Symptomatic Remission and Cognitive Impairment in First-Episode Schizophrenia: A Prospective 3-Year Follow-Up Study

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ABSTRACT

Objective: Cognitive impairment is a core feature of schizophrenia, but its relationship with symptomatic remission has been understudied. This study aimed to examine the concurrent and longitudinal relationships between cognitive functioning and symptomatic remission in first-episode schizophrenia.

Method: The sample comprised 92 Chinese patients, aged 18 to 55 years, who presented with first-episode *DSM-IV* schizophrenia spectrum disorder and were recruited from both outpatient and inpatient psychiatric units covering a defined catchment area in Hong Kong. The study commenced in September 1997 and ended in March 2005. Psychopathological evaluation was conducted using the Positive and Negative Syndrome Scale (PANSS) and the High Royds Evaluation of Negativity (HEN) scale at intake, after clinical stabilization of the first psychotic episode, and at 12, 24, and 36 months. Cognitive functions were measured at clinical stabilization and at 12, 24, and 36 months. Sustained symptomatic remission was operationally defined as fulfillment of mild severity ratings or less at 24 and 36 months on selected PANSS items for positive symptoms and on the basis of Andreasen's criteria and HEN subscales for negative symptoms.

Results: At the end of the 3-year follow-up, 44.6% of patients achieved sustained symptomatic remission. Remitted patients had significantly better concurrent verbal memory ($F = 4.6$, $P < .01$) and functional ($t = -2.4$, $P < .05$) and vocational ($t = 4.8$, $P < .01$) outcomes at 36 months than nonremitted counterparts. Sustained remission attainment was associated with better premorbid adjustment ($t = -3.1$, $P < .01$), better baseline occupational status ($\chi^2 = 4.7$, $P < .05$), better 1-year verbal memory ($F = 6.4$, $P < .01$), and fewer 1-year positive ($t = -2.9$, $P < .01$) and negative ($t = -4.7$, $P < .01$) symptoms. Logistic regression indicated that verbal memory impairment, premorbid functioning, and negative symptom severity independently predicted remission status (Nagelkerke $R^2 = 0.425$, $P < .0001$).

Conclusions: Our findings provide supportive evidence that verbal memory impairment might be specifically related to attainment of sustained remission in the early stage of schizophrenia.

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Cognitive impairment is a core feature of schizophrenia.[1] Substantial evidence demonstrates that patients with schizophrenia exhibit pronounced deficits in most cognitive domains, particularly in memory, attention, and executive functions.[2,3] Literature also indicates that cognitive dysfunction, which is observed in various stages of the illness,[4] is associated with functional disability[5,6] and poor clinical outcome.[7–9] Since the introduction of a consensus-derived definition for symptomatic remission by the Remission in Schizophrenia Working Group (RSWG),[10] there is an increasing amount of research examining clinical predictors and functional outcome in relation to remission status in schizophrenia.[11,12] Despite the fact that cognition is regarded as an important outcome dimension with profound clinical implications, relatively few studies have been conducted to investigate the relationship between cognitive impairment and symptomatic remission. In fact, it is recommended that further research should be carried out to clarify the impact of cognitive functioning on predicting symptomatic remission.[13]

Discrepant findings have been observed with respect to the concurrent relationship between symptomatic remission and cognitive deficits. Whereas several previous studies revealed that nonremission was associated with generalized cognitive dysfunction[14,15] or impairment in specific cognitive domains including verbal memory,[16] executive function,[17–19] and attention,[17] others failed to find such a relationship.[20–25] Alternatively, even fewer studies have evaluated the capacity of cognitive functioning to predict the likelihood of achieving symptomatic remission. Results thus far are mixed, with some studies showing cognitive impairment as an independent predictor of remission,[26,27] but not others.[21,28]

These inconsistent findings may partly be attributable to methodological variations across studies, including differences in sample characteristics, remission criteria adopted, lengths of follow-up, and choice of cognitive assessments administered. It should also be noted that the majority of studies that assessed the relationship between cognition and symptomatic remission recruited patients with chronic schizophrenia.[14–21,23–25] Until now, only 4 studies have been conducted to examine the association of cognitive functioning with remission status in patients presenting with first-episode or early schizophrenia.[20,26–28] Yet, it is recognized that studying a first-episode sample can ensure that the cohort is more homogeneous with regard to illness chronicity and treatment exposure and allow the trajectories of symptom manifestations and cognitive deficits to be better elucidated right from the onset of psychosis.

