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Anxious Depression in Major Depressive Disorder: Key Influences and Prevalence in Chinese Hospitalized Patients

Yali Zhu[1,*], Weijia Yin[2,*], Jun Ma[1], Lin Zhang[1]

[1]Department of Psychiatry, Wuhan Mental Health Center, Wuhan, People's Republic of China; [2]Department of Psychiatry, Suzhou Guangji Hospital, Suzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Lin Zhang, Department of Psychiatry, Wuhan Mental Health Center, No.89, Gongnongbing Road, Wuhan, Hubei, People's Republic of China, Email linzhang16@qq.com

Background: Anxious depression (AUD) is a common subtype of major depressive disorder (MDD) and has a significant negative impact on disease progression and patient prognosis. Our study aimed to determine the frequency of AUD in Chinese patients with MDD during their first hospitalization and to identify factors that may influence the emergence and intensity of these AUD.

Methods: This study enrolled 981 Chinese MDD patients on their inaugural hospital admission. Data on demographic details, clinical profiles, and psychological symptoms-such as depression, anxiety, psychosis, and illness severity scores-were gathered and examined.

Results: The study found that 10.30% of the target population exhibited AUD. Compared with the non-AUD group, the AUD group had higher scores on Hamilton Depression Scale (HAMD), Positive symptom subscale of the Positive and Negative Symptom Scale (PSS), and Clinical Global Impression Scale - Severity of Illness (CGI-SI) and higher levels of fasting blood glucose (FBG), total cholesterol (TC), body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP). In addition, higher scores of HAMD, PSS and CGI-SI were risk factors for increasing the severity of anxiety, higher TC level was contrary.

Conclusion: This study reveals the prevalence of AUD in hospitalized patients with MDD and identifies clinical factors that contribute to the onset and progression of AUD. Reporting these clinical features may help establish potential markers for early recognition and intervention.

Keywords: major depressive disorder, anxious depression, metabolic parameter, clinical characteristic

Introduction

Major depressive disorder (MDD) is a widespread mental health condition marked by enduring feelings of sadness, often coupled with physical symptoms such as weight changes and sleep issues, and potentially self-harm or suicidal thoughts.[1,2] It impacts a significant portion of the global population, with estimates exceeding 350 million individuals.[3] The disorder is multifaceted and debilitating, causing substantial societal and economic burdens, and its incidence appears to be on the rise.[4,5] The lifetime prevalence for MDD in the general population is reported to be 12.9%, with a 7.2% occurrence rate within a single year.[6] In China, the trend is similarly concerning, with an estimated 90 million individuals having experienced MDD.[7] Although therapeutic measures other than antidepressant drugs (eg, deep transcranial magnetic stimulation,[8] continuous theta pulse stimulation,[9] and Stanford neuromodulation therapy[10]) have been actively explored and clinically applied in recent years, the enormous social burden caused by MDD has not changed.

MDD is often accompanied by other mental health issues, most notably anxiety disorders, which have a high co-morbidity rate of 74.6%.[11] Research into the causes of this co-occurrence has been extensive, considering various factors such as inflammation, stress, environmental factors, personality traits, genetic predispositions, sleep disturbances, and brain cell dysfunction, as well as findings from neuroimaging studies.[12–20] Anxious depression (AUD) is a common subtype of MDD,

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the definition of which has been under debate and uncertainty, causing significant problems in the study of the disorder.[21] In order to recognize the clinical significance of ADD and its impact on patients with MDD, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) encapsulates the criterion of the Anxiety Distress Indicator for MDD.[22,23] Related studies have concluded that AUD goes beyond the general sense of MDD co-morbid anxiety, exhibiting clinical features such as more severe suicidal ideation, severity of illness, chronicity, and low treatment response.[23–25] However, the reasons behind AUD manifesting as a more severe clinical trajectory are unclear. Therefore, trying to identify AUD patients early in terms of common clinical parameters is crucial for effective clinical management.

Previous research has successfully identified common clinical variables that contribute to the development of anxiety symptoms in individuals with MDD, such as age of onset,[26] suicide attempts,[27] being female,[28,29] which are recognized as risk factors for more severe anxiety symptoms. However, there is a dearth of clinical studies focusing specifically on AUD within the context of MDD, which hinders the development of targeted clinical management strategies for this subpopulation. This study aims to determine the prevalence of comorbid AUD among a large cohort of first hospitalized Chinese patients diagnosed with MDD. Additionally, by identifying the clinical factors that contribute to the onset and progression of AUD, the study seeks to inform the development of tailored clinical intervention strategies that address the specific needs of this sub-MDD population.

