Prevalence and correlates of severe anxiety in patients with first hospitalization for major depressive disorder combined with dyslipidemia: a large sample cross-sectional study

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Abstract

Background: Anxiety symptoms and dyslipidemia are common comorbidities in patients with major depressive disorder (MDD), and there are complex pathophysiologic as well as clinical mechanisms underlying the association between the three. In this study, we investigated the prevalence and associated factors of severe anxiety in first-time hospitalized patients with MDD with dyslipidemia.

Methods: We included 708 patients with major depressive disorder with comorbid dyslipidemia and collected their sociodemographic and general clinical data as well as biochemical parameters such as lipids, thyroid function and blood glucose. We also completed the Hamilton Anxiety Scale (HAMD), Hamilton Depression Scale (HAMD), Positive Symptom Scale (PSS) and Clinical General Impression Scale (CGI) to assess their clinical symptoms.

Results: The prevalence of severe anxiety disorder in MDD patients with dyslipidemia combined with first hospitalization was 11.02%. HAMD score, PSS score, history of suicide, body mass index (BMI), thyroid-stimulating hormone (TSH) level, and tetra-iodothyronine (FT$_4$) level were the risk factors for the development of severe anxiety disorders in patients with MDD who were comorbid with dyslipidemia. Higher HAMD scores and TSH level may exacerbate the development of severe anxiety symptoms.

Conclusion: This study reports and identifies the prevalence of anxiety symptoms in first-time hospitalized MDD patients with comorbid dyslipidemia, as well as risk factors for anxiety symptoms and severity of anxiety symptoms, and these identified factors may be potentially useful and informative for preventing and intervening in severe anxiety in this target population.

1. Introduction

Major depressive disorder (MDD) is widely recognized as one of the most serious mental health problems[1]. Mild depressive episodes are characterized by sadness, lack of pleasure and feelings of worthlessness, while major depression is characterized by recurrent suicidal thoughts and even suicidal behavior[2, 3]. MDD not only greatly affects patients' social functioning but also reduces their quality of life[4]. According to a meta-analysis on the prevalence of MDD in mainland China in 2021, the point prevalence, 12-month prevalence and lifetime prevalence of MDD in China were 1.1%, 1.6% and 1.8%, respectively[5]. Depression is reported to be the leading cause of mental health-related disease burden and the leading cause of disability globally, affecting approximately 280 million people and causing more than 47 million disability-adjusted life years in 2019 [6].

Many studies have shown that depression and poor lipid metabolism are interrelated. In an animal study in high-fat fed rats, the risk of depressive behavior was higher in rats with chronic mild stress and the same lipid levels [7], and the use of statin lipid-lowering drugs produced antidepressant-like effects in rats exposed to chronic mild stress [8]. In addition, clinical studies have explored the relationship between lipid levels and depression, with depressed patients being at greater risk for dyslipidemia. [9, 10]. All of the
above studies greatly suggest a common pathophysiological mechanism between dyslipidemia and depressive symptoms.

Depression is also highly associated with severe anxiety, and although they are two separate conditions, depression often occurs in conjunction with severe anxiety, and the relationship between anxiety and dyslipidemia is complex and may interact with each other [11]. In clinical practice, depression and anxiety disorders often coexist. Studies have shown that up to 50%-60% of patients with depression also have anxiety symptoms [12]. This may be due to the fact that both mood disorders share some similar mechanisms in neurochemistry, cognition and emotion regulation, and from a biological point of view, they both suffer from immune, hormonal, inflammatory and autonomic system dysregulation [13].

Dyslipidemia may be associated with alterations in neurotransmitter function and inflammatory responses, factors that play an important role in the onset and course of anxiety [14]. First, depressed patients with comorbid dyslipidemia may experience symptoms of anxiety due to the effects of the physical condition and perceived dyslipidemia. Dyslipidemia may increase concerns about cardiovascular health, leading to increased anxiety [15]. Second, depressed patients often have unhealthy lifestyles, such as lack of exercise and poor diet, which may further affect lipid metabolism and cardiovascular health [16]. These lifestyle factors may also be associated with the development of anxiety symptoms.

