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Gender differences in clinical characteristics and influencing factors of suicide attempts in first-episode and drug-naïve major depressive disorder patients with comorbid metabolic syndrome

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Abstract

Backgrounds Patients with major depressive disorder (MDD) have a high rate of metabolic syndrome (MetS), which could worsen disease progression. One of the most serious progressions in MDD is suicide attempts (SAs). Previous studies have found gender differences in MetS and SAs among MDD patients respectively. Therefore, we aimed to explore gender differences of SAs in first-episode and drug-naïve (FEDN) MDD patients with comorbid MetS.

Methods 1718 outpatients with FEDN MDD were recruited. Depression, anxiety and psychotic symptoms were evaluated using the Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA) and Positive and Negative Syndrome Scale (PANSS) positive subscale, respectively. Blood sugar, blood fat, blood pressure and body mass index (BMI) were measured to evaluate MetS.

Results 34.4% patients with FEDN MDD were diagnosed as MetS and those subjects with or without MetS differed in the distribution of SAs and gender. In MetS subgroup, 29.5% and 29.7% of male and female subjects had SAs respectively, without significant differences. However, compared with non-suicide attempters, suicide attempters had higher level of blood pressure in female subjects, while there are no differences in any clinical variables in male subjects. Additionally, the influencing factors for SAs differed by gender. The HAMA scores and BMI were variables associated with SAs in male patients while HAMA scores, marital status and systolic blood pressure (SBP)

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were associated with SAs in female patients. Furthermore, the receiver operating characteristics (ROC) curves, demonstrating the combination all influencing factors by gender, showed good performance and model accuracy.

Conclusions In FEDN MDD patients with comorbid MetS, there were no gender differences in SAs. However, clinical characteristics and influencing factors of SAs differed in different gender groups.

Keywords Major depressive disorder, Metabolic syndrome, Suicide attempts, Gender difference

Introduction

Major depressive disorder (MDD) is a highly prevalent psychiatric disorder with a global prevalence of 3.4%~4.4% in China [1, 2]. More seriously, MDD is one of the most disabling psychiatric disorders and patients with MDD are at high risk of suicide [3, 4]. Previous studies have shown that suicide is the leading cause of death in Asian MDD patients [5]. Particularly in China, approximately 90% of suicide completers and suicide attempters suffered from psychiatric disorders, of which 40–70% were diagnosed with depression [6–9]. Notably, suicide attempts (SAs) are common in patients with MDD and are one of the strongest predictors of death by suicide [10]. Furthermore, studies have shown that the pooled lifetime prevalence of SAs in MDD patients is as high as 23.7%, which is 20 times higher than that in the general population in China [11]. Therefore, it is urgent to find the influencing factors of SAs in MDD patients to screen and prevent suicide effectively.

In recent years, several studies have found that depressed patients with metabolic syndrome (MetS) have a worse prognosis, lower quality of life, and greater despair and suicidal ideation (SI) than patients without comorbid MetS [12]. MetS is a cluster of cardiometabolic risk factors and comorbidities conveying a high risk of both cardiovascular events and cerebrovascular diseases, which could cause significant physical impairments, even premature death [13, 14]. Furthermore, many studies found that patients with MDD had a high prevalence of MetS. A meta-analysis showed that the prevalence of MetS in MDD patients was 30.5% [15]. Another study from India found the prevalence of MetS in hospitalized patients with MDD was as high as 44.3% [16]. Moreover, it has been found that there is bi-directionality between MDD and MetS. On the one hand, MDD patients were more likely to suffer from MetS than healthy subjects; on the other hand, MetS was a predisposing factor for MDD and positively correlated with the severity of depression [17, 18]. The high comorbidity rate and bi-directionality of MDD and MetS suggest that there may be a close correlation in pathophysiology between them. However, to our knowledge, there is no study to explore the clinical characteristics and influencing factors of SAs in MDD patients with comorbid MetS, especially in China.