Subjects and Methods

Subjects

The study strictly adhered to the guidelines set forth in the Declaration of Helsinki and was approved by the Ethics Committee of the Wuhan Mental Health Center (approval number KY20170201.01). All participants provided written informed consent in person or through family members. The study spanned from July 2017 to August 2022 and included 981 MDD patients who underwent hospitalization for their condition at the Wuhan Mental Health Center (which is the largest psychiatric specialty hospital in central China, located in Wuhan, Hubei Province, with an establishment of 950 beds and about 10,000 patients per year).

To qualify for participation in the study, individuals had to satisfy the following conditions: 1) Patients must fulfill the diagnostic criteria for MDD as per the 10th Revision of the International Classification of Diseases (ICD-10); 2) They should not have any record of hospitalization prior to the inpatient interview on admission day; 3) The age range must be between 18 and 60 years, inclusive of both genders; 4) A minimum score of 24 on the 17-item Hamilton Depression Scale (HAMD-17) is required.

Those who met one of the following criteria were excluded from the study: 1) Pregnant or lactating women; 2) Patients with a history of comorbid substance abuse or dependence; 3) Patients with other psychiatric disorders such as schizophrenia, bipolar disorder, or personality disorder; 4) Patients with acute infections, diabetes mellitus, autoimmune diseases, or other serious medical conditions requiring long-term oral medication. 5) Patients who are unable to cooperate with psychometric evaluation due to exacerbation of severe symptoms or other reasons.

Research Design

This study was designed as a cross-sectional study to report the prevalence of AUD in a first-time hospitalized MDD population and to explore the clinical factors that influence the occurrence and severity of AUD.

Data Collection

Upon admission, a customized EXCEL form was used to collect sociodemographic and general clinical data from eligible MDD patients. This data included age, gender, age of onset, illness duration, marital status, and history of outpatient treatment. On the second day of admission, fasting venous blood tests were conducted to measure lipid levels, blood glucose (FBG), and thyroid function. Patient medical records provided information on blood pressure levels, body mass index (BMI), and waist circumference. Table 1 presents the specific parameters assessed.

Table 1 The Demographic and General Clinical Data in Different Clinical Subgroups

Index	Total Patients (n=981)	AUD (n=101)	Non-AUD (n=880)	t/χ^2	*p*
Age-years	35.62±12.44	37.34±12.77	35.42±12.4	−1.47	0.143
Course of disease-months	10.83±4.41	9.73±4.99	10.95±4.33	2.36	0.020*
Onset age-years	34.09±12.36	36.29±12.73	33.84±12.3	−1.89	0.059
HAMD	29.43±2.97	33.51±3.01	28.97±2.58	−14.61	<0.001*
HAMA	20.28±3.49	27.49±1.89	19.45±2.55	−38.95	<0.001*
PSS	8.67±4.39	17.28±6.91	7.69±2.57	−13.85	<0.001*
CGI-SI	5.83±0.71	6.48±0.69	5.75±0.68	−10.13	<0.001*
TSH-uIU/mL	3.98±2.47	7.16±3.66	3.62±2.00	−9.56	<0.001*
FT_3-pmol/mL	4.90±0.69	4.89±0.69	4.90±0.69	0.14	0.889
FT_4-pmol/mL	16.78±3.04	17.27±3.19	16.72±3.01	−1.71	0.088
FBG - mmol/L	5.26±0.63	5.52±0.84	5.23±0.60	−3.41	0.001*
TC-mmol/L	4.79±0.92	5.24±0.96	4.73±0.90	−5.28	<0.001*
HDL-C-mmol/L	1.32±0.23	1.28±0.22	1.32±0.23	1.65	0.100
TG-mmol/L	2.11±0.10	2.08±0.92	2.12±1.00	0.38	0.705
LDL-C-mmol/L	2.67±0.74	2.90±0.76	2.64±0.74	−3.31	0.001*
BMI-kg/m^2	24.18±1.76	24.59±1.9	24.13±1.74	−2.49	0.013*
SBP-mmHg	116.39±11.15	124.11±12.45	115.5±10.64	−6.67	<0.001*
DBP-mmHg	74.62±6.83	78.77±8.74	74.15±6.41	−5.16	<0.001*
WC-cm	79.98±8.40	80.4±8.25	79.94±8.42	−0.52	0.604
Gender				4.24	0.039*
Male	333, 33.90%	25, 24.75%	308, 35.00%		
Female	648, 66.10%	76, 75.25%	572, 65.00%		
Marital status - (n, %)				2.24	0.134
Married	674, 68.70%	76, 75.25%	598, 67.95%		
Others	307, 31.30%	25, 24.75%	282, 32.05%		
Treatment history				1.47	0.225
Yes	636, 64.80%	71, 70.30%	565, 64.20%		
NO	345, 35.20%	30, 29.70%	315, 35.80%		
Educational background				1.68	0.194
High school and below	683, 69.60%	76, 75.25%	607, 68.98%		
Bachelor and above	298, 30.40%	25, 24.75%	273, 31.02%		

Note: *$p<0.05$.