Study shows overlapping genetic predisposition between major depressive disorder and anxiety disorders [17]. And patients with MDD combined with anxiety disorders not only have a higher severity of depression but also have a higher risk of suicide, the study showed that the risk of suicide was 2.46, 26.32, and 54.77 times higher in people with low depression and high anxiety, high depression and low anxiety, and high depression and high anxiety, respectively [18, 19]. In recent studies, anxious depression has emerged as a subtype of MDD and is associated with increased immune dysregulation, more cortical thinning, and cortical limbic dysfunction compared to depression alone.

Several studies have reported an association between abnormal blood lipid levels and anxiety [20, 21]. Although some studies have highlighted a possible association between dyslipidemia and anxiety, few studies have investigated the relationship between dyslipidemia and anxiety symptoms in patients with MDD. Therefore, the risk factors for the development of anxiety symptoms in MDD patients with comorbid dyslipidemia remain uncertain. To our knowledge, this is the first study to explore the incidence and clinical characteristics of severe anxiety in first-time hospitalized MDD patients with comorbid dyslipidemia. Our objectives were to (1) determine the prevalence and clinical characteristics of anxiety in patients with MDD who were first hospitalized and had comorbid dyslipidemia. (2) To identify predictors significantly associated with anxiety in first-time hospitalized MDD patients with comorbid dyslipidemia.

2. Materials and Methods

2.1 Subjects
A total of 708 patients were included in this cross-sectional study between 2017 and 2022. To be included in the study, patients had to meet the following eligibility criteria: (1) Fulfill the diagnostic criteria for MDD according to the 10th revision of the International Classification of Diseases (ICD-10) (2) According to the 2016 guidelines for the management of dyslipidemia in Chinese adults, the thresholds for high TC and TG are 5.20 mmol/L and 1.70 mmol/L, respectively, whereas the thresholds for high LDL-C and low HDL-C are 3.40 mmol/L and 1.00 mmol/L. Dyslipidemia is considered when single or multiple abnormal lipid levels are present. (3) Have no prior history of hospitalization before the inpatient interview on the day of admission. (4) Be aged between 18–60 years old and of Chinese Han nationality. (5) Score ≥ 24 on the Hamilton Depression Scale (HAMD).

Patients were excluded from the study if they met any of the following conditions: (1) Pregnant or breastfeeding. (2) Having a history of substance dependence. (3) Diagnosed with severe physical diseases or personality disorders. (4) Unable to cooperate with psycho-psychological assessments due to severe behavioral disorders or other reasons.

The study received approval from the Ethics Committee of Wuhan Mental Health Center. All participants provided written informed consent, either signed by the patient themselves or by a family member.

### 2.2 Research design

A cross-sectional design was used in this study to determine the prevalence of anxiety among first-time hospitalized patients with MDD combined with dyslipidemia. Factors associated with the occurrence of anxiety were assessed, and demographic and general clinical data were compared between two clinical subgroups with and without anxiety.

We collected demographic information on each patient, including age, duration of illness, gender, marital status and educational background, and history of suicide. The body mass index (BMI) of each patient was calculated by dividing the weight (kg) by the square of the height (cm).

We also collected scales capable of assessing patients’ clinical symptoms, namely the Positive Symptom Subscale (PSS) with items P1-P7 of the Positive and Negative Symptom Scale, the Clinical Global Impression Inventory (CGI), and the HAMD. All patients were asked to fast after 8 p.m. the night before and complete venous blood collection and blood pressure measurement between 6 a.m. and 8 a.m. the next day. All blood samples collected were immediately sent to the hospital laboratory for testing by 11:00 am. The biochemical parameters tested included Total cholesterol (TC); triglycerides (TG); low-density lipoprotein cholesterol (LDL-C); high-density lipoprotein cholesterol (HDL-C); fasting blood glucose (FBG) levels; BMI; waist circumference (WC); blood pressure levels (specifically: systolic blood pressure, SBP; diastolic blood pressure, DBP); and thyroid function (specifically: thyroid stimulating hormone, TSH; free triiodide, TSH; free triiodothyronine, FT$_3$; free tetraiodothyronine, FT$_4$) levels.

