Background: The Remission in Schizophrenia Working Group (RSWG) proposed a set of criteria for remission in patients with schizophrenia. But it is unclear whether these criteria apply to the Taiwan population when assessing rates of remission or when evaluating the clinical correlates of remission and the stability of remission in patients with schizophrenia. Methods: Subjects in this prospective five-year follow-up study comprised 164 inpatients with schizophrenia who were being treated at three hospitals in northern Taiwan. We gathered data of sociodemographic factors and baseline clinical profiles at the time of index admission. Severity of psychiatric symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS) regularly. Remission status was defined according to RSWG criteria. Differences in demographic data, clinical profiles and severity of psychiatric symptoms between achievers and non-achievers of remission were evaluated using logistic regression. Results: Of the 164 inpatients recruited in the study, 34 (20.73%) fulfilled the RSWG criteria for remission. PANSS scores among patients who achieved remission of psychotic symptoms were significantly lower at all follow-up period \((p < 0.05)\). In addition, functional scores were consistently significantly higher among patients in the remission subgroup. Regression analysis revealed that older age at onset \((p < 0.01)\), higher educational level \((p < 0.05)\) and lower severity of negative symptoms \((p < 0.05)\) at index admission were significant predictors of remission of psychotic exacerbations. Conclusion: The remitted and unremitted subgroups remained rather stable and also validated in functional status. Further research is warranted to explore other outcome dimensions that might contribute to remission in schizophrenia including cognitive deficits and brain imaging studies.

Key words: schizophrenia, remission, predictor, stability

Introduction

Schizophrenia is a psychiatric disorder with marked heterogeneity of symptoms and clinical course. A number of definitions of remission and related clinical measurements to evaluate remission of psychotic symptoms, has been used in schizophrenia research. But those different definitions of remission have resulted in large variations in remission rates, making it difficult to compare findings across studies [1]. Lieberman et al. defined remission as a 50% reduction in total Brief Psychiatric Rating Scale (BPRS) scores from baseline with no more than a score of 3 on five BPRS psychosis items and a score of ≤3 on the Clinical Global Impression (CGI) scale [2]. In 2005, the Remission in Schizophrenia Working Group (RSWG) published consensus criteria to define remission of psychotic symptoms in patients with schizophrenia [3]. The criteria for remission are to measure both a symptom criterion for severity of symptoms, and time criterion for duration of sustained mild symptoms or lack of symptoms. The Positive and Negative Syndrome Scale (PANSS), the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), and the BPRS are the most widely used scales that are applied to assess symptoms in patients with a diagnosis of schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. According to RSWG criteria, symptomatic remission has been achieved when patients achieve a score of 3 or less on the PANSS scale, scores of 2 or less on the SAPS and SANS scales, or a BPRS score of 3 or less on all RSWG-chosen items [3]. In the RSWG-proposed time criterion, patients need to maintain their symptom-based scores for a minimum of six months.

The RSWG time criterion is particularly important because of the long-term course of psychotic symptoms in patients with schizophrenia. Being widely used, the RSWG remission criteria have been found in many studies to have good specificity and sensitivity, giving further insight into the prognosis of patients with schizophrenia [4-9].

Al-Aqeel et al. [10] reviewed many studies on symptomatic remission in patients with schizophrenia from 2005 to 2011, and found a wide range in rates of remission (16% to 78%) although all of the reviewed studies were using RSWG criteria. Several studies have tried to determine predictors of remission. For example, Emsley et al. reported that early treatment response and shorter duration of untreated psychosis are predictors of remission in patients with a first episode of psychosis [4]. In addition, Lambert et al. [11] and Rossi et al. [12] independently found that lower baseline PANSS score is a predictor of symptomatic remission in schizophrenic patients with multiple episodes of psychosis. But the results of some studies can not find any predictors of remission [5, 13]. Ciudad et al. evaluated 1,010 stable outpatients with schizophrenia and found that 89.9% patients in the remitted subgroup maintain their remission status for up to one year [14]. In that study, patients in remission have been found to have better premorbid adjustment, good treatment compliance, as well as improvement in depressive symptoms and social cognition during follow-up. However, a longitudinal study of 162 patients with schizophrenia spectrum disorder showed that patient in remission cannot last long. In that study, 40% patients have achieved symptomatic remission initially but only 55%-60% patients have continued to be in remission within 5 years follow-up [15]. But few studies have investigated the clinical correlates of remission or the stability of remission in patients with schizophrenia.
nia in Taiwan. Furthermore, the association between symptomatic remission and functional level remains to be clarified. Therefore, the objective of this longitudinal follow-up cohort study, we intended to evaluate the clinical correlates of remission and stability of remission, as well as to determine the predictors of remission of acute exacerbations in patients with schizophrenia in Taiwan.