Abbreviations: HAMD, Hamilton Depression Scale score; HAMA, Hamilton Anxiety Scale score; PSS, Positive symptom subscale of the Positive and Negative Symptom Scale; CGI-SI, Clinical Global Impression Scale - Severity of Illness; TSH, Thyroid stimulating hormone; FT_3, Free triiodothyronine; FT_4, Free tetraiodothyronine; FBG, Fasting blood glucose; TC, Total cholesterol; HDL-C, High density lipoprotein cholesterol; TG, Triglycerides; LDL-C, Low density lipoprotein cholesterol; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; WC, Waist circumference.

Clinical Evaluation

The severity of depressive symptoms was assessed using the HAMD-17, while the severity of anxiety symptoms was assessed using the HAMA-14. The Positive Symptom Subscale (PSS) of the Positive and Negative Symptom Scale (PANSS) was used to evaluate the severity of psychotic symptoms, and the Clinical Global Impression (CGI) Scale was used to assess overall illness severity.

Psychometric assessments were conducted by two psychiatrists who received uniform training at the primary care level in the respective medical centers where the samples were located.

Data Analysis

Patients who met both of the following were diagnosed with AAD: 1) Anxiety/somatization factor (consisting of six items: psychological anxiety, somatic anxiety, gastrointestinal somatic symptoms, general somatic symptoms, hypochondriasis, and insight) scores on the HAMD-17 were greater than or equal to 7.[30] 2) The 14-item Hamilton Anxiety Scale (HAMA-14)

scores were greater than or equal to 25.[31] The researchers calculated the prevalence of patients with AUD and compared demographic and general clinical data for two clinical subgroups, AUD and non-AUD. Continuous variables were represented by means and standard deviations, while categorical variables were presented as counts. Independent samples t-tests were employed to compare continuous variables among subgroups. The chi-square test was utilized to compare proportions between groups. To validate factors associated with AUD for variables that exhibited significant differences in univariate analyses, Pearson correlation analyses were conducted. These factors related to AUD were introduced as independent variables in binary logistic regression models to investigate their impact on anxiety. For the subgroup experiencing AUD, multiple linear regressions were conducted to determine factors influencing AUD. The factors identified in the binary logistic regression, serving as the independent variables, and the anxiety symptom score were employed as the outcome variable. A *p*-value threshold of less than 0.05 was set to determine statistical significance, with all tests being two-tailed. The statistical software package SPSS version 27 was used to perform all analyses.

Results

Comparison Between AUD Group and Non-AUD Group

Among the 981 MDD patients studied, 101 exhibited AUD, which is 10.30% of the entire cohort. A univariate analysis showed that there were notable differences in clinical characteristics between the two subgroups. The AUD subgroup had a higher proportion of female patients and higher scores on various psychological assessments, including the HAMD, PSS, and Clinical Global Impression Scale - Severity of Illness (CGI-SI). Additionally, this subgroup had higher levels of fasting blood glucose (FBG), total cholesterol (TC), body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP). However, they had a shorter illness duration (refer to Table 1 for details).

Correlation Analysis of AUD Factors

Pearson correlation analysis was conducted to explore the relationship between AUD and the variables that showed significant differences in the univariate analysis. The results indicated that there were significant correlations between AUD and the clinical variables identified in the univariate analysis, with all *p*-values being less than 0.05 (refer to Table 2).

Table 2 Correlation Between the Anxiety and Clinical Variable in MDD Patients

Characteristic	Anxiety Patients (n=101)	
	r	*p*
Course of disease - months	−0.08	0.008*
HAMD	0.47	<0.001*
PSS	0.66	<0.001*
CGI-SI	0.31	<0.001*
TSH - uIU/mL	0.44	<0.001*
FBG - mmol/L	0.14	<0.001*
TC - mmol/L	0.17	<0.001*
LDL-C - mmol/L	0.11	0.001*
BMI - kg/m^2	0.08	0.013*
SBP - mmHg	0.24	<0.001*
DBP - mmHg	0.21	<0.001*
Gender (male vs female)	0.07	0.039*

Note: *$p<0.05$.