Whether there is a gender difference between SAs and MDD remains controversial. Some studies have consistently demonstrated that females comprise a larger proportion of suicidal attempters than males, citing mood disorders are more common in female suicide attempters than in males [19–21]. However, some studies have shown that there is no difference between male and female suicide attempters with MDD [22]. Additionally, previous studies have indicated gender differences in patients with or without MetS. A large-scale study from Norway showed the prevalence of MetS in middle-aged males was slightly higher than that in females (males vs. females: 33% vs. 30%) [23]. Furthermore, one study found not only that the majority of the psychiatric patients had a risk of MetS, but also gender was significantly associated with MetS [24]. They found male psychiatric patients had an 88% decreased risk of MetS compared to female patients.

Therefore, we hypothesize a gender difference exists in clinical characteristics and influencing factors of SAs in first-episode and drug-naïve (FEDN) MDD patients with comorbid MetS. In this study, we will test our hypothesis based on a large population from China by exploring the clinical information of suicide attempters with MDD and comorbid MetS in different genders.

Methods

Study settings and subjects

Patients were recruited from the Department of Psychiatry, First Hospital of Shanxi Medical University between 2015 and 2017. This study was approved by the Institutional Review Board (IRB) of the First Hospital of Shanxi Medical University and written informed consent was obtained from all participants before commencement. The inclusion and exclusion criteria we applied were as follows (Fig. 1):

Inclusion criteria include: [1] Age between 18 and 60 years old; [2] Meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for MDD; [3] The first episode of MDD without antidepressant (ADs) or antipsychotic treatment; [4] the 17-item Hamilton Depression Scale (HAMD-17) scores ≥ 24.

Exclusion criteria include: [1] Diagnosis of the mental illness other than MDD or the organic brain diseases, ongoing infections, immunosuppressive therapy, and other severe physical diseases; [2] Substance abuse or dependence (excluding nicotine); [3] Pregnant or

breastfeeding; [4] refusal to participating in the study or signing informed consent.

Study design and measures

All participants were interviewed face-to-face by the Structure Clinical Interview for DSM-IV (SCID-I/P). Data were collected from self-designed questionnaires and patients' peripheral blood, which were recorded by trained psychiatrists and laboratory physicians. Notably, the questionnaire consisted of demographic and clinical variables. Demographic variables included age, age of depression onset, duration of depression, gender, height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), marital and educational status. Clinical variables were composed of depressive, anxious, and psychotic symptoms. The HAMD-17 was used to evaluate the level of depression in patients [25], the 14-item Hamilton Anxiety Scale (HAMA-14) was applied to assess the severity of anxiety in patients [26], and the Positive and Negative Syndrome Scale (PANSS) positive subscale was used to measure the psychotic symptoms of patients [27]. The Chinese-language version of those scales have good reliability and validity [28–30].

Participants' peripheral blood was collected between 7:00 and 9:00 a.m. and then aliquoted and stored at a temperature below −70 degrees Celsius. The patients were required to fast the night before the blood draw. Blood pressure was also measured between 7:00 and 9:00 a.m. All laboratory physicians carried out biochemical parameter measurements without knowing the experimental hypothesis in advance. Fasting biochemical indexes were measured, including triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and fasting blood glucose (FBG).

Definition of BMI, MetS, and SAs

Body mass index (BMI)

BMI is a statistical index using a person's weight and height to provide an estimate of body fat in males and females of any age. The calculation formula of BMI is weight in kilograms divided by height in meters squared [31].

Metabolic syndrome (MetS)

MetS is a syndrome characterized by a series of metabolic disorders such as abdominal obesity, dyslipidemia, hypertension, and impaired fasting glucose or insulin resistance [14, 32]. According to the revised criteria of the National Cholesterol Education Program (NCEP)-Third Adult Treatment Panel III-A (ATP III-A), the diagnosis of MetS in our study was based on the presence of three or more of the following: [1] enlarged waist circumference (≥80 cm for females and ≥90 cm for males in Chinese patients); [2] TG≥150 mg/dL (1.7 mmol/L) or HDL-C<40 mg/dL (1.03 mmol/L) in males or <50 mg/dL (1.29 mmol/L) in females; [3] SBP≥130 or DBP≥85 mm Hg; [4] FBG≥100 mg/dL (5.6 mmol/L), of which we used BMI (≥25 kg/m2) to replace enlarged waist circumference [33].