Given the clinical significance of symptomatic remission, along with the paucity of data regarding its relationship with cognitive

Clinical Points

- Symptomatic remission is an achievable treatment goal in the early stage of schizophrenia and is associated with better cognitive and psychosocial functioning.
- Assessment of verbal memory function in the initial year of treatment for first-episode schizophrenia may potentially enhance prediction of patients' likelihood of attaining symptomatic remission in the later course of the illness.

impairment, we report a prospective 3-year follow-up study in a representative cohort of Chinese patients presenting with first-episode schizophrenia spectrum disorder, with an aim to examine (1) the concurrent relationship of symptomatic remission and cognitive performance, and (2) the capacity of cognitive impairment to predict symptomatic remission at the end of 3-year follow-up. In this study, a broad range of premorbid, clinical, and functional variables, alongside standardized cognitive measures, were systematically evaluated to enable a better estimation of potential independent contributions of cognitive functioning to remission attainment.

METHOD

Participants

One hundred thirty-eight consecutive patients aged 18–55 years with first-episode schizophrenia, schizophreniform disorder, or schizoaffective disorder were recruited from both outpatient and inpatient psychiatric units covering a defined catchment area in Hong Kong. The study commenced in September 1997 and ended in March 2005. Patients with known neurologic disorder, learning disability, or current substance abuse were excluded from the study. Of the initial cohort, 93 subjects completed the 3-year follow-up, 40 defaulted, 4 committed suicide, and 1 died of medical disease. There were no significant differences between completers and noncompleters in sociodemographics, duration of untreated psychosis, baseline symptom ratings, and cognitive functions. Patients in this study were initially treated with low-dose first-generation antipsychotic medications. The current study was part of a prospective 3-year follow-up study in first-episode schizophrenia spectrum disorders, and findings regarding persistent negative symptoms and the influence of the duration of untreated psychosis on cognitive functioning have been reported elsewhere.[29,30] The study was approved by the local institutional review board, and all of the subjects gave written informed consent before participation.

Assessments

Diagnostic assignment was based on a longitudinal approach, taking into consideration that diagnostic change may take place over time.[31,32] The 3-year diagnosis of each subject was determined according to *DSM-IV* criteria,[33] using all available information encompassing the whole follow-up period including the Chinese-Bilingual Structured Clinical Interview for *DSM-IV* Axis I Disorders, Patient Edition (CB-SCID-I/P)[34] administered at baseline and at 3 years, informant histories, and medical records. A previous validation study[34] showed that CB-SCID-I/P yielded reliable *DSM-IV* diagnoses in Chinese patients with psychotic disorders. Premorbid functioning was measured with the Premorbid Adjustment Scale.[35] Because the onset of prodrome and psychosis usually occur in late adolescence and early adulthood, we included only childhood (≤ 11 years) and early adolescent (12–15 years) periods for assessment to avoid any possible confounding with early symptoms.[36] The Premorbid Adjustment Scale total score was calculated by summing the scores on all items encompassing both childhood and early adolescence periods and dividing by the total possible score (score range, 0 to 1; higher score indicates lower functioning). The Interview for the Retrospective Assessment of the Onset of Schizophrenia[37] was used to confirm first-episode status and to assess duration of untreated psychosis, which was defined as the time interval between the onset of positive psychotic symptoms and treatment initiation.

Positive symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS),[38] with the intraclass correlation coefficient being 0.83 for the positive symptoms subscale. The High Royds Evaluation of Negativity (HEN) scale[39] was employed to measure negative symptoms. The HEN scale comprises 6 subscales and 18 items that are rated along an anchored 5-point severity scale (range, 0–4; higher score indicates more severe negative symptoms). Validation of the HEN for use in Chinese schizophrenia patients has previously been reported.[40] Intraclass correlation coefficients for the subscales ranged from 0.74 (thought) to 0.85 (speech). In this study, we included only 4 of the 6 subscales, ie, affect, behavior, speech, and functioning, for analysis[29] as the remaining 2, namely thought and appearance, were more related to the disorganization dimension. Psychopathological evaluation was conducted for each subject at intake, after clinical stabilization of the first psychotic episode (based on clinical judgment of the treating psychiatrists—a mean of 42.6 days after initial assessment), and at 12, 24, and 36 months. Psychosocial functioning was assessed with the World Health Organization Psychiatric Disability Assessment Schedule (WHO/DAS),[41] which comprises 11 items related to the patient's ability with regard to independent living, relationships, and social and occupational role performance. Each item is scored from 0 to 5, with a higher score indicating greater functional impairment. Each subject was evaluated with WHO/DAS at clinical stabilization and at 12, 24, and 36 months. Data on vocational status were also obtained.