We defined patients with HAMA scores ≥ 25 as the with anxiety subgroup and otherwise as the without anxiety subgroup[22].
2.3 Data analysis

Data collected for normally distributed continuous measures are given as means and standard deviations, while categorical variables are expressed as counts. To compare continuous variables across groups, t-tests for independent samples were used. To compare ratios, chi-square tests were utilized. To examine the variables affecting anxiety, the different variables in the univariate analysis were included as independent variables in a binary logistic regression model with the presence of anxiety as the dependent variable. Finally, we used a multiple linear regression model to assess the factors affecting anxiety in patients with MDD with dyslipidemia who were first hospitalized. Statistical analyses were performed using SPSS 26 (SPSS, Inc, Chicago, IL).

3. Results

3.1 Differences between clinical subgroups with and without anxiety.

A total of 708 patients with MDD associated with dyslipidemia were included in this sample. Table 1 shows significant differences between with anxiety and without anxiety subgroups in terms of disease duration, gender, history of suicide, clinical symptoms (including: HAMD score, PSS score) and metabolism-related indicators (including: DBP, SBP, FBG, TSH, FT$\text{4}$, BIM, TC, LDL-C).
Table 1
Demographic and general clinical data of different clinical subgroups.

<table>
<thead>
<tr>
<th>Index</th>
<th>Total patients (n = 708)</th>
<th>Anxiety Without (n = 630)</th>
<th>Anxiety With (n = 78)</th>
<th>t/χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - years</td>
<td>36.09 ± 12.60</td>
<td>35.88 ± 12.59</td>
<td>37.79 ± 12.56</td>
<td>-1.27</td>
<td>0.206</td>
</tr>
<tr>
<td>Course of disease - months</td>
<td>10.9 ± 4.56</td>
<td>11.05 ± 4.37</td>
<td>9.79 ± 4.98</td>
<td>2.14</td>
<td>0.035*</td>
</tr>
<tr>
<td>HAMD</td>
<td>29.90 ± 2.97</td>
<td>29.41 ± 2.59</td>
<td>33.90 ± 2.79</td>
<td>-14.30</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>PSS</td>
<td>9.01 ± 4.70</td>
<td>7.89 ± 3.00</td>
<td>18.06 ± 6.41</td>
<td>-13.85</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>CGI</td>
<td>5.92 ± 0.72</td>
<td>5.85 ± 0.61</td>
<td>6.54 ± 0.68</td>
<td>-8.37</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>TSH- uIU/mL</td>
<td>4.19 ± 2.64</td>
<td>3.77 ± 2.13</td>
<td>7.58 ± 3.71</td>
<td>-8.91</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>FT₃-mmol/L</td>
<td>4.92 ± 0.67</td>
<td>4.91 ± 0.69</td>
<td>4.96 ± 0.67</td>
<td>-0.67</td>
<td>0.506</td>
</tr>
<tr>
<td>FT₄ - mmol/L</td>
<td>16.77 ± 3.03</td>
<td>16.68 ± 3.00</td>
<td>17.50 ± 3.21</td>
<td>-2.23</td>
<td>0.026*</td>
</tr>
<tr>
<td>FBG - mmol/L</td>
<td>5.29 ± 0.65</td>
<td>5.26 ± 0.61</td>
<td>5.56 ± 0.85</td>
<td>-3.01</td>
<td>0.003*</td>
</tr>
<tr>
<td>TC - mmol/L</td>
<td>4.98 ± 0.96</td>
<td>4.93 ± 0.94</td>
<td>5.45 ± 0.98</td>
<td>-4.60</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>HDL-C -mmol/L</td>
<td>1.30 ± 0.23</td>
<td>1.31 ± 0.23</td>
<td>1.28 ± 0.22</td>
<td>1.17</td>
<td>0.244</td>
</tr>
<tr>
<td>LDL-C - mmol/L</td>
<td>2.74 ± 0.80</td>
<td>2.72 ± 0.97</td>
<td>3.00 ± 0.81</td>
<td>-3.00</td>
<td>0.003*</td>
</tr>
<tr>
<td>TG - mmol/L</td>
<td>2.45 ± 0.97</td>
<td>2.47 ± 0.97</td>
<td>2.33 ± 0.89</td>
<td>1.16</td>
<td>0.247</td>
</tr>
<tr>
<td>BMI - kg/m2</td>
<td>24.20 ± 1.80</td>
<td>24.14 ± 1.77</td>
<td>24.70 ± 1.90</td>
<td>-2.64</td>
<td>0.008*</td>
</tr>
<tr>
<td>SBP - mmHg</td>
<td>117.02 ± 11.43</td>
<td>115.96 ± 10.83</td>
