharge can effectively reduce the rate of SZ relapse. The short-term and long-term influencing factors of SZ relapse were inconsistent. Worse compliance and declined work/study functioning were risk factors of long-term SZ relapse. Medical staff, relative, and social supports contribute to recovery of SZ and prevention of SZ relapse.

Acknowledgement

Our study was supported by Science and Technology Program of Guangdong (Project Number: 2016A020216004) and Science and Technology Program of Guangzhou (Project Number: 2014Y2-00105, 2017010160496; Application Number: 201605122303495).

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