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The incidence and influencing factors of recent suicide attempts in major depressive disorder patients comorbid with moderate-to-severe anxiety: a large-scale cross-sectional study

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Abstract

Background Major depressive disorder (MDD) is a recurrent and persistent mental illness. However, there is a lack of research that distinguishes the severity of comorbid anxiety disorders in MDD, and insufficient evidence exists regarding the prevalence of MDD patients with comorbid moderate-to-severe anxiety in the Chinese population.

Methods The study included 1718 MDD patients (894 with moderate-to-severe anxiety symptoms and 824 without moderate-to-severe anxiety symptoms). Clinical symptoms and development were assessed using the Hamilton Depression Rating Scale-17 (HAMD-17), Hamilton Anxiety Rating Scale-14 (HAMA-14), Positive and Negative Syndrome Scale (PANSS), and Clinical Global Impression (CGI). The blood pressure and thyroid hormone levels were measured.

Results We found that the incidence of MDD patients with moderate-to-severe anxiety symptoms was 52.04%. The prevalence of recent suicide attempts in MDD comorbid moderate-to-severe anxiety patients was 31.8%, which was 4.24 times higher than that in patients without moderate-to-severe anxiety. Additionally, suicide attempters had elevated levels of thyroid stimulating hormone (TSH), anti-thyroglobulin (TgAb), thyroid peroxidases antibody (TPOAb), systolic blood pressure (SBP), and diastolic blood pressure (DBP) compared to non-suicide attempters. We further identified CGI score, TSH, TPOAb, and DBP as influential factors for recent suicide attempts in MDD individuals who had moderate-to-severe anxiety symptoms. These indexes could distinguish between suicide attempts and non-suicide attempts in MDD patients with moderate-to-severe anxiety symptoms.

Conclusions Our findings mainly indicated a high prevalence of recent suicide attempts in MDD patients with moderate-to-severe anxiety. Several clinical correlates, thyroid hormones, and blood pressure might contribute to recent suicide attempts in MDD patients with moderate-to-severe anxiety symptoms.

Keywords Major depressive disorder, Moderate-to-severe anxiety, Suicide, Influencing factors

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Introduction

Major depressive disorder (MDD) is a recurrent and persistent mental illness, which represents the primary cause of mental disability globally [1, 2]. It affects the whole body and mind, leading to a reduced quality of life and imposing significant costs on the healthcare sector and society [3]. The lifetime prevalence of 3.3% and 12-month prevalence of 2.3% in the Chinese population was uncovered by a systematic study that compiled epidemiological surveys of MDD, which resulted in a substantial economic burden on Chinese society [4]. While depression and anxiety are typically classified as separate conditions according to diagnostic criteria, it is rather normal for individuals to have both MDD and symptoms of anxiety simultaneously [5]. It is estimated that over 80% of individuals with depression also have anxiety symptoms [6]. Coexisting anxiety symptoms can exacerbate depression severity and result in more severe social and occupational impairment, decreased quality of life, and a poorer prognosis. Notably, patients with anxiety face a heightened risk of mortality in comparison to those with non-anxiety [7, 8]. Hence, it is imperative to focus on individuals diagnosed with MDD with anxiety.

Previous reports indicated that MDD patients with anxiety exhibit a greater likelihood of suicidal ideation and suicide attempts than those with non-anxiety symptoms [5]. MDD patients experiencing suicidal ideation or behavior are more prone to psychological and somatic symptoms, social dysfunction, and a diminished quality of life compared to those without suicidal ideation or behavior [9]. A meta-analysis suggested that even after adjusting for the severity of depressive symptoms, the incidence of suicidal ideation, suicide behavior, and suicidal attempts was higher in patients with anxiety disorders than in those without anxiety disorders [10]. A significant occurrence of suicide attempts in MDD patients who also had anxiety symptoms was revealed, and several clinical factors, thyroid hormone levels, and metabolic parameters were possible contributors to suicide attempts [11]. However, Mann et al. proposed that anxiety symptoms may actually serve as a protective factor against suicidal thoughts and behaviors rather than a risk factor in individuals with MDD [12]. The reason for inconsistent results may be the heterogeneity of the population. Additionally, these studies only focused on depressive disorders with anxiety and did not differentiate the severity of anxiety. Yet now, in clinical practice, MDD patients who have moderate-to-severe anxiety are more common. Anxiety may be a positive factor when they are mild, but when they reach a moderate-to-severe level, it can cause intense distress in the patients [13]. Thus, it is crucial to recognize the clinical value of differentiating the level of severity of coexisting anxiety in patients with MDD, particularly those with moderate-to-severe anxiety disorders.