<td>125.60 ± 12.53</td>
<td>-6.50</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>DBP - mmHg</td>
<td>74.95 ± 7.08</td>
<td>74.35 ± 6.58</td>
<td>79.79 ± 8.98</td>
<td>-5.18</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>WC - cm</td>
<td>79.73 ± 8.37</td>
<td>79.65 ± 8.37</td>
<td>80.39 ± 8.36</td>
<td>-0.74</td>
<td>0.451</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>5.73</td>
<td>0.017*</td>
</tr>
<tr>
<td>Male</td>
<td>230 32.5%</td>
<td>214 34.0%</td>
<td>16 20.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>478 67.5%</td>
<td>416 66.0%</td>
<td>62 79.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HAMD: Hamilton Depression Scale; PSS: Positive Symptom Subscale; CGI: Clinical Global Impression Scale; TSH: thyroid stimulating hormone; FT₃: free triiodothyronine; FT₄: free tetraiodothyronine; FBG: fasting blood glucose; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference. *p < 0.05
<table>
<thead>
<tr>
<th>Index</th>
<th>Total patients (n = 708)</th>
<th>Anxiety Without (n = 630)</th>
<th>Anxiety With (n = 78)</th>
<th>$t/\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Without (n = 630)</td>
<td>With (n = 78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>504 71.2%</td>
<td>442 70.2%</td>
<td>62 79.5%</td>
<td>2.95</td>
<td>0.086</td>
</tr>
<tr>
<td>High school and below</td>
<td>204 28.8%</td>
<td>188 29.8%</td>
<td>16 20.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelor and above</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td>0.38</td>
<td>0.537</td>
</tr>
<tr>
<td>Unmarried</td>
<td>212 29.9%</td>
<td>191 30.3%</td>
<td>21 26.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>496 70.1%</td>
<td>439 69.7%</td>
<td>57 73.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment history</td>
<td></td>
<td></td>
<td></td>
<td>0.64</td>
<td>0.424</td>
</tr>
<tr>
<td>NO</td>
<td>256 36.2%</td>
<td>231 36.7%</td>
<td>25 32.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>452 63.8%</td>
<td>399 63.3%</td>
<td>53 67.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidal history</td>
<td></td>
<td></td>
<td></td>
<td>186.47</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>YES</td>
<td>105 14.8%</td>
<td>53 8.4%</td>
<td>52 66.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>603 85.2%</td>
<td>577 91.6%</td>
<td>26 33.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HAMD: Hamilton Depression Scale; PSS: Positive Symptom Subscale; CGI: Clinical Global Impression Scale; 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; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference. *$p$ 0.05

**3.2 Determinants of anxiety in MDD patients with dyslipidemia: a binary logic-based model.**

We constructed a binary logistic regression model (backward: Wald) to explore the risk factors for severe anxiety symptoms in the target population, using variables that differed in univariate analyses as independent variables and co-morbid severe anxiety symptoms as outcomes. Results showed that HAMD score ($B = 0.21$, $p = 0.001$, OR = 1.32), PSS score ($B = 0.18$, $p < .001$, OR = 1.11), TSH ($B = 0.14$, $p = 0.046$, OR = 1.15), FT$_4$ ($B = 0.12$, $p = 0.040$, OR = 1.13), BMI ($B = 0.28$, $p = 0.019$, OR = 1.32), and history of suicide ($B = 1.58$, $p < .001$, OR = 6.35) were risk factors for severe anxiety symptoms. TC ($B = -0.52$, $p = 0.024$, OR = 0.59) was a protective factor. Table 2 summarizes these results.
Table 2
Binary logistic regression analysis of the determinants of anxiety in MDD patients with dyslipidemia.