Methods

Subjects

Subjects in this prospective 5-year follow-up study were recruited from a cohort of 225 consecutive patients with schizophrenia who were admitted to the acute psychiatric inpatient wards of three hospitals, National Taiwan University Hospital, Taipei City Hospital Songde Branch and Taoyuan Psychiatric Center in northern Taiwan. The institutional review boards of all three participating hospitals approved this project with the requirement to obtain written informed consent from all participants. The recruitment procedures used in this study are described in detail elsewhere [16-18]. Schizophrenia was diagnosed in all patients according to the Diagnostic and Statistical Manual of Mental Disorders, the Fourth Edition (DSM-IV) criteria. All participants received a standard set of clinical management with drug treatment, family and psychosocial intervention, and occupational therapy. The diagnosis of schizophrenia was confirmed at the time of discharge by consensus among three senior psychiatrists using data available from clinical observations, medical records, and key informants. Severity of psychiatric symptoms was assessed by the Positive and Negative Syndrome Scale (PANSS) [19] at index admission, at discharge, and then at 3, 6 months, 1 year, 2, 3, 4, and 5 years at follow-up.

Criteria for remission

Remission was defined according to the RSWG criteria, to meet both symptom severity and 6-month duration criteria. Symptomatic remission was defined according to the RSWG operational criteria, namely a score of $\leq 3$ on each of the following PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), N1 (blunted affect), N4 (social withdrawal), N6 (lack of spontaneity), G5 (mannerisms/posturing), and G9 (unusual thought content). Patients who met the criteria for remission in the severity domain of the RSWG-defined criteria for remission at either 3-month or 6-month follow-up and were also determined to have maintained remission at 1-year follow-up were defined as having achieved remission and were included in the remitted subgroup. Patients who did not fulfill the above-mentioned criteria of remission were included in the unremitted subgroup. Cross-sectional symptomatic remission at 2-, 3-, 4-, and 5-year follow-up was defined by fitting symptom severity criterion only without taking into consideration the 6-month duration component.

Functional evaluation

We used an in-house questionnaire to evaluate social function. The instrument is divided into four domains, interpersonal relationships (Domain 1), achievements (Domain 2), time arrangement of daily activities (Domain 3), and family-life functioning (Domain 4). Each item in each domain is rated on a seven-point Likert scale and scored from 1 to 7 on a response scale. Domain scores were scaled in a positive direction, with higher scores meaning better overall condition. The validity, sensitivity, and internal consistency of the scale have been reported previously [16, 20, 21]. The total scores of the above four domains
were also counted to represent for the over-all social function.

**Statistical analysis**

We used the chi-square test to compare categorical variables such as sex and marital status. We used independent \( t \) test to test differences between groups in means of continuous variables such as demographic data, clinical profiles, severity of psychiatric symptoms, and the functional evaluation. Significant predictors in the univariate analyses were then included in a logistic regression model to identify the most important clinical predictors of remission. Differences between groups were considered significant if \( p \)-values were smaller than 0.05. All statistical analyses were computed using Statistical Package of Social Science software version 18 for Windows (SPSS Inc., Chicago, Illinois, USA).

**Results**

Of the 225 subjects who fulfilled the inclusion criteria, 164 completed the 1-year follow-up. There were no significant differences between completers and non-completers in baseline symptom ratings and in most sociodemographic variables with the exception of years of education and the length of index admission, which were both longer among completers than among those who dropped out of the study (\( p < 0.05 \)). The 164 patients who completed the first year evaluation ranged in age from 16 to 45 years (mean, 30.81 years) and comprised 83 men and 18 women. The mean age at index admission was 30.82 ± 7.25 years, the mean educational level was 11.23 ± 2.90 years, and the mean duration of illness was 7.96 ± 5.66 years. The interclass correlation (ICC) of 91.1% items of the PANSS were above acceptable (0.4 - 0.7) and only 9.1% of the items were poor (below 0.4) [22].

Of the 164 patients who completed the one-year follow-up, 34 (20.73%) fulfilled the criteria for symptomatic remission at either three-month or six-month follow-up and at one-year follow-up and were, therefore, stratified into the remitted subgroup. The remaining 130 patients (79.27%) were stratified into the unremitting subgroup. Table 1 is the comparisons of socio-demographics and baseline clinical characteristics between the remitted and unremitting subgroup. Table 2 is the total scores of four function domains of the two subgroups on each following year.