A comprehensive battery of cognitive assessments was administered to all subjects, comprising a logical memory test (verbal memory) and visual reproduction test (visual memory) from the Wechsler Memory Scale-Revised,[42] a forward digit span test (working memory) from the Wechsler Adult Intelligence Scale,[43] the category verbal fluency test (executive function), and the Modified Wisconsin Card Sorting Test (executive function).[44] General verbal

intelligence was estimated at baseline using the information subscale from the Wechsler Adult Intelligence Scale.[43] To maximize cooperation and to reduce state effects of acute psychosis, cognitive assessment undertaken when patients were clinically stabilized was regarded as the baseline cognitive measure. Cognitive assessment was readministered to each subject at 12, 24, and 36 months after entry. A group of healthy controls, matched by age, sex, and educational level, were recruited via advertisements and were evaluated with the same battery of cognitive assessments as patients at baseline only.

Symptomatic remission criteria were derived and modified on the basis of the RSWG operational definition.[10] We opted for the HEN scale rather than the 3 selected items of the PANSS (ie, blunted affect, lack of spontaneity, and social withdrawal)[10] in defining remission of negative symptoms as the HEN scale provides a more comprehensive evaluation of the negative symptom construct including the avolition subdomain,[39] which is otherwise not incorporated in the PANSS selected items. Patients were classified as achieving symptomatic remission if they obtained a rating of ≤ 3 on each of the following PANSS items indicating psychoticism and disorganization dimensions[10]—P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), G5 (mannerisms/posturing), and G9 (unusual thought content)—and if they obtained a global rating of ≤ 2 (mild or less) on each of the 4 HEN subscales for negative symptoms. Sustained symptomatic remission attained at the end of 3-year follow-up was defined as simultaneous fulfillment of the following criteria: (1) achieving symptomatic remission at 24 and 36 months, and (2) no psychiatric admission in the last 12 months of the study period.

Statistical Analysis

Differences between patients who achieved sustained symptomatic remission (remission group) and those who did not (nonremission group) in sociodemographics, premorbid adjustment, treatment characteristics, and baseline and 1-year clinical parameters were examined using χ^2 test and an independent *t* test as appropriate. Baseline and 1-year cognitive profiles between remission and nonremission groups were compared using multivariate analysis of variance followed by univariate analyses of variance for individual cognitive domains, with Bonferroni correction performed (adjusted $P < .01$) due to multiple comparisons. Those premorbid, baseline, and 1-year variables that were found to be significantly different between the 2 groups were then entered into binary logistic regression analysis (backward logistic regression model) to determine which factors independently predicted sustained symptomatic remission at the end of 3-year follow-up. Change in −2 log likelihood for each significant variable included in the final model was also examined. We also assessed group differences in cognitive, global functional, and vocational outcomes at 3 years. Duration of untreated psychosis was log-transformed due to its skewed distribution, and standardized *z* scores for cognitive functions were computed for analyses on the basis of performance of healthy controls, with a mean score of 0 and a standard deviation of 1. The level of statistical significance for all analyses was set at $P < .05$.

RESULTS

Characteristics of the Sample

Of the 93 subjects who were followed up for 3 years, 1 did not complete assessment at 24 months. The final sample of the study thus comprised 92 subjects who were predominantly single (73.9%); 45.7% were male. The mean (SD) age of the sample at intake was 31.2 (9.7) years (range, 18–55 years), and the mean (SD) educational level was 10.6 (2.9) years. The median duration of untreated psychosis for the sample was 180 days (mean [SD] = 466.2 [788.1] days). Diagnoses for the cohort were schizophrenia (n = 74), schizophreniform disorder (n = 13), and schizoaffective disorder (n = 5). Patients performed significantly worse than healthy controls on all cognitive tests, with a range from 0.4 (forward digit span) to 1.0 (logical memory) standard deviations below that of controls, with the exception of the visual reproduction test, which yielded no significant differences between the 2 groups.