<table>
<thead>
<tr>
<th></th>
<th>Coefficients</th>
<th>Std. error</th>
<th>Wald</th>
<th>p-value</th>
<th>95% CI for EXP (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td>Exp(B)</td>
</tr>
<tr>
<td>Constant</td>
<td>-20.49</td>
<td>4.11</td>
<td>24.90</td>
<td>0.001*</td>
<td>1.32</td>
</tr>
<tr>
<td>HAMD</td>
<td>0.28</td>
<td>0.09</td>
<td>10.44</td>
<td>&lt;.001*</td>
<td>1.32</td>
</tr>
<tr>
<td>PSS</td>
<td>0.18</td>
<td>0.04</td>
<td>19.61</td>
<td>&lt;.001*</td>
<td>1.20</td>
</tr>
<tr>
<td>TSH</td>
<td>0.14</td>
<td>0.07</td>
<td>3.97</td>
<td>0.046*</td>
<td>1.15</td>
</tr>
<tr>
<td>FT&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0.12</td>
<td>0.06</td>
<td>4.24</td>
<td>0.040*</td>
<td>1.13</td>
</tr>
<tr>
<td>TC</td>
<td>-0.52</td>
<td>0.23</td>
<td>5.08</td>
<td>0.024*</td>
<td>0.59</td>
</tr>
<tr>
<td>BMI</td>
<td>0.28</td>
<td>0.12</td>
<td>5.51</td>
<td>0.019*</td>
<td>1.32</td>
</tr>
<tr>
<td>Suicidal history</td>
<td>1.85</td>
<td>0.43</td>
<td>18.67</td>
<td>&lt;.001*</td>
<td>6.35</td>
</tr>
</tbody>
</table>

HAMD: Hamilton Depression Scale; PSS: Positive Symptom Subscale; TSH: thyroid stimulating hormone; FT<sub>4</sub>: free tetraiodothyronine; TC: total cholesterol; BMI: body mass index. *p 0.05

3.3 Factors influencing anxiety in MDD patients with dyslipidemia: a multiple linear regression model.

After multiple linear regression analysis, a total of seven factors including HAMD score, PSS score, TSH, FT<sub>4</sub>, TC, BMI, and previous suicide history were entered into the regression equation. The correlation coefficient of the regression equation was R = 0.725, the coefficient of determination was R<sup>2</sup> = 0.525, and the adjusted R<sup>2</sup> = 0.520. The significance test of the regression equation: F = 110.551, p = 0.000, indicated that the multiple regression equation was statistically significant. The standard regression coefficients (β) indicated that: Among patients with dyslipidemia with MDD who were hospitalized for the first time, the seven independent variables regarding anxiety were, in order: PSS score, previous history of suicide, TSH, HAMD score, TC, FT<sub>4</sub>. These results are summarized in Table 3.

Table 3
Multiple linear regression analysis of factors associated with the occurrence of anxiety in MDD patients with dyslipidemia.