Abbreviations: HAMD, Hamilton Depression Scale score; PSS, Positive symptom subscale of the Positive and Negative Symptom Scale; CGI-SI, Clinical Global Impression Scale - Severity of Illness; TSH, Thyroid stimulating hormone; FBG, Fasting blood glucose; TC, Total cholesterol; LDL-C, Low density lipoprotein cholesterol; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.

Logistic Regression Analysis of AUD Determinants

To delve deeper into the factors contributing to AUD, a binary logistic regression model (backward: Wald) was utilized. AUD was the dependent variable, and the significant variables from the correlation analysis were the independent variables. The findings revealed that being female (B = 0.70, p =0.044, OR = 2.01, 95% CI: 1.02–3.97), higher HAMD scores (B = 0.30, $p < 0.001$, OR = 1.35, 95% CI: 1.18–1.54), higher PSS scores (B = 0.18, $p < 0.001$, OR = 1.20, 95% CI: 1.12–1.27), higher CGI-SI (B = 0.51, $p = 0.031$, OR = 1.67, 95% CI: 1.05–2.66), higher TSH levels (B = 0.17, $p = 0.002$, OR = 1.19, 95% CI: 1.06–1.33), higher BMI (B = 0.20, $p = 0.023$, OR = 1.22, 95% CI: 1.03–1.45) were risk factors for AUD. However, TC (B = −0.53, $p = 0.006$, OR = 0.59, 95% CI: 0.41–0.86) was identified as a protective factor (refer to Table 3 for a summary).

Multivariate Analysis of Anxiety Symptom Scores

Lastly, a multivariate linear model was constructed to assess the factors influencing the severity of anxiety symptoms in AUD patients. The model's independent variables were the factors linked to anxiety from the logistic regression analysis (Back: Wald), and the dependent variable was the anxiety symptom scores. The findings, as shown in Table 4, indicated that higher HAMD scores (B = 0.46, $p < 0.001$, 95% CI: 0.39–0.54), higher PSS scores (B = 0.29, $p < 0.001$, 95% CI: 0.25–0.34), and higher CGI-SI scores (B = 0.52, $p < 0.001$, 95% CI: 0.25–0.78) were risk factors for increased anxiety severity, while higher TC levels (B = −0.33, $p = 0.002$, 95% CI: −0.53–0.12) were protective factors.

Table 3 Binary Logistic Regression Analyses of Determinants of Anxiety in MDD Patients

	Coefficients	Std. Error	Wald	*p*-value	95% CI for Exp(B)		
	B				Exp(B)	Lower	Upper
Constant	−20.13	3.28	37.58				
Gender (male vs female)	0.70	0.35	4.05	0.044*	2.01	1.02	3.97
HAMD	0.30	0.07	18.25	<0.001*	1.35	1.18	1.54
PSS	0.18	0.03	32.88	<0.001*	1.20	1.12	1.27
CGI-SI	0.51	0.24	4.65	0.031*	1.67	1.05	2.66
TSH	0.17	0.06	9.17	0.002*	1.19	1.06	1.33
TC	−0.53	0.19	7.63	0.006*	0.59	0.41	0.86
BMI	0.20	0.09	5.17	0.023*	1.22	1.03	1.45

Note: *p<0.05.
Abbreviations: HAMD, Hamilton Depression Scale score; PSS, Positive symptom subscale of the Positive and Negative Symptom Scale; CGI-SI, Clinical Global Impression Scale - Severity of Illness; TSH, Thyroid stimulating hormone; TC, Total cholesterol; BMI, Body mass index.

Table 4 Factors Influencing Anxiety Symptom Severity: a Multiple Linear Regression Model

	Coefficients	Std. Error	t	*p*-value	95% CI	
	B				Lower	Upper
Constant	2.64	0.95	2.78	0.006	0.78	4.50
HAMD	0.46	0.04	11.64	<0.001*	0.39	0.54
PSS	0.29	0.02	12.72	<0.001*	0.25	0.34
CGI-SI	0.52	0.13	3.87	<0.001*	0.25	0.78
TC	−0.33	0.10	−3.12	0.002*	−0.53	−0.12

Note: *p<0.05.
Abbreviations: HAMD, Hamilton Depression Scale score; PSS, Positive symptom subscale of the Positive and Negative Symptom Scale; CGI-SI, Clinical Global Impression Scale - Severity of Illness; TC, Total cholesterol.

Discussion

Our study reported the prevalence of anxiety symptoms in a Chinese population with a diagnosis of MDD at first hospitalization and identified correlates that influence AUD development and its severity. This enriches the Chinese characterization of the clinical pattern of AUD in MDD patients and will help to target prevention and intervention to Chinese MDD patients.