However, there is a lack of research that distinguishes the severity of comorbid anxiety disorders in MDD, and insufficient evidence exists regarding the prevalence of MDD patients with comorbid moderate-to-severe anxiety in the Chinese population. The objectives of this study were (1) to examine the prevalence of moderate-to-severe anxiety disorders in patients with MDD, (2) to investigate the occurrence of suicide attempts in MDD patients with moderate-to-severe anxiety, and (3) to explore additional factors that may influence the likelihood of suicide in MDD patients with moderate-to-severe anxiety.

Materials and methods

Participants

From 2015 to 2017, all participants were recruited from the psychiatry department of Shanxi Medical University's First Clinical Medical College. The inclusion criteria were: (1) matching the DSM-IV criteria for major depressive disorder; (2) with a score greater than 24 on the Hamilton Depression Scale, 17-item version (HAMD-17); (3) first episode and not taking any psychotropic medication; (4) age between 18 and 60 years. The following were not eligible: (1) any other significant Axis I disorder; (2) substance abuse or dependency (not including tobacco); (3) severe physical illnesses including infections or inflammatory disorders; (4) alcohol and substance use disorder; and (5) women who were nursing or pregnant. The protocol for the research project had been approved by the Institutional Review Board (IRB) of the First Hospital of Shanxi Medical University (ID number: 2016-Y27).

Clinical assessment

To evaluate patients' depression symptoms, the Hamilton Depression Rating Scale-17 (HAMD-17) was used [14]. In order to quantify the anxiety symptoms, the Hamilton Anxiety Rating Scale-14 (HAMA-14) was administered [15]. A cut-off score of 21 was defined as MDD patients with moderate-to-severe anxiety symptoms [16]. The Positive and Negative Syndrome Scale (PANSS) was utilized for measuring psychotic symptoms, and the Clinical Global Impression (CGI) scale was carried out to document disease severity and level of clinical development [17]. All scales had a Cronbach's $\alpha > 0.8$, indicating excellent reliability. Furthermore, the Structured Clinical Interview for DSM-IV (SCID-IV) was administered to patients by two separate psychiatrists, and the inter-observer correlation coefficient between the two was greater than 0.8.

This study used in-person interviews to measure the number of suicide attempts across a person's lifetime.

The "Have you ever attempted suicide in your lifetime?" question was adapted from the World Health Organization multicenter study's original instrument [18]. "Yes" or "no" was chosen to encode the response. If the respondent answered "yes," we recorded this idea's specific date, time, and method.

Biochemical analysis

Venous blood samples were collected from subjects following an overnight fast. The biochemical analysis was performed by a technician blind to the clinical status of the participants. The biochemical indexes were measured, including diastolic blood pressure (DBP), systolic blood pressure (SBP), anti-thyroglobulin (TgAb), thyroid stimulating hormone (TSH), free triiodothyronine (FT3), thyroid peroxidases antibody (TPOAb) and free thyroxine (FT4).

Statistical analysis

A Kolmogorov–Smirnov one-sample test was chosen to evaluate the normal distribution. With respect to variables that did not follow a normal distribution, the Mann–Whitney U test was utilized. Analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables were used to compare the groups. Furthermore, to investigate which characteristics increase the risk of suicide attempts in patients with MDD comorbid moderate-to-severe anxiety, we conducted univariate analyses of patients who attempted suicide and those who did not. Moreover, the logistic regression (Backward: Wald) took into account the components that were statistically distinct. In order to distinguish between individuals who attempted suicide and those who did not, we used the Receiver Operating Characteristic (ROC) curve analysis. We used SPSS 23.0 (IBM, Chicago, IL, USA) for all of our statistical analysis. Visualization was accomplished using GraphPad Prism 6.0. The $p < 0.05$ indicated statistical significance.