Comparison Between Remission and Nonremission Groups in Baseline and 1-Year Characteristics

By the end of the 3-year follow-up, 44.6% of the cohort (n = 41) met the criteria for sustained symptomatic remission. As shown in Table 1, there were no significant differences between remission and nonremission groups with respect to demographics, duration of untreated psychosis, and psychopathological ratings at initial presentation. The 2 groups also did not differ in symptom severity, cognitive performance, global functioning, and treatment characteristics at clinical stabilization. Nonetheless, patients who failed to achieve remission were significantly more likely to be unemployed at intake and to have had poorer premorbid adjustment. At 12 months, patients in the remission group had significantly fewer positive and negative symptoms than patients in the nonremission group. Multivariate analysis of variance revealed significant difference between the 2 groups in cognitive functions (Wilks $\lambda = 0.90$, $F_{5,85} = 1.84$, $P < .05$), with subsequent univariate analysis showing that remitted patients exhibited better 1-year logical memory function than nonremitted counterparts ($F_{1,89} = 6.4$, $P < .01$). Remitted patients received a lower chlorpromazine-equivalent dose[45,46] of antipsychotic medications than nonremitters. No significant differences were observed between the 2 groups in treatment adherence and the use of second-generation antipsychotics (Table 2).

Comparison Between Remission and Nonremission Groups in 3-Year Outcomes

Differences between patients who achieved sustained remission and those who did not in 3-year cognitive and functional outcomes are presented in Table 3. Compared with nonremitters, patients who met criteria for sustained remission had more favorable global functioning

Table 1. Demographics, Premorbid Adjustment, and Baseline Characteristics of Patients With and Without Sustained Symptomatic Remission at the End of 3-Year Follow-Up

Variable	Remission Group (n = 41)	Nonremission Group (n = 51)	Statistic[a]	*df*	*P* Value
Sociodemographics					
Age at entry,[b] mean (SD), y	31.2 (9.9)	31.2 (9.5)	−0.01	90	.99
Male sex, n (%)	18 (43.9)	24 (47.1)	0.1		.76
Years of education, mean (SD)	11.2 (3.0)	10.1 (2.7)	1.7	90	.09
Unemployed, n (%)	14 (34.1)	29 (56.9)	4.7		.03
Premorbid adjustment					
Premorbid Adjustment Scale total score, mean (SD)	0.3 (0.1)	0.4 (0.1)	−3.1	85	< .01
Baseline clinical characteristics					
Onset within 4 weeks, n (%)	22 (53.7)	20 (40.8)	1.5		.22
Log duration of untreated psychosis, mean (SD)	4.6 (1.9)	5.2 (1.6)	−1.7	81	.10
Symptom severity					
Positive symptom[c] score at intake, mean (SD)	19.9 (6.4)	19.7 (4.7)	0.2	90	.84
Negative symptom[d] score at intake, mean (SD)	13.6 (11.9)	13.6 (11.2)	0.003	90	.99
Positive symptom[c] score at clinical stabilization, mean (SD)	9.3 (2.7)	9.3 (1.8)	0.03	90	.98
Negative symptom[d] score at clinical stabilization, mean (SD)	10.6 (8.8)	11.7 (10.5)	−0.5	90	.61
Cognitive functions[e] at clinical stabilization					
WAIS-R-HK information subscale, mean (SD)	−0.44 (1.2)	−0.64 (1.1)	0.5	89	.43
Logical memory, mean (SD)	−0.78 (0.82)	−0.90 (0.92)	0.8	88	.51
Visual reproduction, mean (SD)	0.04 (0.81)	−0.30 (1.04)	2.4	88	.10
Forward digit span, mean (SD)	−0.21 (0.80)	−0.48 (1.34)	1.4	89	.25
Category verbal fluency, mean (SD)	−0.44 (0.79)	−0.55 (0.82)	0.4	89	.51
MWCST perseverative error,[f] mean (SD)	−0.37 (1.81)	−1.09 (2.67)	1.8	89	.14
Global functioning at clinical stabilization					
WHO/DAS total score, mean (SD)	2.3 (3.9)	2.1 (5.0)	0.2	89	.87
Treatment characteristics at clinical stabilization					
Chlorpromazine-equivalent dose,[45,46] mean (SD), mg/d	349.8 (390.0)	343.7 (344.6)	0.8	90	.94
Taking second-generation antipsychotic medication,[g] n (%)	1 (2.4)	1 (2.0)	0.024		.90
Duration from entry to clinical stabilization,[h] mean (SD), d	43.2 (28.2)	45.5 (43.2)	−2.9	90	.77

