## **Regular Article**

# Remission in schizophrenia: A community-based 6-year follow-up study in Bali

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*Aim:* The purpose of this naturalistic study was to investigate the rate and predictors of remission at medium-term follow up of individuals with schizophrenia in a community setting in Bali.

*Methods*: Subjects comprised 37 individuals with schizophrenia, including 19 never-treated cases, screened from 8546 general residents. Outcome was evaluated using the standardized symptomatic remission criteria based on Positive and Negative Syndrome Scale scores and operational functional remission criteria at 6-year follow up.

*Results:* Ten individuals (27%) achieved symptomatic remission, 12 (32%) achieved functional remission, and 10 (27%) achieved complete remission (i.e.

**R**EMISSION IS ONE of the major issues in current outcome studies in schizophrenia. For many years, schizophrenia was regarded as an illness inevitably leading to a non-remitting end state, described by Kraepelin as dementia praecox. However, recent long-term outcome studies have revealed that the course of schizophrenia is more heterogeneous, with a significant portion of patients exhibiting remission.<sup>1,2</sup> This altered viewpoint necessitated the development of a new and operationalized definition of attainable treatment outcomes in patients with schizophrenia.<sup>3</sup> In this context, standardized remission criteria for schizophrenia were proposed by the symptomatic and functional remission). Lower Positive and Negative Syndrome Scale negative symptom score at baseline and receipt of psychiatric treatment for more than half of the follow-up period were predictors of complete remission.

*Conclusions:* The majority of community-screened individuals with schizophrenia failed to achieve complete remission at the 6-year follow up. These results suggest that strategies promoting mental health service utilization among individuals with schizophrenia are essential in Bali.

Key words: developing countries, outcome assessments, remission, schizophrenia.

Remission in Schizophrenia Working Group.<sup>4</sup> These criteria have been clinically validated and demonstrated to be more useful than prior subjective and heterogeneous evaluations of clinical stability.<sup>5–7</sup> In addition to symptomatic remission, another treatment goal in schizophrenia is functional remission, which allows the reintegration of patients into the community and workplace and reduces social burden.<sup>8,9</sup> Little is known, however, about the symptomatic and functional remission status of individuals with schizophrenia in community settings in developing countries.

We previously reported the clinical condition of community-screened individuals with schizophrenia evaluated by the Positive and Negative Syndrome Scale (PANSS);<sup>10</sup> however, we were unable to determine the symptomatic remission rate of the participants due to the cross-sectional study design, which did not enable us to include a 6-month time

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criterion. Furthermore, we did not determine the functional remission rate in the previous study. The present study therefore aimed to examine the outcome, indicated by the rates of symptomatic and functional remission based on operational criteria with a 6-month time criterion, and predictors of remission at the 6-year follow up of community-screened individuals with schizophrenia in Bali, approximately half of whom had never received treatment at baseline.

### **METHODS**

#### Study area

Bali is one of more than 15 000 islands that make up Indonesia, which is categorized among the lowermiddle income countries.<sup>11</sup> While Bali is famous as a tourist resort, most Balinese people engage in primary industries. The basic unit of society, a community referred to as a *banjar*, consists of up to several hundred households. In 2001 (baseline of the present study), Bali had 260 psychiatric beds. This number increased to 310 in 2007 (at the 6-year follow up); however, the number of psychiatric beds per 10 000 population remains low (1.0).

#### Case detection

Details about the sampling method are described elsewhere.<sup>10</sup> In brief, in the first stage, nine banjars comprising 1966 households with 8546 residents were randomly and consecutively selected in Bali. The first author (T.K.) performed face-to-face family interviews between June 2001 and July 2002 with one key family member from each of the 1966 households in order to determine whether each household included a member with schizophrenia. As the targeted age was above 15, 6038 of 8546 residents were selected as subjects for case detection. Of these, no individuals were admitted to psychiatric facilities. Family History Research Diagnostic Criteria (FH-RDC)<sup>12</sup> were used to detect possible cases that fulfilled the criteria either for schizophrenia or schizophreniform disorder classified in the DSM-III-R.13 For the suspected cases, the first author conducted a direct interview using the Structured Clinical Interview for DSM-III-R (SCID)<sup>14</sup> NP version to examine whether the cases actually fulfilled the DSM-III-R criteria for schizophrenia or schizophreniform disorder. The reliability of the diagnosis of schizophrenia by the first author was established.<sup>15</sup> In total, 39 subjects with schizophrenia were detected, including three whose initial diagnosis was schizophreniform disorder but who were rediagnosed as having schizophrenia 6 months after the onset of illness.

