Seven-year functional outcomes and influencing factors in patients with first-episode depressive disorder: postprint

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Abstract

Background Depression is associated with a high disability rate and is projected to become the leading cause of disability worldwide by 2030. Even after clinical symptom remission following treatment, patients with depression commonly experience persistent functional impairment. At present, there is a lack of domestic research on long-term functional outcomes and their influencing factors in first-episode depressive patients. Objective To investigate the overall functional outcome 7 years after first-episode depressive disorder and to explore the factors associated with unfavorable functional outcomes. Methods Outpatients and inpatients (n=346) treated at Hebei Mental Health Center from May 2013 to May 2016 were enrolled. All patients met the following criteria: a 17-item Hamilton Depression Rating Scale (HAMD-17) total score $ $18, age 18–60 years, and a diagnosis of single-episode major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Through naturalistic follow-up, demographic data, clinical characteristics, and treatment information were collected. At the 7-year follow-up, the Treatment Emergent Symptom Scale (TESS), the Medication Adherence Rating Scale (MARS), and the Global Assessment of Functioning (GAF) were used to assess current adverse drug reactions, adherence to pharmacological treatment, and overall functional level, respectively. Patients in remission at 7 years were grouped according to their GAF scores: GAF >70 constituted the good overall functioning group, and GAF $ $70 constituted the poor overall functioning group. Multivariate logistic regression analysis was used to identify factors associated with unfavorable functional outcomes. Results A total of 138 patients completed the 7-year follow-up, of whom 127 were in remission. Among these, 46 (36.2%) were in the good overall functioning group and 81 (63.8%) in the poor overall functioning group. At baseline, there were statistically significant differences between

the poor and good functioning groups in terms of occupational type and educational level (P<0.05). During the 7-year period, the poor functioning group had a higher total number of episodes, a higher proportion of episodes with psychotic symptoms, and higher TESS scores at the 7-year follow-up than the good functioning group (P<0.05). Multivariate logistic regression analysis showed that a greater total number of episodes over 7 years (OR=1.509, 95%CI=1.083-2.102) and higher TESS scores at 7 years (OR=1.067, 95%CI=1.002-1.136) were risk factors for poor overall functional outcome at 7 years (P<0.05), whereas higher educational level at baseline (OR=0.486, 95%CI=0.268-0.878) was a protective factor (P<0.05). Conclusion Among patients with first-episode depressive disorder, 63.8% had poor overall functioning 7 years later. More frequent relapses and greater adverse drug reactions increase the risk of unfavorable outcomes, whereas patients with higher educational levels tend to have relatively better functional outcomes after 7 years.

Full Text

Functional Outcomes and Influencing Factors in Patients with First-episode Major Depressive Disorder after 7 Years

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Abstract

Background: Depression has a high disability rate and is projected to become the leading cause of disability worldwide by 2030. Real-world evidence indicates that even after systematic treatment and clinical symptom remission, functional impairment often persists among depression patients. However, there is a lack of research on long-term functional outcomes and influencing factors in first-episode depression patients in China.

Objective: To investigate the overall functional outcome of patients with first-episode depressive disorder after 7 years and to analyse the influencing factors of adverse functional outcome.

Methods: A total of 346 patients were enrolled from outpatient and inpatient settings at the Hebei Mental Health Center between May 2013 and May 2016. Eligible participants met the following criteria: Hamilton Depression Scale-17 (HAMD-17) score $\geq$ 18, aged 18~60 years, who met the diagnostic criteria for single episode of major depressive disorder in the Diagnostic and Statistical

Manual of Mental Disorders, Fourth Edition (DSM-IV). Through naturalistic observational follow-up, demographic characteristics, disease features, and treatment details were collected. At the 7-year follow-up, the Treatment Emergent Symptom Scale (TESS) was used to assess adverse drug reactions, the Medication Adherence Rating Scale (MARS) evaluated treatment adherence, and the Global Assessment of Functioning (GAF) measured overall functional level. Patients in remission at the 7-year follow-up were divided into two groups based on GAF scores: the good functional outcome group (GAF>70) and the poor functional outcome group (GAF $\leq$ 70). Multivariate Logistic regression analysis was performed to identify factors associated with poor functional outcomes.