[a]Statistical analysis: χ^2 test was applied for categorical variables; independent *t* test was applied for continuous variables, except for cognitive functions, which were analyzed using multivariate analysis of variance followed by univariate analysis of variance (*F*) for individual cognitive tests, with Bonferroni-adjusted α level of .01.
[b]The age ranges of remission and nonremission groups at entry were 16–53 years and 19–55 years, respectively.
[c]Positive symptoms were measured using the positive symptoms subscale of the Positive and Negative Syndrome Scale.
[d]Negative symptoms were measured using the total score of the High Royds Evaluation of Negativity scale, excluding the appearance and thought subscales.
[e]Standardized *z* scores (mean = 0, SD = 1) were computed for cognitive tests on the basis of performance of healthy controls.
[f]MWCST perseverative error *z* score was multiplied by −1 so that a higher score indicated better performance (ie, less errors).
[g]Fisher exact test was applied as the assumption of χ^2 test was not met.
[h]Range of duration from entry to clinical stabilization: remission group (14–117 days); nonremission group (14–180 days).
Abbreviations: MWCST = Modified Wisconsin Card Sorting Test, SD = standard deviation, WAIS-R-HK = Wechsler Adult Intelligence Scale-Revised (Cantonese version, Hong Kong), WHO/DAS = World Health Organization Psychiatric Disability Assessment Schedule.

and higher likelihood of maintaining full-time employment. Multivariate analysis of variance showed that the 2 groups differed in cognitive profiles (Wilks $\lambda = 0.91$, $F_{5,85} = 1.61$, $P < .05$). Univariate analysis found that remitted patients scored significantly higher on the logical memory test than nonremitted patients ($F_{1,89} = 4.6$, $P < .01$). There were no significant differences between the 2 groups in treatment characteristics.

In an attempt to further examine any difference between remission and nonremission groups in longitudinal change of logical memory function over 3 years, a repeated-measures analysis of variance was conducted with remission groups as between-subject factor and time points as within-subject levels. The group × time interaction was significant (Greenhouse-Geisser correction was made as sphericity assumption was not met: $F_{2.7,228.5} = 3.4$, $P < .05$), with the within-subject contrast test showing a significant change lying between clinical stabilization and 12 months after intake ($F_{1,86} = 7.4$, $P < .01$). The results thus showed that remitted patients exhibited improved logical memory function from clinical stabilization to 12 months after entry, while nonremitted patients showed declined performance on logical memory tests within the same period. There was no significant main between-subject effect of remission status on logical memory function.

Predictors of Sustained Symptomatic Remission

We employed binary logistic regression analysis to identify variables obtained at baseline and 1-year assessments that predicted sustained remission at the end of 3-year follow-up. Those variables that were found to be significantly associated with remission status, namely premorbid adjustment, occupational status at entry, severity of positive and negative symptoms at 12 months, and logical memory function at 12 months were included in the regression model. Analysis revealed that premorbid functioning,

Table 2. Differences Between the Sustained Symptomatic Remission Group and Nonremission Group in Symptom Severity, Cognitive Performance, Functioning, and Treatment Characteristics at 1-Year Follow-Up