#### Baseline interview for screened subjects

At least two key relatives who played a central role in caring for the subjects were selected. Interviews with 39 subjects and their key relatives were performed by the first author. Clinical symptoms were evaluated using PANSS.<sup>16</sup> The validity and reliability of the Indonesian version of PANSS has been established.<sup>17</sup> Eguma's Social Adjustment Scale (ESAS)<sup>18</sup> was used to assess social adjustment. The reliability of the clinical interviews carried out by the first author was established.<sup>15</sup> In addition to these assessments, sociodemographic and clinical data (e.g. violent behavior in the past, treatment status) of the subjects were also obtained. In this study, treatment was defined as antipsychotic medical treatment; treatment provided by native healers (which was received by all subjects) was not taken into account. At baseline, for relatives of subjects with never-treated schizophrenia, treatment was recommended after explaining the effectiveness of psychiatric medication.

#### Follow-up assessment

The first author (T.K.) conducted follow-up interviews at 5.5 and 6 years from baseline to assess the medium-term outcome of subjects, including clinical symptoms evaluated by PANSS and social functioning, over a 6-month period. All evaluations were based on interviews with the subjects as well as information obtained from family members. At least two family members who were living with the subjects were chosen for interviews similar to those conducted for baseline assessment.

The study protocol was approved by the Indonesian Institute of Science, and all participants gave written informed consent to participate.

#### Criteria for symptomatic remission

In order to assess symptomatic remission, the standardized remission criteria for schizophrenia by the Remission in Schizophrenia Working Group<sup>4</sup> were employed. These criteria comprise a severity criterion and a time criterion. With regard to the severity criterion, a score of mild (3) or less was required for all eight core symptoms of PANSS, including 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 concept. With regard to the time criterion, the symptom severity mentioned above must have been maintained for at least 6 months. In the present study, subjects who met the severity criterion at both 5.5- and 6-year follow up and showed no relapse during the intervening 6 months were considered to have achieved symptomatic remission.

## Criteria for functional remission

In the present study, functional remission was defined as follows. Patients were required to attain the following three criteria simultaneously: (i) vocational functioning (paid or unpaid work [e.g. housewife] for more than half a day); (ii) independent living (independent living without supervision by family members); and (iii) peer relationships (meeting with non-family members more than once per week). These domains are essential in assessing the functional outcome of schizophrenia,<sup>19</sup> and have been widely used in outcome studies as an index of functional remission.<sup>20-23</sup> In the present study, subjects who met the criteria for the entirety of the 6 months immediately preceding the 6-year follow up were considered to have achieved functional remission. Regarding social function, we employed ESAS<sup>18</sup> at baseline; however, we did not employ ESAS at follow up, as this scale combines several dimensions of social function into a single scale and is rather vague.

## Criteria for complete remission

In the present study, subjects who achieved symptomatic remission and functional remission simultaneously were considered to be in complete remission.

## Statistical analysis

Univariate logistic regression analysis was performed to examine the individual effect of each baseline sociodemographic factor (i.e. age at onset, sex, marital status, work status, and educational period), baseline clinical factor (i.e. duration of illness, PANSS positive symptom score, PANSS negative symptom score, and PANSS general psychopathology score), and post-baseline clinical factor (i.e. receipt of treatment) on complete remission. Odds ratios and their 95% confidence intervals were calculated. Variables with *P*-values <0.1 were then entered into a multivariate logistic regression model to identify a final stable model of predictors.

## RESULTS

## Subject characteristics

Of 8546 individuals, 39 individuals with schizophrenia were detected at baseline. Excluding the three individuals diagnosed with schizophreniform disorder at screening but whose diagnosis was subsequently changed to schizophrenia, a point prevalence for schizophrenia of 4.2 per 1000 was found. Of 39 individuals screened at baseline, 37 (95%) could be followed up for 6 years. Two were withdrawn due to death by natural causes. Baseline characteristics are shown in Table 1; only data for followed up subjects are included. Subjects were more likely to be male, and approximately half of them had never been treated at baseline. All subjects

 Table 1.
 Subject characteristics

Baseline sociodemographic data	
Age at onset; years, mean (SD)	24.0 (7.4)
Age at baseline; years, mean (SD)	38.2 (14.4)
Sex; male, <i>n</i> (%)	23 (62)
Marital status; married, $n$ (%)	15 (41)
Number of family members, mean (SD)	6.6 (3.4)
Family history of psychosis; present, n (%)	17 (46)
Work status; employed, $n$ (%)	19 (51)
Educational period; years, mean (SD)	4.4 (3.7)
Baseline clinical data	
Duration of illness; years, mean (SD)	14.6 (12.3)
PANSS positive symptom score, mean	19.43 (7.32)
(SD)	
PANSS negative symptom score, mean (SD)	19.43 (8.42)
PANSS general psychopathology score, mean (SD)	38.41 (12.07)
Treatment status; history of psychiatric	18 (49)
treatment, n (%)	
Post-baseline clinical data	
Receipt of treatment; more than half of	11 (30)
follow-up period, n (%)	

PANSS, Positive and Negative Syndrome Scale.