Results: A total of 138 cases completed the 7-year follow-up, including 127 cases in remission stage. The good overall function group comprised 46 cases (36.2%). The poor overall function group comprised 81 cases (63.8%). At the initial onset, there were significant differences between the overall poor-function group and the good-function group in terms of occupation and educational level (P<0.05). The total number of episodes during the 7-year period in the group with overall poor function, the proportion of episodes with psychotic symptoms, and the TESS total score at follow-up after 7 years were higher than those in the group with good function (P<0.05). The multivariate Logistic regression analysis results showed that a higher total number of episodes over 7 years (OR=1.509, 95%CI=1.083-2.102) and a higher TESS total score at 7-year follow-up (OR=1.067, 95%CI=1.002-1.136) were risk factors for poor global functional outcomes in patients after 7 years, while a higher education level at first onset (OR=0.486, 95%CI=0.268-0.878) served as a protective factor (P<0.05).

Conclusion: Among patients with first-episode depressive disorder, 63.8% had poor global functioning after 7 years. A higher number of relapses and more severe medication side effects increased the risk of adverse outcomes, while patients with higher education levels had relatively better functional outcomes at the 7-year follow-up.

Key words: Depressive disorder; First episode; Prospective study; Global functional outcome; Root cause analysis

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Introduction

According to the WHO Global Burden of Disease Study, depression accounts for 10% of disability caused by non-communicable diseases and is projected to become the leading cause of disability worldwide by 2030, surpassing all cardiovascular diseases combined. Therefore, depression recovery should focus not only on symptom remission but also on functional restoration. Real-world studies have found that after systematic treatment, while clinical symptoms may disappear, many patients fail to restore social functioning and cannot fulfill their pre-morbid social roles. Whether this is due to disease factors or adverse drug reactions remains to be further investigated. Most domestic studies on func-

tional outcomes in first-episode depression patients are based on retrospective analysis or short-term follow-up, with a lack of long-term longitudinal research. Based on these research questions and current status, this study was conducted to follow first-episode depression patients for 7 years, understand their disease characteristics and treatment status over this period, assess their functional outcomes after 7 years, and analyze the influencing factors of functional outcomes to provide reference for early intervention and improved functional prognosis.

Methods

1.1 Study Participants

A single-center consecutive sampling method was used to enroll outpatients and inpatients from the Hebei Provincial Mental Health Center between May 2013 and May 2016. Inclusion criteria were: (1) aged 18-60 years; (2) meeting diagnostic criteria for a single episode of major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); (3) Hamilton Depression Scale-17 (HAMD-17) score $\geq$ 18. Exclusion criteria were: (1) severe physical illness, dementia, mental retardation, epilepsy, alcohol or drug dependence/abuse; (2) pregnant or lactating women. This study was approved by the Ethics Committee of Hebei Provincial Mental Health Center [Approval No.: 冀精伦审（科）202117 号], and all enrolled patients or their guardians provided written informed consent.

1.2 Diagnostic and Data Collection Methods

1.2.1 Diagnostic Method Patients initially screened as having a single episode of major depressive disorder in outpatient and inpatient settings were diagnosed by attending psychiatrists or higher-level physicians who had received training in the Structured Clinical Interview for DSM-IV Axis I Disorders Patient Edition (SCID-I/P) diagnostic tool and passed consistency tests. SCID-I/P was used to confirm diagnosis through structured interviews.