Variable	Remission Group (n = 41)	Nonremission Group (n = 51)	Statistic[a]	*df*	*P* Value
Symptom severity at 12 months					
PANSS positive symptom score, mean (SD)	8.1 (2.4)	10.2 (4.1)	−2.9	89	< .01
HEN total score, mean (SD)	6.7 (7.6)	16.2 (10.8)	−4.7	89	< .01
Cognitive functions[b] at 12 months					
Logical memory, mean (SD)	−0.55 (0.81)	−0.98 (0.80)	6.4	89	< .01
Visual reproduction, mean (SD)	−0.05 (0.90)	−0.21 (0.96)	0.6	89	.44
Forward digit span, mean (SD)	0.23 (0.73)	−0.18 (1.22)	3.4	89	.07
Category verbal fluency, mean (SD)	−0.11 (0.88)	−0.37 (0.79)	0.4	89	.53
MWCST perseverative error,[c] mean (SD)	0.54 (0.61)	0.09 (1.30)	4.1	89	.04
Global functioning at 12 months					
WHO/DAS total score, mean (SD)	2.5 (3.7)	4.4 (6.6)	−1.6	87	.09
Treatment characteristics at 12 months					
Good treatment adherence,[d] n (%)	35 (85.4)	36 (70.6)	2.3		.13
Chlorpromazine-equivalent dose,[45,46] mean (SD), mg/d	195.6 (170.3)	360.8 (422.4)	−2.3	89	.01
Taking second-generation antipsychotic medication,[e] n (%)	3 (7.3)	5 (9.8)	0.15		.70

[a]Statistical analysis: χ^2 test was applied for categorical variables; independent *t* test was applied for continuous variables, except for cognitive functions, which were analyzed using multivariate analysis of variance followed by univariate analysis of variance (*F*) for individual cognitive tests, with Bonferroni-adjusted α level of .01.
[b]Standardized *z* scores (mean = 0, SD = 1) were computed for cognitive tests on the basis of performance of healthy controls.
[c]MWCST perseverative error *z* score was multiplied by −1 so that a higher score indicated better performance (ie, less errors).
[d]Subjects were considered as having good treatment adherence if they took more than 70% of prescribed medications (assessed on the basis of reports from both subjects and their relatives[47]).
[e]Fisher exact test was applied as the assumption of χ^2 test was not met.
Abbreviations: HEN = High Royds Evaluation of Negativity scale, MWCST = Modified Wisconsin Card Sorting Test, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation, WHO/DAS = World Health Organization Psychiatric Disability Assessment Schedule.

Table 3. Differences Between the Sustained Symptomatic Remission Group and Nonremission Group in Cognitive, Functional, and Vocational Outcomes and Treatment Characteristics at the End of 3-Year Follow-Up

Variable	Remission Group (n = 41)	Nonremission Group (n = 51)	Statistic[a]	*df*	*P* Value
Cognitive functions[b] at 36 months					
Logical memory, mean (SD)	−0.33 (0.88)	−0.72 (0.83)	4.6	89	< .01
Visual reproduction, mean (SD)	0.35 (0.67)	−0.02 (1.02)	4.0	89	.049
Forward digit span, mean (SD)	0.07 (0.83)	−0.26 (1.17)	2.2	89	.14
Category verbal fluency, mean (SD)	−0.27 (0.93)	−0.35 (0.91)	0.2	89	.68
MWCST perseverative error,[c] mean (SD)	0.76 (0.51)	0.29 (1.43)	3.8	89	.04
Global functioning at 36 months					
WHO/DAS total score, mean (SD)	2.6 (3.3)	5.6 (7.3)	−2.4	87	.018
Vocational outcome					
Full-time work > 6 months in year 3, n (%)	26 (63.4)	10 (19.6)	18.3		< .01
Full-time work in year 3, mean (SD), mo	7.5 (5.4)	2.5 (4.4)	4.8	90	< .01
Treatment characteristics at 36 months					
Good treatment adherence,[d] n (%)	34 (82.9)	40 (78.4)	1.5		.23
Chlorpromazine-equivalent dose,[45,46] mean (SD), mg/d	185.2 (186.6)	274.8 (364.3)	−1.4	90	.13
Taking second-generation antipsychotic medication, n (%)	6 (14.6)	12 (23.5)	1.1		.29

[a]Statistical analysis: χ^2 test was applied for categorical variables; independent *t* test was applied for continuous variables, except for cognitive functions, which were analyzed using multivariate analysis of variance followed by univariate analysis of variance (*F*) for individual cognitive tests, with Bonferroni-adjusted α level of .01.
[b]Standardized *z* scores (mean = 0, SD = 1) were computed for cognitive tests on the basis of performance of healthy controls.
[c]MWCST perseverative error *z* score was multiplied by −1 so that a higher score indicated better performance (ie, less errors).
[d]Subjects were considered as having good treatment adherence if they took more than 70% of prescribed medications (assessed on the basis of reports from both subjects and their relatives[47]).
Abbreviations: MWCST = Modified Wisconsin Card Sorting Test, SD = standard deviation, WHO/DAS = World Health Organization Psychiatric Disability Assessment Schedule.