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Std. Error</th>
<th>β</th>
<th>t</th>
<th>p</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>16.944</td>
<td>2.131</td>
<td>7.951</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAMD</td>
<td>0.267</td>
<td>0.063</td>
<td>0.414</td>
<td>4.356</td>
<td>&lt;.001*</td>
<td>1.022</td>
</tr>
<tr>
<td>TSH</td>
<td>0.174</td>
<td>0.048</td>
<td>0.348</td>
<td>3.662</td>
<td>&lt;.001*</td>
<td>1.022</td>
</tr>
</tbody>
</table>

HAMD: Hamilton Depression Scale; TSH: thyroid stimulating hormone. *p 0.05
4. Discussion

To our knowledge, this is the first study to examine the prevalence and clinical characteristics of anxiety in first-time hospitalized MDD patients with comorbid dyslipidemia. The main findings of our study were as follows: (1) The prevalence of anxiety among target group was 11.02%; (2) Our study showed that among target group, anxiety and non-anxiety subgroups were significantly different in terms of disease duration, gender, history of suicide, clinical symptoms (including: HAMD score, PSS score), metabolism-related indicators (including: DBP, SBP, FBG, TSH, FT$_4$, BIM, TC, LDL-C) were significantly different; (3) HAMD score, PSS score, history of suicide, BMI, TSH, FT$_4$ were risk factors for anxiety in for the first time, while TC was a protective factor; (4) Higher HAMD scores and TSH levels may exacerbate the development of severe anxiety symptoms in MDD patients with comorbid dyslipidemia.

In our study, the prevalence of comorbid anxiety among MDD patients with dyslipidemia was 11.02%. Although some studies have reported a complex relationship between dyslipidemia and anxiety, as well as a complex relationship between dyslipidemia and depression. However, to our knowledge, the incidence of anxiety in MDD patients with comorbid dyslipidemia has rarely been reported. Moreover, there is a high degree of heterogeneity in the current reports on the prevalence of comorbid anxiety symptoms in MDD patients. For example, one study found that approximately 53.2% of outpatients with major depression also had clinically significant levels of anxiety[23]. And among inpatients participating in the third phase of the German algorithm project, 46% of patients with depressive episodes had anxiety symptoms[24]. In a study on the acute phase cognitive treatment of patients with anxious depression versus non-anxious depression, anxiety symptoms were present in approximately 50.4% of patients with recurrent MDD depression[25]. But in a recent Chinese study of first-episode unmedicated psychotic depression with comorbid anxiety disorders, the prevalence was about 22.8%[26]. The heterogeneity of study results may be due to the fact that these differences may be due to sample differences as well as differences in the methods used to assess and define anxiety. For example, some studies have used a HAMD anxiety/panic factor score $\geq$ 7 as an indicator of depression combined with anxiety in their diagnostic assessment[27]. However, in our study, a HAMA score $\geq$ 25 was defined as severe anxiety [28], so it is possible that some patients with anxiety symptoms but not severe enough were excluded from our trial.

Our study found that higher PSS scores, HAMD scores suggest that patient patients may be at risk for suffering more anxiety. There is a strong co-morbidity between anxiety and depression, as we believe. And as the severity of depression progresses, anxiety-related symptoms usually increase[29]. In recent years, a study has shown that patients with MDD with psychotic symptoms have a 14.89-fold increase in the prevalence of severe anxiety (24.28%) compared to patients with MDD without psychotic symptoms[26]. Furthermore, previous studies have shown that patients with MDD who have psychotic symptoms are more likely to experience anxiety. For example, Koyanagi et al. found that anxiety was significantly associated with coexisting psychotic symptoms in patients with depression[30], and Gaudiano et al. found a higher prevalence of certain anxiety disorders in patients with major depressive
disorder who had psychotic symptoms[31]. However, the association between anxiety and psychotic symptoms in patients with MDD is unclear and requires further study.