Our study revealed that the prevalence of AUD in individuals with MDD was 10.30%. Currently, there is a great deal of heterogeneity in reports on the prevalence of AUD, and multiple factors are responsible for this heterogeneity. Firstly, different studies have used different assessment tools to measure AUD, which may affect the reported rates. For example, some scholars reported a 22.8% prevalence rate using HAMA-14 scores as a definition of AUD.[32] Secondly, differences in the source of subjects (eg, inpatient MDD patients versus outpatients) as well as differences in the cutoff value for anxiety disorders can affect the consistency of prevalence rates.[33–36] A study conducted during the COVID-19 pandemic reported that AUD accounted for 40.3% of the total MDD population in China surveyed.[30] This highlights the impact of major public health events on the reported rates of MDD subtypes. In conclusion, although there are multiple confounders that can cause the reported rate of AUD to exhibit variation, for our target population and the methodology used to define AUD, our prevalence rate of 10.30% is lower than what is currently known to be reported.

Traditionally, females have been considered more susceptible to anxiety symptoms. Studies have demonstrated that women with MDD have a higher incidence of comorbid anxiety disorders compared to men.[37,38] This disparity is often attributed to the influence of gonadal hormones on the development, maintenance, and persistence of anxiety disorders in women.[29] Additionally, other psychological symptom scores of MDD patients, such as PSS score, HAMD score, and CGI-SI score, have been identified as risk factors for the emergence of anxiety symptoms. Our findings support the findings of previous studies that suggest patients with AUD exhibit more severe pathology compared to non-AUD.[39] A study conducted in Korea also found significantly higher HAMA scores in psychotic MDD patients compared to nonpsychotic patients.[40] Furthermore, in our study, certain metabolic indicators were found to significantly contribute to the development of AUD, with TSH levels being the most prominent.[41,42] An animal study has proposed a mechanism linking TSH levels and anxiety-like behavior, suggesting that thyroid function regulates brain-derived neurotrophic factor levels in the hippocampus, thereby modulating anxiety behavior in rats.[43] Above all, the risk factors for AUD that we identified in first hospitalized patients with MDD have provided insights for differentiating and identifying subgroups with anxiety and have facilitated clinical management.

Finally, we have identified relevant factors that influence the severity of AUD. Previous studies have reported that the severity of depressive symptoms is a risk factor for the severity of anxiety symptoms, which substantiates our findings.[44] Researchers have recognized the importance of amygdala connectivity strength in mediating the relationship between anxiety and depression in MDD patients.[45] Similarly, consistent with our findings, psychotic symptoms (PSS scores) have been identified as significant predictors of comorbid anxiety symptoms in MDD patients,[27,46] and patients with psychotic MDD tend to have a higher prevalence of specific anxiety disorders.[47] This is corroborated by findings indicating that individuals with comorbid anxiety are more likely to experience psychotic symptoms and have more severe depressive symptoms, particularly in younger Chinese patients with MDD.[48] Interestingly, our study also suggests that TC levels may serve as a potential protective factor against anxiety severity, although research on this particular aspect appears to be limited. Non-directional and Bayesian network analyses have shown a strong association between high TC levels and thyroid dysfunction, clinical symptoms, and metabolic disorders in MDD patients.[49] Although that study highlighted the significance of TC in MDD pathophysiology, this finding contrasts with the results of the present study. However, a cross-sectional study indicated a negative correlation between anxiety scores and HDL-C levels, but not TC levels, in depressed patients.[50] Great heterogeneity means that more in-depth studies are needed to better understand the role of TC levels in the development of patients with AUD.

It is important to acknowledge several limitations inherent to this research. First and foremost, the cross-sectional nature of the study precludes the establishment of causality between AUD and clinical variables. Secondly, the relatively small sample size of patients with AUD may restrict the broad applicability of the regression analysis findings. Thirdly, the inclusion of many patients who had previously received outpatient care introduces potential confounding variables that could affect the results. Lastly, the study did not account for other influential factors such as smoking habits, alcohol

intake, and medication usage. To address these limitations, future studies will be designed with a more rigorous prospective approach, aiming to provide a clearer understanding of the relationships and factors at play.

Conclusion

Our study showed that 10.3% of patients with MDD exhibited AUD during their first hospitalization. More importantly, we identified several clinical factors associated with the onset and severity of AUD in the target group. Understanding these clinical characteristics may offer insights into early identification and intervention in AUD among MDD patients.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The ethics committees of the Wuhan mental health center reviewed and approved this study. All subject guardians knew about this study and signed informed consent. All procedures carried out in studies conformed to the 1964 helsinki Declaration and its subsequent amendments or similar ethical standards.

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Disclosure

The authors declare that they have no competing interests.

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