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Table 2. Remission status of subjects at 6-year follow up

Symptomatic remission	Functional remission	n (%)	
Yes	Yes	10 (27)	
Yes	No	0	
No	Yes	2 (5)	
No	No	25 (68)	

were residents of rural areas, as the targeted communities were all located in rural areas, which predominate in Bali. More than half of the subjects were employed (51%), and most were farmers or household industry workers. Mean PANSS score was 77.3, indicating that the subjects had moderate symptoms; a PANSS score of 75 corresponds to a classification of 'moderately ill' on the Clinical Global Impressions.<sup>24</sup>

Of 19 subjects who had never been treated at baseline, five (26%) started to receive psychiatric treatment after our initial baseline assessment interview, and 14 (74%) remained untreated during the follow-up period. All treated individuals received psychiatric treatment for more than half of the follow-up period. Of 18 subjects who had a history of psychiatric treatment at baseline, six (33%) received treatment for more than half of the follow-up period,

Table 3. Predictors of complete remission at 6-year follow up

six (33%) had received treatment for 50% or less of the follow-up period, and six (33%) completely discontinued treatment and were not on medication at any point during follow up. In total, 11 (30%) of 37 subjects received psychiatric treatment for more than half of the follow-up period.

#### **Clinical outcome**

At the 6-year follow up, PANSS positive symptom, negative symptom, general psychopathology, and total scores were 17.43 (SD 7.32), 21.51 (SD 10.46), 40.54 (SD 14.80), and 79.49 (SD 31.14), respectively. Ten (27%) of 37 subjects achieved symptomatic remission, 12 (32%) achieved functional remission, and 10 (27%) achieved complete remission (i.e. symptomatic and functional remission). All 10 subjects who achieved symptomatic remission concurrently achieved functional remission, and the number of subjects who attained complete remission was therefore 10 (Table 2). Two subjects achieved functional remission only, and 25 (68%) achieved neither symptomatic nor functional remission.

#### Predictors of complete remission

Table 3 illustrates the result of logistic regression analysis examining the effect of potential

	Odds ratio	95% CI	P-value
		5570 01	
Univariate logistic regression analysis			
Baseline sociodemographic factors			
Age at onset <sup>†</sup>	0.93	(0.83-1.04)	0.22
Sex (male/female)	3.20	(0.57 - 18.0)	0.19
Marital status (single/married)	1.70	(0.39-7.36)	0.48
Work status (employed/unemployed)	2.92	(0.62–13.8)	0.18
Educational period <sup>†</sup>	1.03	(0.84-1.25)	0.80
Baseline clinical factors			
Duration of illness <sup>†</sup>	0.98	(0.92 - 1.04)	0.45
PANSS positive symptom score <sup>†</sup>	0.92	(0.82 - 1.04)	0.17
PANSS negative symptom score <sup>†</sup>	0.83	(0.70 - 0.98)	0.02
PANSS general psychopathology score <sup>†</sup>	0.95	(0.88-1.03)	0.19
Post-baseline clinical factors			
Receipt of treatment (>50%/ $\leq$ 50% of the follow-up period)	6.60	(1.34-32.53)	0.02
Multiple logistic regression analysis			
PANSS negative symptom score <sup>†</sup>	0.83	(0.70-0.98)	0.03
Receipt of treatment (>50%/ $\leq$ 50% of the follow-up period)	7.23	(1.09-47.88)	0.04

<sup>†</sup>Continuous variables.

PANSS, Positive and Negative Syndrome Scale.

sociodemographic and clinical predictors of complete remission at the 6-year follow up. Univariate logistic regression analysis revealed that PANSS negative symptom score at baseline and receipt of psychiatric treatment for more than half of the follow-up period were possible predictors of complete remission. Using a multiple logistic regression model, both factors were shown to be significant independent predictors; subjects with higher PANSS negative symptom scores at baseline were less likely to achieve complete remission, while subjects who received psychiatric treatment for more than half of the follow-up period were more likely to achieve complete remission compared with those who had received psychiatric treatment for 50% or less of the follow-up period. The rate of complete remission was 55% (6/11) for those who received psychiatric treatment for more than half of the follow-up period and 15% (4/26) for those who had received psychiatric treatment for 50% or less of the follow-up period.