The dropout rates in the remitted group were 29.4% at second-year follow-up, 38.2% at third-year follow-up, 26.5% at fourth-year follow-up and 35.3% at fifth-year follow-up. Among the group that did not achieve remission, the dropout rates were 24.6% at second-year follow-up, 33.9% at third-year follow-up, 30% at fourth-year follow-up and 51.5% at fifth-year follow-up.

**Stability**

About 56.0%-70.8% of patients in the remitted subgroup still met the criteria for remission at each of the subsequent follow-up time points (years 2-5). In the unremitting subgroup, 71.4%-76.9% of patients did not achieve remission at any of the subsequent follow-up time points (Figure 1). We compared the scores on the five PANSS symptom dimensions in the subsequent 4 years of follow-up between the two subgroups and found that patients in the unremitting subgroup had significantly higher mean scores on the negative symptoms, delusion/hallucination, hostility/excitement, and disorganized thoughts dimensions at all follow-up time points than patients in the remitted subgroup (Figures 2A-E).
Table 1. The comparisons of socio-demographics and baseline clinical characteristics between the remitted and unremitted subgroup (N = 164)

<table>
<thead>
<tr>
<th></th>
<th>Remitted group</th>
<th>Unremitted group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 34</td>
<td>n = 134</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>16/18</td>
<td>67/63</td>
</tr>
<tr>
<td>Age, years</td>
<td>32.26 ± 8.58</td>
<td>30.44 ± 6.84</td>
</tr>
<tr>
<td>Age of onset, years*</td>
<td>25.53 ± 7.37</td>
<td>22.16 ± 5.97</td>
</tr>
<tr>
<td>Duration of illness, years</td>
<td>6.74 ± 5.55</td>
<td>8.28 ± 5.67</td>
</tr>
<tr>
<td>Education, years*</td>
<td>12.41 ± 3.05</td>
<td>10.92 ± 2.79</td>
</tr>
<tr>
<td>Duration of hospitalization, days</td>
<td>59.91 ± 54.37</td>
<td>69.23 ± 43.18</td>
</tr>
<tr>
<td>Marriage, single/married</td>
<td>22/24</td>
<td>102/28</td>
</tr>
<tr>
<td>Job, jobless/job or student*</td>
<td>10/24</td>
<td>72/58</td>
</tr>
<tr>
<td>Number of admissions, times</td>
<td>2.16 ± 1.90</td>
<td>2.95 ± 2.53</td>
</tr>
<tr>
<td>Times of ECT, times*</td>
<td>0.18 ± 1.03</td>
<td>1.45 ± 2.33</td>
</tr>
<tr>
<td>PANSS negative symptom dimension score*</td>
<td>16.79 ± 8.78</td>
<td>20.78 ± 9.22</td>
</tr>
<tr>
<td>PANSS disorganized thoughts dimension score</td>
<td>11.82 ± 5.69</td>
<td>11.71 ± 5.23</td>
</tr>
<tr>
<td>PANSS hostility/excitement dimension score</td>
<td>16.53 ± 9.76</td>
<td>17.01 ± 9.44</td>
</tr>
<tr>
<td>PANSS delusion/hallucination dimension score</td>
<td>13.21 ± 3.44</td>
<td>13.28 ± 3.80</td>
</tr>
<tr>
<td>PANSS anxiety/depression dimension score</td>
<td>6.03 ± 2.99</td>
<td>6.18 ± 2.69</td>
</tr>
<tr>
<td>Total scores of PANSS</td>
<td>82.65 ± 24.11</td>
<td>89.13 ± 24.12</td>
</tr>
<tr>
<td>Highest daily CPZ equivalent dosage during index admission, mg/day*</td>
<td>716.55 ± 541.73</td>
<td>996.64 ± 742.10</td>
</tr>
<tr>
<td>Daily CPZ equivalent dosage on discharge, mg/day*</td>
<td>397.10 ± 407.45</td>
<td>613.61 ± 565.22</td>
</tr>
</tbody>
</table>

*p < 0.05 using independent t-test
ECT, Electroconvulsive therapy; PANSS, the Positive and Negative Syndrome Scale; CPZ, chlorpromazine