Table 4. Binary Logistic Regression Analysis for Predictors of Sustained Symptomatic Remission[a]

Variables in the Equation	B	SE	Wald	*df*	Significance, *P*	Exp(B)	95% CI	Change in −2 Log Likelihood	Significance of the Change, *P*
PAS total score	4.801	2.410	3.97	1	.046	121.69	1.082–13,689.567	4.336	.037
HEN total score at 12 months	0.108	0.032	11.77	1	.001	1.114	1.048–1.185	15.532	< .001
Logical memory at 12 months	−0.723	0.354	4.166	1	.041	0.486	0.243–0.972	4.502	.034
Constant	−2.983	0.948	9.896	1	.002	0.050			

Final model: Nagelkerke $R^2 = 0.425$, $\chi^2 = 32.65$, $P < .0001$
Hosmer and Lemeshow test supported the goodness of fit of the model ($\chi^2_8 = 4.755$, $P = .783$)

[a]PANSS positive symptom score at 12 months and baseline occupational status, which were entered in the stepwise logistic regression model, were excluded as predictors of remission after analysis.
Abbreviations: HEN = High Royds Evaluation of Negativity scale, PANSS = Positive and Negative Syndrome Scale, PAS = Premorbid Adjustment Scale, SE = standard error.

negative symptom severity, and logical memory function at 12 months independently predicted sustained remission (Table 4). Results also showed that negative symptom level at 12 months was found to contribute the largest share to the explained variance of the final model. Overall, 74.4% of the patients were predicted correctly with the model (66.7% and 80.0% for remission and nonremission groups, respectively), which accounted for 42.5% of the variance.

DISCUSSION

Consistent with the literature,[12,48,49] our results demonstrated that remitted patients had better functional and vocational outcomes cross-sectionally than those who failed to achieve remission. Contrary to those studies that revealed either lack of relationship between cognition and remission status[20–25] or significant association of symptomatic remission with generalized cognitive dysfunction,[14,15,26] we found that patients in remission exhibited better concurrent verbal memory, visual memory, and executive function (although results for executive function and visual memory became nonsignificant when Bonferroni correction was applied) than nonremitted counterparts. Thus, our findings concurred with a number of previous studies[16–19] that showed that symptomatic remission may be more related to specific cognitive domains, particularly verbal memory.[16]

We replicated findings of earlier reports indicating that better premorbid adjustment predicted symptomatic remission.[50,51] Our results that negative symptom severity contributed a significant proportion to the explained variance of remission attainment at follow-up were also in agreement with several past studies,[12,50,51] thereby highlighting the significance of negative symptoms as a potential rate-limiting factor for clinical remission.[13] Conflicting findings were noted in the literature regarding the role of cognitive functioning in predicting symptomatic remission in schizophrenia. Some researchers[21,28] observed no significant association between cognitive functioning and the likelihood of achieving remission, while others[26] revealed that better generalized cognitive ability predicted remission at follow-up. Our results, on the other hand, were in accord with 1 recent study that suggested that verbal memory impairment might be a cognitive predictor of symptomatic remission.[27,52]

It should, however, be noted that, thus far, very few studies have been conducted to investigate the relationship between cognition and symptomatic remission in schizophrenia, and the majority were cross-sectional in design. To date, only 4 published studies[21,26–28] have prospectively examined the capacity of cognitive impairment to predict remission. Inconsistent findings were noted, and methodological variations across studies might be an important contributing factor. First of all, operational criteria that were adopted in defining symptomatic remission varied among studies. The majority of studies applied only a symptom-severity criterion without taking into consideration the duration component, which is nonetheless regarded as a key element in conceptualizing remission.[10] In fact, it has been proposed that meeting a symptom-severity criterion only should be reported as symptom resolution or cross-sectional remission, which should be differentiated from symptomatic remission that requires simultaneous fulfillment of both symptom-severity and time criteria.[53] Another possible reason for such discrepancy was differences in choice of cognitive measurement employed, such as a battery of cognitive tests, the Mini-Mental State Examination, or clinical rating instruments. Further, the use of a single composite score to represent patients' general cognitive functioning in some studies may obscure potentially significant associations of remission status with individual cognitive domains.[21,22] In addition, the varying lengths of follow-up, ranging from 6 months to 5 years[21,26–29] among those few prospective studies, may also contribute to the mixed results in longitudinal relationship between cognition and symptomatic remission in schizophrenia.