1.2.2 Baseline Data Collection The baseline information collection questionnaire was designed by psychiatrists in our research team who were trained and familiar with the study protocol. Contents included: (1) demographic information such as gender, age, occupation type, marital status, education level, and BMI. Occupation was categorized by income stability into stable types (workers, service personnel, professional technicians, administrative staff, military personnel, etc.) and unstable types (farmers, self-employed, temporary workers, unemployed, etc.). (2) Disease characteristics such as positive family history of mental illness, precipitating factors, suicidal behavior, and psychotic symptoms. (3) Treatment status such as duration of untreated psychosis (DUP), acute phase treatment duration, and whether maintenance treatment was received. (4) HAMD-17, administered by psychiatrists trained in the scale and who passed consistency tests (intraclass correlation coefficient, ICC=0.89).

HAMD-17 contains 17 items, generally assessing the previous week, with most items using a 0-4 five-point scoring system and a few using a 0-2 three-point system. The score can well reflect disease severity, with >17 points indicating moderate to severe depression. The scale has good reliability and validity and is often used as a parallel validity check tool for new depression scales.

1.2.3 Follow-up Methods and Content Through naturalistic observational follow-up, research physicians completed questionnaires based on patients' outpatient and inpatient medical records, face-to-face or telephone interviews with patients or informants, and scale raters completed scale assessments (all ICC > 0.80). Follow-up contents included: (1) demographic information at follow-up such as occupation, marital status, education level, and BMI; (2) longitudinal disease characteristics such as number of recurrences, clinical features of recurrences, switching status, number of hospitalizations, and comorbid features; (3) at the 7-year follow-up, the Treatment Emergent Symptom Scale (TESS) was used to assess adverse drug reactions. TESS contains 33 symptom items and 3 supplementary items, all using a 0-3 four-point scoring system. Among various scales for assessing adverse events in psychiatric treatment, TESS is relatively detailed and practical, and is frequently used in clinical drug trials; (4) the Medication Adherence Rating Scale (MARS) was used to assess medication adherence. MARS is a widely used adherence measurement method with good reliability and validity for measuring medication adherence in psychiatric patients, providing important information about medication adherence. It contains 10 items, with items 7 and 8 scoring 1 point for "yes" responses and all other items scoring 1 point for "no" responses. Higher scores indicate better adherence, with scores <6 considered low adherence; (5) the Global Assessment of Functioning (GAF) was used to assess overall functional level. GAF evaluates psychological, social, and occupational functioning at the highest level in the current or past year. It contains a single item with a score range of 0-100, with each 10 points representing a level, for a total of 10 levels. Higher scores indicate better functioning. The 71-80 level and above indicates no symptoms or only mild, transient symptoms that are normal reactions to psychosocial stressors, with excellent functioning in all areas or only mild impairment; the 60-70 level and below indicates mild or greater symptoms or some difficulty in one or more areas of functioning. This scale does not have a clearly defined cutoff value, but most existing studies use 70 points as the threshold for good versus poor functioning.

1.2.4 Grouping Method Based on GAF scores, patients were divided into two groups: the good overall functioning group (GAF > 70) and the poor overall functioning group (GAF ≤ 70).

1.3 Statistical Methods

SPSS 26.0 statistical software was used for data analysis. Categorical data were expressed as relative numbers and compared between groups using the χ^2 test. Normally distributed continuous data were expressed as ($\bar{x}\pm s$) and compared using independent samples t-test. Non-normally distributed continuous data were expressed as M(P25, P75) and compared using the Kruskal-Wallis H test. Since each patient had a different total number of episodes during the 7-year period, for comparability, the ratio of episodes with different characteristics to total episodes was used for analysis. Multivariate Logistic regression analysis was used to analyze influencing factors of poor overall functional outcomes in first-episode depression patients after 7 years. Variable selection used the enter method, the Hosmer-Lemeshow test was used to assess model fit, and variance inflation factor was used to detect multicollinearity among independent variables. All tests were two-sided with significance level α=0.05.

Results

2.1 Follow-up Results

Among 346 patients enrolled at baseline, 86 withdrew and 122 were lost to follow-up, leaving 138 patients who completed the 7-year follow-up, for a completion rate of 39.9%. Among these, 47 were male (34.1%) and 91 were female (65.9%), with first-episode age ranging from 18-59 years. At the 7-year follow-up, 127 patients (127/138, 92.0%) were in remission stage, including 46 cases (36.2%) in the good overall functioning group and 81 cases (63.8%) in the poor overall functioning group.