Suicide attempts (SAs)

SAs refers to an individual's attempt to end his/her life by some degree of self-harm. SAs were measured using the question, "Have you ever attempted suicide in your lifetime?", with the answer encoded as "yes" or "no". If the respondent answered "yes" to this question, he/she was classified as a suicide attempter. Otherwise, he/she was a non-suicide attempter [34]. Then, the following details would be collected: the exact date of each suicide attempt, the times, and the method of attempts. If the patient could not give a clear answer, additional interviews with family and/or friends to clarify the information would be conducted.

Statistical analysis

The nonparametric Mann- Whitney U test was used for continuous variables while Pearson's Chi-Square test was used for the categorical variables. The Kolmogorov-Smirnov test or the Shapiro-Wilk test was used to detect the normality of the distribution of the variables. The median/inter-quartile range was used for continuous variables that did not conform to the normality of the distribution, and the number of case/percentage was used for categorical variables. Additionally, Bonferroni correction was used to adjust for multiple testing. Logistic regression analysis was used to calculate the odds ratio (OR) of SAs in FEDN MDD patients with or without MetS. The variables were screened by using univariate logistic regression analysis ($P=0.20$) with male and female patients with comorbid MetS diagnosed with SAs as the dependent variable and other variables as the independent. Multivariable logistic regression analysis (Backward: LR) was then performed for variables that were statistically significant in the univariate logistic regression analysis, with P-value criteria of 0.01 and 0.05 for entry and exclusion, respectively. Finally, the receiver operating characteristics (ROC) curve was drawn to test the predictive power of the model for suicide attempters with FEDN MDD and comorbid MetS by gender. All tests were two-sided and the statistical significance was set at $P<0.05$. Data analysis was calculated by SPSS version 23.0 and ROC curves were performed using the pROC R language package [35].

Table 1 Demographic and clinical characteristics of FEDN MDD patients with or without comorbid MetS

FEDN MDD (*N* = 1718)				
	Without MetS	**With MetS**	**Z/X2**	**P**
Sample size	1127 (65.6%)	591 (34.4%)		
Age	32.00 (21.000)	39.00 (22.000)	-5.967	< 0.001
Age of depression onset	32.00 (21.000)	39.00 (22.000)	-5.983	< 0.001
Duration of depression (months)	4.50 (5.000)	6.00 (6.000)	-4.803	< 0.001
Education (years)	12.00 (4.000)	12.00 (7.000)	-4.012	< 0.001
HAMD scores	30.00 (4.000)	32.00 (4.000)	-10.655	< 0.001
HAMA scores	20.00 (4.000)	21.00 (5.000)	-6.099	< 0.001
PANSS positive subscale scores	7.00 (0.000)	7.00 (3.000)	-8.941	< 0.001
Marital status				
single	362 (32.1%)	140 (23.7%)	13.328	< 0.001
married	765 (67.9%)	451 (76.3%)		
Suicide attempts				
No	956 (84.8%)	416 (70.4%)	50.247	< 0.001
Yes	171 (15.2%)	175 (29.6%)		
Gender				
Male	432 (38.3%)	156 (26.4%)	24.535	< 0.001
Female	695 (61.7%)	435 (73.6%)		

Notes:

FEDN: first-episode and drug naïve;

MDD: major depressive disorder;

MetS: metabolic syndrome;

HAMD: Hamilton Depression Scale;

HAMA: Hamilton Anxiety Scale;

PANSS positive subscale: Positive and Negative Syndrome Scale positive subscale

Table 2 The ORs and 95%CIs of SAs in FEDN MDD patients with comorbid MetS compared with those without comorbid MetS