Table 2. The total scores of four function domains on each following year

<table>
<thead>
<tr>
<th></th>
<th>Remitted group (mean ± SD)</th>
<th>Unremitted group (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-year follow-up***</td>
<td>17.10 ± 3.44</td>
<td>12.31 ± 3.99</td>
</tr>
<tr>
<td>Two-year***</td>
<td>15.93 ± 4.16</td>
<td>11.85 ± 4.22</td>
</tr>
<tr>
<td>Three-year**</td>
<td>15.90 ± 4.25</td>
<td>12.83 ± 4.45</td>
</tr>
<tr>
<td>Four-year**</td>
<td>16.08 ± 3.88</td>
<td>13.37 ± 4.49</td>
</tr>
<tr>
<td>Five-year</td>
<td>15.59 ± 5.15</td>
<td>14.13 ± 5.01</td>
</tr>
</tbody>
</table>

**p < 0.01, ***p < 0.001 using independent t-test
SD, standard deviation
Predictors of remission

Significant variables in the univariate analyses were included in a logistic regression model to determine the most important predictors of remission. As shown in Table 3, age at onset, education level were significantly positive predictors for remission status, and negative symptom dimension on the PANSS scale was significantly a negative predictor for remission status.

Discussion

Remission rate

In our study, about 20% of patients with schizophrenia achieved remission of acute exacerbations according to RSWG-determined severity and duration criteria within 1 year after admission. The previous remission rate in first-episode schizophrenia or schizoaffective disorder has been reported as ranging from 17% to 78% and for multiple-episode group was about 16.0% to 57.5% [10]. The variation in remission rates across studies may be due to different remission criteria used, differences in patient characteristics, or the use of antipsychotic drugs. Many studies that used remission criteria only measured the symptom-based severity criterion, but did not take into consideration the time requirement. But the time criterion (> 6 months) is regarded as a key element in establishing whether a patient has achieved remission [3]. A big difference exists between that the schizophrenic subjects meeting only severity criterion, and those requires fulfillment of both severity and duration criteria [23]. Additional 6-month criterion in remission requirement can enhance the predictive validity on symptom severity during follow-up [7]. Other studies have reported similar findings. For example, a research, which recruited schizophrenia patients of the same ethnic population as ours and measured psychiatric symptoms 1 month after discharge from acute admission, reported 36.7% resolution
Figure 2. The display of five symptom dimension scores of the remitted and unremitted subgroup during the follow up period. (The first year: remitted n = 34, unremitted n = 130; the second year: remitted n = 24, unremitted n = 98; the third year: remitted n = 21, unremitted n = 86; the forth year: remitted n = 25, unremitted n = 91; the fifth year: remitted n = 22, unremitted n = 63)

*p < 0.05, **p < 0.01, ***p < 0.001. 2A: Negative symptom dimension, 2B: Disorganized thoughts dimension, 2C: Hostility/Excitement symptom dimension, 2D: Delusion/Hallucination symptom dimension, 2E: Anxiety/depression symptom dimension.
rate using the cross sectional severity criteria of RSWG [24]. In our study, we used both criteria. This finding may be the reason why our result has lower remission rate compared to that in the previous report [24].

Regarding patients’ characteristics, several previous studies included subjects with schizoaffective disorder and other affective psychoses [25, 26]. Since the consensus of remission criteria was only for schizophrenia initially, the related clinical validity for affective psychosis needs further clarification. Therefore, patients with different diagnose may cause different remission rates across studies. In addition, the total number of acute episodes differs markedly across studies, with some studies enrolling patients only with a first episode and others including subjects with multiple episodes. Most of our patients had multiple episodes with a mean duration of illness of 7.96 years, which may have contributed to the lower remission rate. Furthermore, our study patients with acute exacerbations received follow-up from the index admission rather than follow-up from the outpatient stage. It may take longer for patients with severe exacerbations to attain remission.

The use of different types of antipsychotic drugs may have caused different remission rates. For example, in the CATIE study [27], the highest remission rates at six-month follow-up are associated with olanzapine (12.4%), followed by quetiapine (8.2%), perphenazine (6.8%), ziprasidone (6.5%), and risperidone (6.3%). A higher remission rate (62%) can be reached in first-episode psychosis using risperidone long-acting injection (LAI) [28]. Most of the patients in our study received first-generation (typical) antipsychotic agents whereas only 11.6% received second-generation (atypical) antipsychotics such as risperidone. This may be another reason for the lower remission rate in our study.

**Stability**

We found that the scores in the psychiatric symptoms domains of the PANSS scale in the unremitted subgroup were consistently higher than those in the remitted group, with the exception of scores in the depression/anxiety symptom dimension during the follow-up periods. Functional status in the remitted subgroup was also consistently higher than that in the unremitted group. This finding indicates that the stratification of patients into one of the two subgroups based on first-year illness course after admission remained valid in the symptom and function dimension during follow-up.