2.2 Comparison of Baseline Clinical Data Between Poor and Good Functioning Groups

At initial onset, there were statistically significant differences between the poor and good overall functioning groups in occupation type and education level (P<0.05). No statistically significant differences were found in gender, age, marital status, BMI, positive family history of mental illness, precipitating factors, suicidal behavior, psychotic symptoms, HAMD-17 score, DUP duration, acute phase treatment duration, or receipt of maintenance treatment (P>0.05), see .

2.3 Comparison of Disease Characteristics and Treatment Status Between Groups During the 7-Year Period

The poor overall functioning group had higher total number of episodes during the 7-year period, higher proportion of episodes with psychotic symptoms, and higher TESS scores at 7-year follow-up compared to the good functioning group, with statistically significant differences (P<0.05). No statistically significant differences were found between the two groups in the proportion of manic episodes, depressive episodes, switching episodes, hospitalization frequency, or

the proportion of patients with MARS scores $ $6 at 7-year follow-up (P>0.05), see .

2.4 Influencing Factors of Poor Overall Functional Outcomes After 7 Years

Using 7-year overall functional outcome as the dependent variable (assignment: good overall functioning group=0, poor overall functioning group=1) and variables with statistically significant differences in Tables 1 and 2 as independent variables [assignment: occupation at first onset, stable type=0, unstable type=1; education level at first onset as an ordinal categorical variable, primary school and below=1, junior high school=2, high school/technical secondary school=3, college and above=4; total number of episodes during 7 years, proportion of episodes with psychotic symptoms during 7 years, and TESS score at 7-year follow-up included as actual values], multivariate Logistic regression analysis was performed. Results showed that education level at first onset (OR=0.486, 95%CI=0.268-0.878), total number of episodes during 7 years (OR=1.509, 95%CI=1.083-2.102), and TESS score at 7-year follow-up (OR=1.067, 95%CI=1.002-1.136) were influencing factors of patients' overall functional outcomes after 7 years (P<0.05). The Hosmer-Lemeshow test result was χ^2=2.866, P=0.942, indicating good model fit, see .

Discussion

Depressive disorder is often considered to have an episodic course, but clinical observation reveals that even after antidepressant treatment and remission, patients still experience significant functional limitations, including impairments in work efficiency and social role functioning. This 7-year follow-up study of first-episode depression patients found that among those in remission at year 7, approximately 63.8% had poor overall functioning. A prospective 5-year follow-up study of depressive disorder patients reported similar data, with 54.1% experiencing functional impairment. A cross-sectional survey of 1,503 depressive disorder patients found 39.1% had social dysfunction. Our higher rate may be related to different methods and assessment tools: that study was cross-sectional using the self-rated Sheehan Disability Scale (SDS), while ours was a prospective long-term follow-up using the clinician-rated GAF scale.

Regarding age of onset and functional prognosis, one 12-week follow-up study of antidepressant-responsive depression patients found that early onset was an independent risk factor for poor functioning in adult first-episode patients. A 6-month follow-up of post-acute treatment patients found those aged <45 had more residual symptoms and more severe social functional impairment. Our study found no significant difference in age at first onset between the poor and good functioning groups after 7 years, possibly due to the longer follow-up duration. The aforementioned studies had short follow-ups, while our 7-year longitudinal study allowed more factors to influence functional outcomes.

Additionally, our study only included adult patients, which may have weakened age' s influence.

Our baseline occupation classification by income stability showed differences between groups, with the poor functioning group having a higher proportion of unstable occupations at first onset. A large Korean cohort study of 11,555 subjects from 2009-2022 found that employment instability, insufficient income, and lack of labor protection were associated with depressive episodes. Multiple studies have confirmed that unstable employment negatively impacts mental health, increasing risks of depression, anxiety, and suicidal ideation. However, occupation was not identified as an independent influencing factor in our study, possibly because its effect on 7-year functional outcomes involves many confounding factors that may be masked by stronger predictive variables, or its effect may be indirect rather than independently associated. UTZET et al. also noted that research on employment precariousness and mental health needs to integrate multiple individual and contextual variables.