	Model A		**Model B**	
	OR (95%CI)	**P**	**OR (95%CI)**	**P**
all subjects	2.352 (1.850–2.990)	< 0.001	1.691 (1.288–2.22)	< 0.001
male	2.319 (1.505–3.574)	< 0.001	1.773 (1.084–2.899)	0.022
female	2.369 (1.768–3.173)	< 0.001	1.647 (1.180–2.299)	0.003

Notes:

SAs: Suicide attempts;

FEDN: first-episode and drug naïve;

MDD: major depressive disorder;

MetS: metabolic syndrome;

Model A did not adjust any confounding parameters;

Model B adjusted the full confounding parameters (age, age of onset, duration of illness, level of education, marital status, HAMD scores, HAMA scores, and PANSS positive subscale scores);

HAMD: Hamilton Depression Scale;

HAMA: Hamilton Anxiety Scale;

PANSS positive subscale: Positive and Negative Syndrome Scale positive subscale

Results

The demographic and clinical characteristics of MetS in FEDN MDD patients

Table 1. presents the demographic and clinical characteristics of FEDN MDD patients with or without MetS. Of the 1718 patients with FEDN MDD in this study, 34.4% (591/1718) were diagnosed with MetS. This study also showed significant differences between the two groups in terms of the distribution of SAs and gender, both being more female than male patients (without MetS: 61.7% vs. 38.3%, with MetS: 73.6% vs. 26.4%). After further analysis, our results showed that the MetS group was more likely to suffer from SAs than the non-MetS group regardless of gender in model A without adjusting any confounding parameters (OR $_{whole}$=2.352, 95%CI $_{whole}$: 1.850–2.990, P_{whole}< 0.001; OR $_{male}$=2.319, 95%CI $_{male}$: 1.505–3.574, P_{male}< 0.001; OR $_{female}$=2.369, 95%CI $_{female}$: 1.768–3.173, P_{female}< 0.001) (Table 2.). In model B with adjusting the full confounding parameters (age, age of depression onset, duration of depression, education, marital status,

Table 3 Demographic and clinical characteristics of male and female FEDN MDD patients with MetS

	FEDN MDD with MetS (*N* = 591)			
	Male (*N* = 156)	**Female (*N* = 435)**	**Z/X²**	**P**
Sample size	156 (26.4%)	435 (73.6%)		
Age	35.50 (24.000)	40 (22.000)	-1.743	0.081
Age of depression onset	35.00 (24.000)	40.00 (22.000)	-1.829	0.067
Duration of depression (months)	6.00 (7.000)	6.00 (6.000)	-0.460	0.646
Education (years)	12.00 (7.000)	12.00 (7.000)	-1.497	0.134
HAMD scores	32.00 (4.000)	31.00 (4.000)	-1.307	0.191
HAMA scores	21.00 (5.000)	21.00 (5.000)	-0.375	0.708
PANSS positive subscale scores	7.00 (3.000)	7.00 (3.000)	-0.444	0.657
Marital status				
single	43 (27.6%)	97 (22.3%)	1.761	0.185
married	113 (72.4%)	338 (77.7%)		
Suicide attempts				
No	110 (70.5%)	306 (70.3%)	0.002	0.969
Yes	46 (29.5%)	129 (29.7%)		
BMI	25.27 (2.000)	25.30 (2.100)	-0.778	0.436
TG	2.33 (1.270)	2.41 (1.060)	-0.014	0.999
HDL-C	0.93 (0.460)	1.08 (0.360)	-1.900	0.057
SBP	126.00 (11.000)	126.00 (12.000)	-0.232	0.816
DBP	78.00 (10.000)	78.00 (10.000)	-1.247	0.212
FBG	5.90 (0.570)	5.78 (0.860)	-1.274	0.203
the number of MetS components	3.00 (1.000)	3.00 (1.000)	-1.275	0.202

Notes:

FEDN: first-episode and drug naïve;

MDD: major depressive disorder;

MetS: metabolic syndrome;

HAMD: Hamilton Depression Scale;

HAMA: Hamilton Anxiety Scale;

PANSS positive subscale: Positive and Negative Syndrome Scale positive subscale

HAMD scores, HAMA scores, and PANSS positive subscale scores), the SAs in patients with MetS were still significantly higher than subjects without MetS in whole, male and female groups (OR $_{whole}$=1.691, 95%CI $_{whole}$: 1.288–2.220, P_{whole}< 0.001; OR $_{male}$=1.773, 95%CI $_{male}$: 1.084–2.899, P_{male}= 0.022; OR $_{female}$=1.647, 95%CI $_{female}$: 1.180–2.299, P_{female}= 0.003).