Previous studies have shown that remission is a dynamic state, and it is part of the fluctuating natural course of schizophrenia. For example, a study recruited 93 first episode schizophrenia patients and followed up for average 5 years [29]. The investigators found that 59.5% of the patients have met remission criteria for the first 2 years.
but that 71.5% of those patients cannot maintain their remission status. But 57% of those who lost their remission status can get remitted again [29]. This finding has been demonstrated in several other studies as well [30-32]. In our study (Figure 1), about 75% (range, 71.4% - 76.9%) of patients who did not achieve remission by one year after the index admission never achieved remission compared to about a half to two thirds (56.0% - 70.8%) of the remitted subgroup who remained in remission during the follow-up period. Progression of illness or non-compliance with medications, resulting in relapse of psychosis in the remitted subgroup, might explain why patients in the unremitting subgroup seemed more stable than those in the remitted group.

If we were to consider symptom severity only, then the remitted subgroup would comprise 60 patients and the non-remitted subgroup would comprise 104 patients. In that scenario, the stability in the remitted subgroup would be poorer (around 60% compared to 70% in the original subgroup) and that in the unremitting subgroup would be better (around 80% - 85% compared to 75% - 80% in the original subgroup). Therefore, the time component of the RSWG-proposed criteria for remission is important when determining achievement and maintenance of remission of exacerbations in patients with schizophrenia.

**Predictors of remission**

We found that older age of onset \((p < 0.01)\), higher educational level \((p < 0.05)\) and less severe negative symptoms \((p < 0.05)\) at the index admission were significantly predictive of remission status 1 year later (Table 3). Several studies have reported that older age at onset of psychosis is associated with better chance of achieving remission [33, 34]. In addition, other studies have also shown that higher education level at baseline is predictive of achieving symptom remission [35, 36]. The predictors of RSWG remission status were also investigated by the German Research Network on Schizophrenia (GRNS) group, which showed that early treatment response quick to reach remission than those with late remitter [4, 37].

Lower degree of clinical symptom severity at baseline may be a suitable predictor of remission. But when we divided the symptoms into positive and negative symptoms, we found different predictive values for the two symptom dimensions. Some studies have reported that both lower degree of severity of positive and negative symptoms at baseline are predictive of remission [11, 12]. However, other studies have shown that only lower degree of severity of negative symptoms at baseline can predict remission [29, 31]. These finding agree well with our study results (Table 3). Further studies are needed to better understand the predictors of remission of acute exacerbations in patients with schizophrenia.

**Study limitations**

There are some limitations in this study that need to be addressed.

- Although we assessed stability of remission at 2-year through 5-year follow-ups, we defined remission only by the severity criterion, which may have resulted in overestimating of the remission rate.
- In the remission subgroup, the fulfillment of 6-month duration of symptomatic remission was based on psychopathological assessments using the PANSS instrument at only two time points, at 3 months or 6 months after index admission and at 12 months after admission. This method of estimating remission may have resulted in the misclassification of subjects who shifted out of and subsequently shifted back into remission within the 6-month interval,
which may have resulted in overestimating the remission rate.

- The number of patients included in the study was small and the attrition rate at the 5th year follow-up was quite high (48.12%). But no significant differences existed in demographic variables, with the exception of gender, between patients who completed the 5th year evaluation and patients who dropped out before the end of the study. We found that patients who dropped out of the study had higher scores on the Delusion/Hallucination and Anxiety/Depression symptom dimensions than patients who completed the five-year follow-up study ($p < 0.05$). We suggest that the unremitted patients are more likely to be lost to follow-up, which may have resulted in a biased estimation.

- We evaluated the condition of patients on an annual basis after the first year of follow-up, but we did not have any data in the intervening period between yearly assessments.

**Summary**

We found that about 20% of patients with schizophrenia met RSWG-defined remission criteria (both severity and duration criteria) one year after index admission for acute exacerbation. The severity of psychiatric symptoms and the functional status of patients who achieved remission were more favorable than those who could not achieve remission in the following 2 to 5 years. The subgroups remained rather stable throughout the study period. Older age of onset, higher educational level and lower severity of negative symptoms at index admission were predictive of remission status 1 year later. Further research are warranted to explore other outcome dimensions that might contribute to be predictive factors including cognitive deficits and brain imaging studies for remission in schizophrenia.

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**References**