## DISCUSSION

In this naturalistic study, we clarified the rate and predictors of remission among community-screened individuals with schizophrenia. To our knowledge, this is the first study to examine symptomatic remission of schizophrenia using the standardized remission criteria proposed by the Schizophrenia Working Group in developing countries. The strengths of this study include its low attrition rate and the community-based sampling method, which ensured that subjects were representative of individuals with schizophrenia in Bali, where many affected people do not receive psychiatric treatment. The results demonstrated that 27% of subjects achieved complete remission, and those with less severe negative symptoms at baseline and those who had received psychiatric treatment for more than half of the follow-up period were more likely to achieve complete remission at medium-term follow up.

In previous studies investigating symptomatic remission of schizophrenia using standardized remission criteria in developed countries, the reported remission rates range from 24% to 55%.<sup>3,25-27</sup> The rates of functional remission employing similar criteria in developed countries are between 13% and 46%.<sup>20-23</sup> Although different study designs and sample characteristics make it difficult to compare remission rates among studies, rates of symptomatic

and functional remission in the present study (27% and 32%, respectively) were within the range of those found in developed countries, indicating that symptomatic and functional outcomes in Bali are comparable to those found in developed countries. Therefore, our study results support the findings reported by Cohen *et al.*,<sup>28</sup> suggesting that it is time to re-examine the commonly held notion that schizophrenia outcomes in low- and middle-income countries, which was supported by three WHO studies.<sup>29–31</sup> Alem *et al.*,<sup>32</sup> also recently reported that schizophrenia outcome in developing countries is heterogeneous rather than uniformly favorable.

In the present study, all individuals who achieved symptomatic remission concurrently achieved functional remission, and rates of symptomatic and functional remission were 27% and 32%. In contrast, in a study of 10 European countries, Lambert et al.21 demonstrated that 47% of patients achieved symptomatic remission, whereas only 27% achieved functional remission. San et al.33 also reported that 45% of patients achieved clinical remission but only 10% showed adequate social and/or vocational functioning in an outpatient setting in Spain. The difference between our study results and those from developed countries may result from different employment rates among study sites. A European schizophrenia cohort study revealed that the employment rate of individuals with schizophrenia was 12.9% in the UK, 11.5% in France and 30.3% in Germany.34 The employment rate in the present study (51%) was much higher. In the present study, as most of the subjects were farmers or household industry workers rather than employees at competitive jobs as is common in Western countries, they did not need to apply for jobs and were allowed to work according to their decreased level of ability. Such a social background may have caused the functional remission rate to be higher than the symptomatic remission rate in the present study, a result that contrasts sharply with the large drop in functional remission rates as compared to symptomatic remission rates observed in developed countries.

Receipt of psychiatric treatment for more than half of the follow-up period was a significant predictor of complete remission. This finding is similar to that reported in a community-based study conducted in Ethiopia.<sup>32</sup> As antipsychotic medication is the cornerstone of treatment for individuals with schizophrenia, reducing the medication access barrier is an important strategy that should be addressed in developing countries. Meanwhile, it is reported that symptom-free patients tend to discontinue treatment completely over the long term, and thus sustained symptomatic recovery is most commonly observed outside of the clinical setting.<sup>35</sup> Further investigation of whether those with complete remission in the present study eventually attain recovery without medication may shed light on the long-term outcome of schizophrenia.

Higher PANSS negative symptom score at baseline predicted a lower likelihood of complete remission at 6-year follow up in the present study. This finding is consistent with other studies demonstrating that a higher level of negative symptoms at baseline predicted a longer time to response to treatment<sup>36</sup> and lower remission rate.<sup>23,26,37,38</sup>

This study has several limitations. First, the small number of participants made the interpretation of the results rather difficult. Second, evaluation of symptoms and function was conducted only at baseline, 5.5 years, and 6 years. Third, neurocognitive function, which is a potential predictor of remission, was not investigated at baseline. Fourth, the rater was not blind to treatment status and previous evaluations. Future studies should address these problems and comprehensively investigate recovery from schizophrenia and the factors associated with nonreceipt of treatment in order to increase mental health service utilization among individuals with schizophrenia in Bali.

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