The demographic and clinical characteristics of suicide attempters vs. non-suicide attempters in FEDN MDD with comorbid MetS by gender

Table 3 shows that 29.6% (175/591) of FEDN MDD patients with comorbid MetS had attempted suicide, and 29.7% of female FEDN MDD patients with comorbid MetS suffered from SAs, which was similar to the male groups (29.5%). Then, we explored differences in clinical variables between male and female FEDN MDD patients with comorbid Mets and found no statistical differences between them in all variables, including SAs. After further analysis, the results showed that gender was not an influencing factor for SAs in FEDN MDD patients with MetS in model A without adjustment for any confounding parameters, or in model B with adjustment for all confounding parameters (age, age of depression onset, duration of depression, education, marital status, HAMD score, HAMA score, and PANSS positive subscale score) (Table 4.).

Table 4 The ORs and 95%CIs of SAs in male or female FEDN MDD patients with MetS

	OR (95%CI)	***P***
Model A	1.008(0.675, 1.505)	0.969
Model B	1.020(0.636, 1.634)	0.936

Notes:

SAs: Suicide attempts;

FEDN: first-episode and drug naïve;

MDD: major depressive disorder;

MetS: metabolic syndrome;

Model A did not adjust any confounding parameters;

Model B adjusted the full confounding parameters (age, age of onset, duration of illness, level of education, marital status, HAMD scores, HAMA scores, and PANSS positive subscale scores);

HAMD: Hamilton Depression Scale;

HAMA: Hamilton Anxiety Scale;

PANSS positive subscale: Positive and Negative Syndrome Scale positive subscale

Furthermore, the differences in clinical variables between suicide attempters and non-suicide attempters with FEDN and comorbid MetS in different gender groups were compared (Table 5.). Overall, suicide attempters had higher HAMD, HAMA, and PANSS positive subscale scores than non-suicidal attempters both in male and female groups (all $P<0.05$). Moreover, we found that the female suicide attempters differed with non-suicide attempters in MetS components such as TG, HDL-C, the level of blood pressure including SBP and DBP, and FBG (all $P<0.05$). After Bonferroni correction for differences of those MetS components, only the level of blood pressure including SBP and DBP still had statistical significance (all $P_{\text{Bonferroni correction}} < 0.0083$). However, there was a statistically significant difference in FBG between those with and without SAs among male subjects, and this difference disappeared after Bonferroni correction. Additionally, the significant difference in the number of MetS components was found between suicide attempters and non-suicide attempters with FEDN MDD and comorbid MetS in the female population ($P<0.012$), but this difference was not found in the male population.

The influencing factors for SAs in FEDN MDD patients with MetS by gender

As shown in Table 6, some significantly different variables were included in the multivariate logistic regression analysis (Backward: LR) based on the results of the univariate logistic regression analysis (Table S1 and Table S2; test level was set to $P=0.2$). The results showed that HAMA scores (OR=1.326, 95%CI: 1.174–1.497, $P<0.001$) and BMI (OR=0.789, 95%CI: 0.649–0.960, $P=0.018$) were associated with SAs in male FEDN MDD patients with comorbid MetS. Furthermore, marital status (OR=1.335, 95%CI: 1.237–0.547, $P<0.001$); HAMA scores (OR=0.289, 95%CI: 0.153–1.439, $P<0.001$) and

Table 5 The demographic and clinical characteristics of suicide attempters vs. non-suicide attempters in FEDN MDD with comorbid MetS by gender