Table 1 Socio-demographic and clinical characteristics between MDD with and without moderate-to-severe anxiety

Variables	MDD without moderate-to-severe anxiety (*N* = 824)	MDD with moderate-to-severe anxiety (*N* = 894)	x^2	*P*
Gender			1.249	0.264
Male	293 (35.6%)	295 (33.0%)		
Female	531 (64.4%)	599 (67.0%)		
Marital status			0.517	0.472
Single	234(28.4%)	268 (30.0%)		
Married	590 (71.6%)	626 (70.0%)		
Suicide attempters			156.687	**< 0.001**
No	762 (92.5%)	610 (68.2%)		
Yes	62 (7.5%)	284 (31.8%)		
Variables	**MDD without moderate-to-severe anxiety (*N* = 824)**	**MDD with moderate-to-severe anxiety (*N* = 894)**	***F***	***P***
Age, years	34.45 ± 12.23	35.26 ± 12.60	1.347	0.178
DUI, months	6.13 ± 4.70	6.47 ± 4.75	1.472	0.141
HAMD	28.81 ± 2.45	31.67 ± 2.67	23.002	**< 0.001**
PPS	7.16 ± 1.12	10.41 ± 5.55	16.455	**< 0.001**
CGI	5.66 ± 0.63	6.23 ± 0.75	16.702	**< 0.001**
TSH, uIU/mL	4.49 ± 2.07	5.60 ± 2.83	9.164	**< 0.001**
TgAb, IU/L	67.69 ± 213.63	110.60 ± 257.45	3.742	**< 0.001**
TPOAb, IU/L	57.44 ± 146.84	85.92 ± 176.93	3.614	**< 0.001**
FT3, pmol/L	4.88 ± 0.73	4.92 ± 0.71	0.981	0.327
FT4, pmol/L	16.71 ± 3.10	16.68 ± 3.09	0.209	0.834
BMI	24.34 ± 1.95	24.38 ± 1.89	0.362	0.717
SBP, mmHg	117.99 ± 10.61	120.86 ± 11.01	5.498	**< 0.001**
DBP, mmHg	75.04 ± 6.54	76.79 ± 6.81	5.433	**< 0.001**

The significance of bold emphases in the table is $P < 0.05$

DUI duration of untreated illness, *HAMD* Hamilton depression rating scale, *PPS* psychotic positive score, *CGI* Clinical Global Impression, *TSH* Thyroid Stimulating Hormone, *TgAb* anti-thyroglobulin, *TPOAb* thyroid peroxidases antibody, *FT3* free triiodothyronine, *FT4* free thyroxine, *BMI* Body Mass Index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Results

Prevalence of recent suicide attempts of MDD patients with moderate-to-severe anxiety symptoms vs. those without moderate-to-severe anxiety symptoms

The prevalence of MDD patients with moderate-to-severe anxiety symptoms was 52.04% (894/1718). As shown in Table 1, suicide attempts were more common among MDD patients with moderate-to-severe anxiety symptoms ($n = 284$, 31.80%) compared to those without these symptoms ($n = 62$, 7.5%). The results showed that MDD patients with moderate-to-severe anxiety symptoms had higher HAMD, CGI, and psychotic positive scores and higher levels of TSH, TgAb, and TPOAb compared to MDD patients without these symptoms (all $p < 0.001$). Similar results were found in SBP and DBP ($p < 0.001$).

Among patients with recent suicide attempts, 71.3% occurred within the past week, and 62.4% took place in the morning. The methods included drug overdose (46.8%), hanging (35.6%), wrist-cutting (10.7%), and other methods (6.9%), such as jumping from heights, drowning, or lying on railway tracks.

Clinical characteristics and biochemical parameters of suicide attempters vs. non-suicide attempters in MDD patients with comorbid moderate-to-severe anxiety

As shown in Table 2, compared to non-suicide attempters, suicide attempters showed significant variations in clinical parameters, such as HAMD score, PANSS positive symptom score, and CGI score (all $p<0.05$). Additionally, suicide attempters had elevated levels of TSH, TgAb, TPOAb, SBP, and DBP compared to non-suicide attempters (all $p<0.05$).

The related factors of recent suicide attempts in MDD patients comorbid with moderate-to-severe anxiety

In Table 3, we analyzed the risk factors of suicide attempts in MDD patients comorbid with moderate-to-severe anxiety. The results suggested the risk factors of suicide attempts in MDD patients with moderate-to-severe anxiety were as follows: CGI score ($B=0.805$, $p<0.001$, OR = 2.237), TSH ($B=0.103$, $p=0.008$, OR = 1.108), TPOAb ($B=0.003$, $p<0.001$, OR = 1.003) and DBP ($B=0.033$, $p=0.043$, OR = 1.034). To further investigate the role of the risk factors in MDD patients with moderate-to-severe anxiety, ROC curve analysis was conducted. The area under the curve (AUC) of ROC indicated the following values for each risk factor: CGI score was 0.695, TSH was 0.705, TPOAb was 0.632, and DBP was 0.617 (Fig. 1).