In fact, our findings that verbal memory, which is one of the most consistent and severe cognitive dysfunctions in schizophrenia,[2,3,54] predicted symptomatic remission add to the growing evidence relating memory impairment to poor clinical outcome. Studies demonstrated that verbal memory deficits were associated with greater symptom severity,[7,9,55] treatment resistance,[56] and an elevated risk of rehospitalization.[7] Recent imaging studies further revealed that nonremitted patients displayed significantly smaller volume in the posterior hippocampus and parahippocampus, the brain regions that are critically involved in the memory system,[57] when compared to those who achieved remission,[52,58] with such cortical volume reductions being found to be positively correlated with verbal memory performance.[52] Taken together, neuroanatomical and

behavioral data provide supportive evidence linking verbal memory impairment to worse symptomatic outcome in schizophrenia.

Several methodological limitations warrant consideration in interpreting the study results. First, we applied modified RSWG remission criteria by using the HEN instead of the PANSS to measure and define the severity threshold for remission of negative symptoms, and, thus, the comparability of our results with other studies may be compromised. However, this possibility is unlikely as the HEN comprises subscales that are similar, in terms of negative symptom construct evaluated, to the 3 selected items of the PANSS.[10] Additionally, we opted for the HEN as it may confer an advantage by incorporating the avolition subdomain, which is not included in the PANSS items selected for operationalizing negative symptom remission.[10] Second, it should be noted that we focused on symptomatic remission sustained for a period longer than that required by the RSWG criteria as we did not evaluate patients at a 6-month interval.[10] As well, fulfillment of a 12-month duration criterion of symptomatic remission was based on psychopathological assessments conducted at 2 time points only (ie, at 24 and 36 months of follow-up). The relative infrequency of symptom evaluations may have failed to capture those subjects who shifted out of and subsequently returned to remission within a 12-month interval and, hence, may have lead to biased estimates of remission rate. Third, our final sample comprised slightly more women than men, which was contrary to many,[59] but not all,[51,60] first-episode studies that showed male preponderance, and thus may limit generalizability of our results. The relatively older mean age of our cohort (our study adopted as an inclusion criterion a wider age range than the majority of first-episode studies) may also render our findings less comparable to the literature of first-episode research as there may be significant variations in illness impacts on clinical and cognitive outcomes between patients with a more typical age at onset (ie, late adolescence or early adulthood) and those whose psychosis manifests in later years. Fourth, healthy controls were assessed once at baseline without being followed up in parallel with schizophrenia patients for 3 years; therefore, the magnitude of practice effect on trajectories of cognitive functions could not be addressed in this study. Fifth, the number of subjects included in this study was modest, and the dropout rate of 29% may compromise the validity of our results. The potential attrition bias may partly be minimized by the lack of significant differences between completers and noncompleters with regard to sociodemographics, psychopathological scores, and cognitive functions at baseline. Our dropout rate was also comparable to that of several previous longitudinal first-episode studies (approximately 25%–35% within a 1-year to 4-year follow-up).[61–63] Nonetheless, replication by further studies with a large sample size is warranted to confirm our findings of an independent contribution of verbal memory impairment to symptomatic remission.

In conclusion, our results indicated that cognitive function, particularly verbal memory impairment, was associated with symptomatic remission in the early phase of schizophrenia. Owing to limited data on the longitudinal relationship between cognitive dysfunction and the likelihood of remission attainment, more prospective research with longer follow-up duration should be conducted to clarify whether deficits in verbal memory specifically predict occurrence of symptomatic remission. In addition, the possibility that early rehabilitative interventions such as aerobic exercise[64] and cognitive remediation[65] may offer neuroprotective effects resulting in enhancement of memory functions in schizophrenia patients with consequent improved symptomatic outcome deserves further investigation.

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