FEDN MDD with comorbid MetS (*N*=591)								
	Male (*N*=156)				Female (*N*=435)			
	Without SAs	With SAs	Z/X2	P	Without SAs	With SAs	Z/X2	P
Sample size	110 (70.5%)	46 (29.5%)			306 (70.3%)	129 (29.7%)		
Age	36.00 (24.000)	33.00 (23.000)	-0.774	0.439	40.00 (22.000)	40.00 (24.000)	-0.817	0.414
Age of depression onset	35.50 (24.000)	33.00 (23.000)	-0.768	0.442	39.00 (22.000)	40.00 (24.000)	-0,772	0.440
Duration of depression (months)	5.00 (7.000)	6.00 (8.000)	-0.792	0.428	6.00 (5.000)	6.00 (6.000)	-1.152	0.249
Education (years)	12.00 (7.000)	12.00 (7.000)	-0.681	0.496	12.00 (3.000)	12.00 (7.000)	-0.440	0.660
HAMD scores	32.00 (4.000)	32.50 (3.000)	-2.318	0.020	31.00 (3.000)	33.00 (4.000)	-6.982	< 0.001
HAMA scores	20.00 (5.000)	23.00 (6.000)	-4.773	< 0.001	20.00 (4.000)	24.00 (5.000)	-9.581	< 0.001
PANSS positive subscale scores	7.00 (2.000)	7.00 (13.000)	-2.548	0.011	7.00 (1.000)	9.00 (13.000)	-7.841	< 0.001
BMI	25.32 (1.900)	25.11 (2.900)	-1.730	0.084	25.35 (2.100)	25.12 (2.200)	-1.280	0.201
TG	2.28 (1.060)	2.65 (1.230)	-1.164	0.244	2.36 (0.980)	2.63 (1.380)	-2.154	0.031
HDL-C	0.92 (0.440)	0.97 (0.440)	-0.634	0.526	1.10 (0.360)	0.98 (0.330)	-2.514	0.012
SBP	124.00 (11.000)	128.50 (14.000)	-1.718	0.086	124.00 (12.000)	130.00 (12.000)	-6.049	< 0.001[a]
DBP	78.00 (10.000)	80.00 (11.000)	-1.473	0.141	78.00 (7.000)	80.00 (11.000)	-5.160	< 0.001[a]
FBG	5.80 (0.680)	6.03 (0.460)	-2.074	0.038	5.75 (0.870)	5.92 (0.920)	-2.443	0.015
the number of MS components	3.00 (1.000)	3.00 (1.000)	-0.894	0.371	3.00 (1.000)	4.00 (1.000)	-2.500	0.012
Marital status								
single	32 (29.1%)	11 (23.9%)	0.436	0.509	62 (20.3%)	35 (27.1%)	2.472	0.116
married	78 (70.9%)	35 (76.1%)			244 (79.7%)	94 (72.9%)		

Notes:

FEDN: first-episode and drug naïve;

MDD: major depressive disorder;

MetS: metabolic syndrome;

HAMD: Hamilton Depression Scale;

HAMA: Hamilton Anxiety Scale;

PANSS positive subscale: Positive and Negative Syndrome Scale positive subscale;

BMI: Body mass index;

TG: Triglycerides;

HDL-C: High-density lipoprotein cholesterol;

SBP: Systolic blood pressure;

DBP: Diastolic blood pressure;

FBG: fasting blood glucose

Table 6 , results of multivariate logistic regression analysis: influencing factors for male and female suicide attempters or non-attempters with FEDN MDD and comorbid MetS

variables	Wald	df	*P*	OR	95% CI	
					Lower	Upper
Male						
HAMA	20.776	1	0.000	1.326	1.174	1.497
BMI	5.596	1	0.018	0.789	0.649	0.960
Female						
Marital status	56.095	1	0.000	1.335	1.237	0.547
HAMA	14.550	1	0.000	0.289	0.153	1.439
SBP	28.238	1	0.000	1.083	1.052	1.116

Notes:

FEDN: first-episode and drug naïve;

MDD: major depressive disorder;

MetS: metabolic syndrome;