Our study found baseline education level differed between groups, and Logistic regression analysis identified education level as a protective factor for poor overall functional outcomes after 7 years, suggesting that higher education was associated with better functional outcomes. A 5-year follow-up study of depression patients found similar results, with higher education being a major protective factor for cognitive ability in remitted patients and associated with better quality of life. ZHU et al. also proposed that education represents a certain level of intelligence that can partially offset functional impairment in depression patients. CAMBRIDGE et al. and KNIGHT et al. emphasized that cognitive function is closely related to long-term functional prognosis in depression patients, and that management strategies should consider improving patients' education levels and cognitive function.

Research on the relationship between disease episodes and long-term functional outcomes has relatively consistent conclusions. ZU et al. found that recurrent episodes increased functional impairment in depression patients. THAPAR et al. proposed that poor outcomes in depression patients were related to recurrence frequency. Our study similarly found that the poor functioning group had more disease recurrences during the 7-year period, and that recurrence frequency was an independent risk factor for poor functional outcomes after 7 years.

Over 25% of depression patients experience episodes with psychotic symptoms, which complicates the disease and further increases disease burden and risk of poor outcomes. In our study, 25.2% of patients had psychotic symptoms at first onset, and patients with a higher proportion of psychotic symptom episodes among total recurrences had poorer overall functioning after 7 years, supporting this view.

Existing research conclusions on functional outcomes in unipolar versus bipolar depression are inconsistent. FAVALE et al. and BARYSHNIKOV et al. proposed that bipolar depression shows more severe social functional impairment than

unipolar depression, while SCHWARZ et al. found no difference in functioning during remission between bipolar and unipolar depression. Our study found no difference between groups in the proportion of patients who switched from unipolar to bipolar disorder after experiencing manic or hypomanic episodes during the 7-year period, possibly due to small sample size and not incorporating switching time, severity, or bipolar subtypes into the analysis. Our team will conduct further analysis on disease and functional prognosis in switched versus non-switched first-episode depression patients.

The NICE guideline on Depression in Adults: Treatment and Management mentions that maintenance treatment can reduce relapse risk and functional impairment caused by recurrent episodes, but the potential risks of long-term medication should also be considered. It recommends fully discussing with patients to balance benefits and risks before determining long-term treatment plans. PASTUSZAK et al. also noted that any treatment must focus on promoting functional recovery, emphasizing that long-term maintenance treatment plans need optimization to promote overall functional recovery and improve quality of life. Our longitudinal investigation of medication status found no difference in medication adherence between groups, but differences in adverse drug reactions. The final results showed that adverse drug reactions were an independent influencing factor for poor overall functional outcomes after 7 years, increasing the risk of adverse outcomes. This suggests that clinicians should fully assess and dynamically monitor adverse drug reactions when developing long-term maintenance treatment plans, paying attention to their impact on functional recovery.

Study limitations include: (1) long follow-up duration with high dropout rate and inevitable attrition bias, so results can only represent patients with good follow-up compliance; (2) the study only grouped and discussed different functional outcomes after 7 years without comparing switching and different comorbid features. Future work plans include: (1) continuing to extend follow-up duration to understand more distant disease characteristics and functional outcomes in first-episode depression patients; (2) intervening on risk factors to explore effective measures for improving functional prognosis.

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Author Contributions

YU Chao was responsible for data collection, data collation, statistical analysis, manuscript drafting, and revision. SONG Lihua, WANG Linyan, and LU Yunping were responsible for data collection and collation. WANG Linyang was responsible for figure/table and reference editing and collation. CUI Wei was responsible for research conception and design, quality control and review, manuscript revision guidance, final version revision, and overall responsibility for the paper.

Conflict of Interest

The authors declare no conflict of interest.

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