Some studies also have found that elevated BMI predicts the long-term development of depression and anxiety symptoms[32, 33]. In rodent model studies, rats prone to obesity exhibit higher levels of anxiety-like behavior compared to resistant rats when maintained on a standard diet[34]. Although it is widely accepted that obesity is associated with the onset of depression, the exact mechanisms by which these two disease entities interact remain unclear. Gut microbial imbalances, inflammatory responses as emotional disorders, and obesity are now well established[35–37]. In addition, one study found that the dorsal striatal terminal dorsal bed nucleus was found to play a key role in the reciprocal control of the comorbidity of obesity and mood disorders. High-fat diet-mediated desensitization reduces GABAergic output from AgRP neurons to downstream melanocortin 4 receptors in the dorsal striatal terminal dorsal bed nucleus neurons, leading to severe mood disorders[38]. In general agreement with previous reports, patients with anxiety depression had a higher frequency of major depressive episodes and a higher risk of suicidal ideation and previous suicide attempts compared to patients with non-anxiety depression[24, 39]. A review explains the functional characteristics and nature of 5-HT receptor involvement in the regulation of pathological behavior, highlighting the role of 5-HT receptors in behavioral conditions such as suicide, depression, and anxiety[40].

Our study also demonstrated that TSH and FT₄ were risk factors for the development of anxiety in first hospitalization MDD patients with comorbid dyslipidemia and TSH levels with significant positive effect. Similar to our findings, a study of correlation between thyroid function and anxiety in medication-free MDD patients verified that elevated serum TSH levels were a risk factor for anxiety [41]. On the contrary, in another study, a negative correlation between anxiety levels and TSH was found[42]. A study points out that no correlation between serum TSH levels and anxiety or depression[43]. However, the exact relationship between TSH and anxiety symptoms in MDD patients has not been fully revealed and needs to be further explored. Regarding the association between FT₄ and anxiety symptoms, studies have reported that higher FT₄ in subclinical hyperthyroidism and within the normal range is associated with poorer cognitive outcomes[44]. Another animal experiment found that high levels of FT₄ may induce anxiety and depressive behavior in rats[44, 45]. However, the heterogeneity of the relevant studies is high; for example, no significant differences in serum FT₄ levels were observed between MDD patients with and without anxiety in the study by Zhang et al. [41].

Several limitations should be addressed in our study. First, this cross-sectional preliminary study could not explain the causal relationship between anxiety severity and risk factors in patients with MDD, which needs to be confirmed in a future prospective cohort study. Second, because there are many causes of anxiety symptoms, we could only include a subset of variables as independent variables and did not analyze the effects of somatic conditions, social and family support, and adverse life events. Third, because this study included patients who were hospitalized for the first time, who are usually in the acute phase of the disease, our study could not be extrapolated to patients with stable disease. Fourth, our
study included more women (67.5%), which could be a potential confounder due to the fact that women are more prone to anxiety than men\[46\]. More importantly, our study did not use such scales as the Mood Disorders Questionnaire (MDQ) or the 32-item Hypomania Checklist (HCL-32) to identify and exclude patients who may have bipolar disorder, this may also increase the confounding factors of the study. Future studies should aim to control for these confounding factors.

In conclusion, the prevalence of severe anxiety symptoms among first hospitalized MDD patients with dyslipidemia was 11.02%. We found that HAMD score, PSS score, history of suicide, BMI, TSH and FT\(_4\) were risk factors for severe anxiety symptoms in this patient group. Further, higher HAMD scores and TSH levels were predictors of anxiety symptom severity in the target group. These identified factors may provide potential biological indicators for clinical intervention and prevention of severe anxiety symptoms in this population.

**Abbreviations**

MDD  
Major depressive disorder  
HAMD  
Hamilton Depression Scale  
PSS  
Positive Symptom Subscale  
CGI  
Clinical Global Impression Scale  
TSH  
thyroid stimulating hormone  
FT3  
free triiodothyronine  
FT4  
free tetraiodothyronine  
FBG  
fasting blood glucose  
TC  
total cholesterol  
HDL-C  
high density lipoprotein cholesterol  
LDL-C  
low density lipoprotein cholesterol  
TG  
triglycerides  
BMI
Declarations

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Authors’ contributions

Jun Ma and Xuebing Liu made significant contributions to the conceptualization and design of this study. Huimin Yin drafted the manuscript. Yanting Zhan embellished and revised the language and logic of the article. Yi Li was responsible for setting up, adding and revising the content of the manuscript. Jun Ma finalized the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on 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.

Consent for publication

Not applicable.
Competing interests

The authors declare that they have no competing interests.

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