Discussion

To our knowledge, this study was the first to investigate the incidence and influencing factors of suicide attempts in MDD patients comorbid with moderate-to-severe anxiety. Our results showed that (1) the incidence of MDD comorbid moderate-to-severe anxiety patients was 52.04%; (2) the prevalence of recent suicide attempts in MDD comorbid moderate-to-severe anxiety patients was 31.8%, which was 4.24 times higher than that in patients without moderate-to-severe anxiety; (3) CGI score, TSH, TPOAb, and DBP could distinguish between suicide attempts and non-suicide attempts in MDD individuals who had moderate-to-severe anxiety symptoms.

Our study revealed that 52.04% of MDD patients exhibited moderate-to-severe anxiety symptoms, which added to the growing body of research on the special anxiety symptoms of MDD patients. It is worth mentioning that the current study focused on moderate or higher anxiety (HAMA scores ≥ 21). Previous studies have primarily emphasized the prevalence of MDD patients

Table 2 Socio-demographic and clinical characteristics between suicide attempters and non-suicide attempters in MDD comorbid moderate-to-severe anxiety

Variables	Non-suicide attempters ($N=610$)	Suicide attempters ($N=284$)	x^2	P
Gender			0.172	0.678
Male	204 (33.4%)	91 (32.0%)		
Female	406 (66.6%)	193 (68.0%)		
Marital status			3.049	0.081
Single	194 (31.8%)	74 (26.1%)		
Married	416 (68.2%)	210 (73.9%)		
Variables	**Non-suicide attempters ($N=610$)**	**Suicide attempters ($N=284$)**	F	P
Age, years	34.85 ± 12.81	36.13 ± 12.13	1.416	0.157
DUI, months	6.20 ± 4.70	7.03 ± 4.81	2.409	0.016
HAMD	31.19 ± 2.52	32.70 ± 2.70	8.179	**< 0.001**
PPS	9.48 ± 4.58	12.41 ± 6.80	7.568	**< 0.001**
CGI	6.06 ± 0.74	6.59 ± 0.64	10.385	**< 0.001**
TSH, uIU/mL	4.94 ± 2.53	7.01 ± 2.92	10.782	**< 0.001**
TgAb, IU/L	89.42 ± 230.45	156.08 ± 303.02	3.629	**< 0.001**
TPOAb, IU/L	54.14 ± 115.31	154.19 ± 251.62	8.154	**< 0.001**
FT3, pmol/L	4.89 ± 0.70	4.96 ± 0.74	1.274	0.203
FT4, pmol/L	16.63 ± 3.04	16.79 ± 3.18	0.690	0.490
BMI	24.41 ± 1.77	24.32 ± 2.13	0.609	0.543
SBP, mmHg	119.10 ± 10.21	124.64 ± 11.72	7.191	**< 0.001**
DBP, mmHg	75.84 ± 6.29	78.82 ± 7.41	6.217	**< 0.001**

The significance of bold emphases in the table is $P<0.05$

DUI duration of untreated illness, *HAMD* Hamilton depression rating scale, *PPS* psychotic positive score, *CGI* Clinical Global Impression, *TSH* Thyroid Stimulating Hormone, *TgAb* anti-thyroglobulin, *TPOAb* thyroid peroxidases antibody, *FT3* free triiodothyronine, *FT4* free thyroxine, *BMI* Body Mass Index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Table 3 The related factors of suicide attempt in MDD patients comorbid with moderate-to-severe anxiety

Variables	B	Std. error	Wald	*P*	OR	95% CI
Constant	−10.856	1.641	43.781	**< 0.001**	< 0.001	
DUI, months	0.010	0.017	0.346	0.556	1.010	0.977–1.045
HAMD	0.028	0.042	0.456	0.500	1.028	0.948–1.116
PPS	0.023	0.017	1.824	0.177	1.023	0.990–1.058
CGI	0.805	0.139	33.361	**< 0.001**	2.237	1.702–2.939
TSH, uIU/mL	0.103	0.038	7.128	**0.008**	1.108	1.028–1.195
TgAb, IU/L	0.000	0.000	0.643	0.423	1.000	0.999–1.000
TPOAb, IU/L	0.003	0.001	25.032	**< 0.001**	1.003	1.002–1.004
SBP, mmHg	0.003	0.011	0.054	0.817	1.003	0.980–1.025
DBP, mmHg	0.033	0.017	4.093	**0.043**	1.034	1.001–1.068

The significance of bold emphases in the table is $P < 0.05$

DUI duration of untreated illness, *HAMD* Hamilton depression rating scale, *PPS* psychotic positive score, *CGI* Clinical Global Impression, *TSH* Thyroid Stimulating Hormone, *TgAb* anti-thyroglobulin, *TPOAb* thyroid peroxidases antibody, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

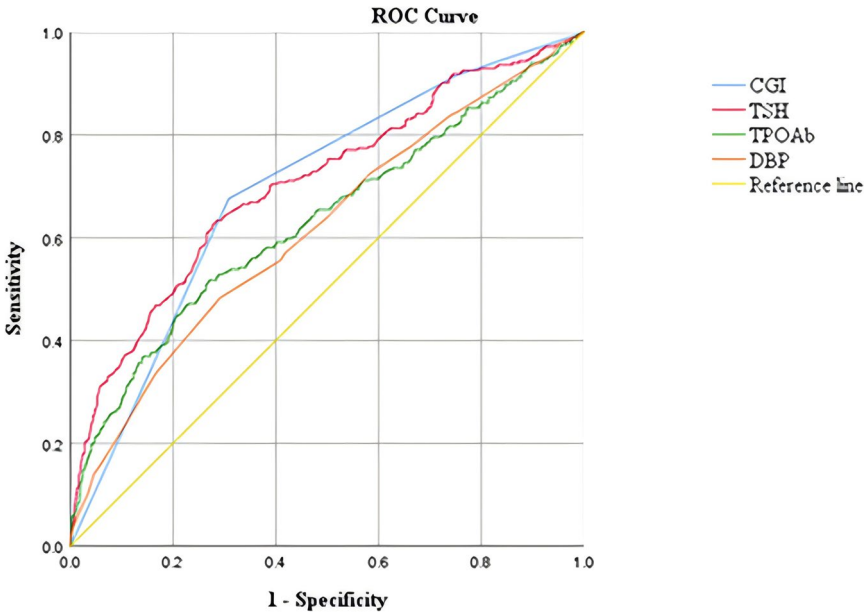

Fig. 1 The discriminatory capacity of related factors for distinguishing between patients with and without suicide attempts in MDD comorbid with moderate-severe anxiety. The area under the curve was 0.695 for CGI, 0.705 for TSH, 0.632 for TPOAb, and 0.617 for DBP, respectively

with concomitant anxiety symptoms [19]. Patients with a diagnosis of MDD with mixed features may have rates of anxiety comorbidity in the range of 45–65% [20–22]. Besides, we have also reported a 79.2% incidence of first-episode drug-naïve MDD with anxiety symptoms (HAMA scores ≥ 18) [16]. One possible explanation for the contradictory results is the diverse study population. Furthermore, a randomized controlled trial of 968 individuals with depression found that 788 were classified as having anxious depression, resulting in a prevalence of depression with anxiety symptoms of 81.4% [23]. The higher incidence may be attributed to different scoring criteria, which utilized an anxiety/somatization factor score ≥ 7 in the HAMD scale to assess anxiety symptoms, not the HAMA scale. These results suggest that there is a consistent pattern: individuals with MDD are more likely to have additional symptoms of anxiety. Nevertheless, there is currently less research on the incidence of patients with MDD with moderate-to-severe anxiety, a population that is at greater risk of causing suicide or other problems, and more attention should be paid to this population in the future.

Suicidal ideation and behavior have a profound impact on individuals, families, and society [24]. Prior research

has suggested that the distressing sensation of anxiety might increase the likelihood of both long-term suicide risk and immediate suicidal conduct, especially among young individuals [25]. One of the principal findings of our study was that the incidence of suicide attempts among MDD comorbid moderate-to-severe anxiety patients was 31.8%. In contrast, Xin et al. showed a very low incidence of suicide attempts (4.51%) in MDD patients with anxiety symptoms [26]. This paradoxical result may be due to the varying severity of anxiety in patients with MDD. Patients with moderate-to-severe anxiety had a 28-fold higher risk of suicide attempts or plans compared to those with mild anxiety, according to the healthy minds study, which suggests that the severity of anxiety or depression is associated with a significantly increased incidence of suicide attempts [27]. Moreover, we also observed that MDD patients with comorbid moderate-to-severe anxiety had a 4.24-fold elevated risk of suicide compared to those without moderate-to-severe anxiety symptoms. However, Grunebaum et al. showed that MDD patients who had attempted suicide had lower levels of anxiety compared to those who had not attempted suicide [28]. Inconsistency in results may be because of different definitions of anxiety symptoms. Grunebaum et al. defined anxiety symptoms using one of the five factors in the 24-item HAMD scale- anxiety factor, while we employed the HAMA scale, which has been validated for its reliability and validity [29].

In this study, we further found that CGI score and DBP were influential factors for recent suicide attempts in MDD patients comorbid with moderate-to-severe anxiety. Consistent with our findings, previous studies have demonstrated a significant positive correlation between CGI scores and depression severity, and MDD patients with suicide attempts have higher scores on the HAMA and CGI scales [30, 31]. A recent systematic review has indicated that mental illness, particularly MDD and anxiety, can lead to substantial increases in blood pressure variability [32]. Elevated diastolic blood pressure has been associated with more severe depressive symptoms, suicidal ideation, and suicide attempts [33], although the population in the referenced study differs significantly from ours, with unique confounding factors, these findings suggest a potential link that warrants further exploration across diverse populations.

Our study also confirmed this finding. Some studies suggested that inflammatory cytokines might play an important role, as heightened levels of inflammatory cytokines were linked not only to hypertension but also to suicide [34, 35]. However, our study did not measure inflammatory cytokine levels, thus necessitating further investigation to elucidate biological mechanisms.

Besides, we also identified thyroid hormones, TSH, and TPOAb as influential factors for suicide attempts in MDD individuals who had moderate-to-severe anxiety symptoms. Our previous study showed that elevated TSH levels were positively correlated with anxiety severity in patients with MDD [36]. Two earlier studies also affirmed the potential of TSH in predicting suicide attempts. Liu et al. showed that compared to non-suicide attempters, suicide attempters exhibited higher HAMD and HAMA ratings, along with elevated levels of TSH [37]. Among individuals with MDD, Zhang et al. found that TSH levels were a strong predictor of suicidal ideation and behavior [38]. In addition, our earlier studies have demonstrated that MDD patients with elevated TPOAb levels tend to have higher levels of anxiety as well [39]; besides, the more severe the anxiety, the greater the risk of suicidal ideation and behavior. Thyroid hormones might be determinants of suicidal ideation in MDD patients suffering from extreme anxiety, according to the aforementioned research. Interventions targeting thyroid function may effectively reduce suicide risk in MDD comorbid moderate-to-severe anxiety patients. Consequently, routine monitoring of dynamic changes in TSH and TPOAb levels in MDD patients with comorbid moderate-to-severe anxiety is warranted.

Several limitations should be noted regarding this investigation. First, it was a cross-sectional study and could not prove a causal relationship between CGI score, DBP, TSH, TPOAb, and suicide attempts in MDD individuals with comorbid moderate-to-severe anxiety. Second, smoking and alcohol were not collected, which might be significantly related to hormone secretion. Third, the determination of the history of suicide attempts was conducted through interviews, which may be subject to recall bias. Fourth, we did not explore the factors influencing the specific information of suicide attempts. However, the method and time of suicide were very important for MDD patients, especially the prevention of suicide was extremely critical. Therefore, future research could explore the factors that influence suicide patterns and explore ways to prevent them.

Conclusion

Our findings mainly revealed that almost half of the patients with MDD had concomitant moderate-to-severe anxiety. Furthermore, compared to individuals without symptoms of moderate-to-severe anxiety, MDD patients with this condition were significantly more likely to attempt suicide. Recent suicide attempts in MDD patients with moderate-to-severe anxiety were associated with CGI score, TSH, TPOAb, and DBP.

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Authors' contributions
Xiangyang Zhang: Conceptualization, Resources, Writing—review & editing. Guoshuai Luo: Software, Methodology, Supervision. Lina Ren, Yeqing Dong and Xiaojing Zhou: Data curation, Formal analysis, Writing—original draft, Writing—review & editing. Chuhao Zhang, Jiajia Gao, Lulu Li, Xiao Zhang, and Min Zeng: Data curation, Formal analysis, Software, Visualization. All authors contributed to and have approved the final manuscript.

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Data availability
The authors declare that all relevant data from this study are available within the article or from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The protocol for the research project had been approved by the Institutional Review Board (IRB) of the First Hospital of Shanxi Medical University (ID number: 2016-Y27) and had therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All informed consent forms of patients were obtained, and their anonymity was protected.

Consent for publication
The authors declare no conflicts of interest and agree to publish.

Competing interests
The authors declare no competing interests.

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