HAMA: Hamilton Anxiety Scale;

BMI: Body mass index;

SBP: Systolic blood pressure

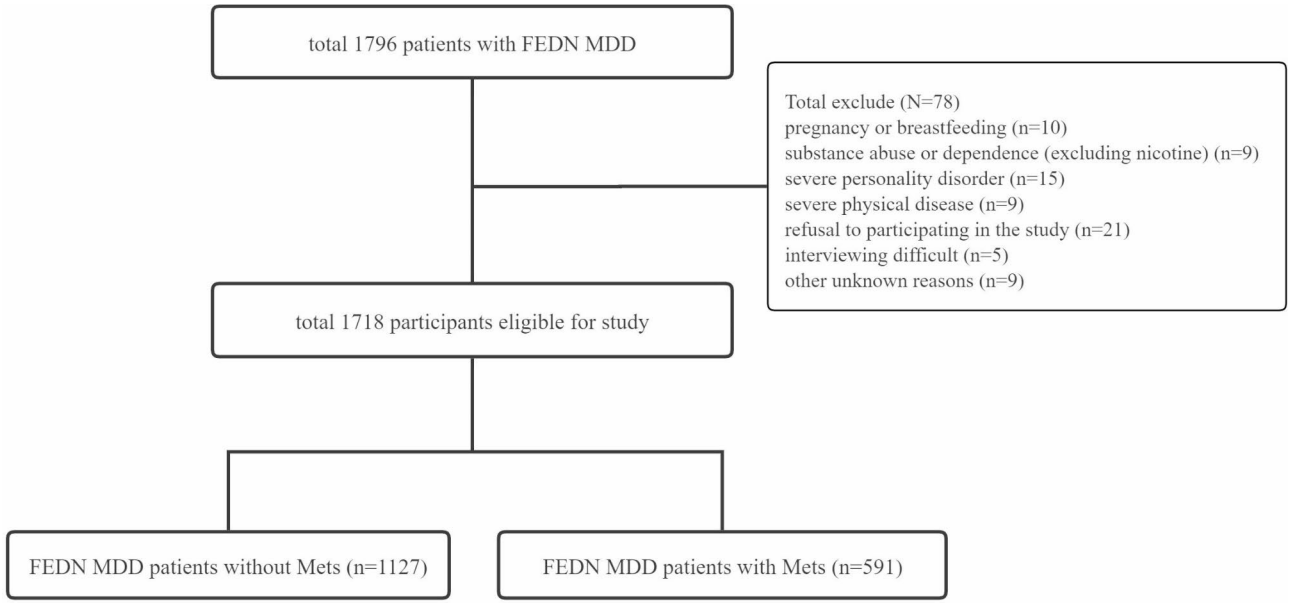

Fig. 1 Flowchart of this study

SBP (OR=1.083, 95%CI: 1.052–1.116, $P<0.001$) were strongly associated with SAs in female FEDN MDD patients with comorbid MetS.

The ROC curve in Fig. 2 showed the following values for each influencing factor of male patients: HAMA scores was 0.74 and BMI was 0.59. The combination of HAMA scores and BMI had a higher AUC value of 0.76 to distinguish suicide attempters from non-attempters in male group after combining above parameters ($P<0.001$, 95%CI=0.67–0.84).

The ROC curve in Fig. 3 showed the following values for each influencing factor of female patients: HAMA scores was 0.79, marital status was 0.47, and SBP was 0.68. The combination of HAMA scores and BMI had a higher AUC value of 0.82 to distinguish suicide attempters from non-attempters in female group after combining above parameters ($P<0.001$, 95%CI=0.78–0.87).

Discussion

As far as we know, this study was the first large-scale study to report the SAs in FEDN MDD patients with comorbid MetS by gender in China. Firstly, we explored the proportion of FEDN MDD patients with comorbid MetS. Then, the study showed that there were significant differences in the distribution of SAs and gender between those with or without comorbid MetS, and further showed that the SAs of the MetS group were higher than that of non-MetS group. Further analysis demonstrated

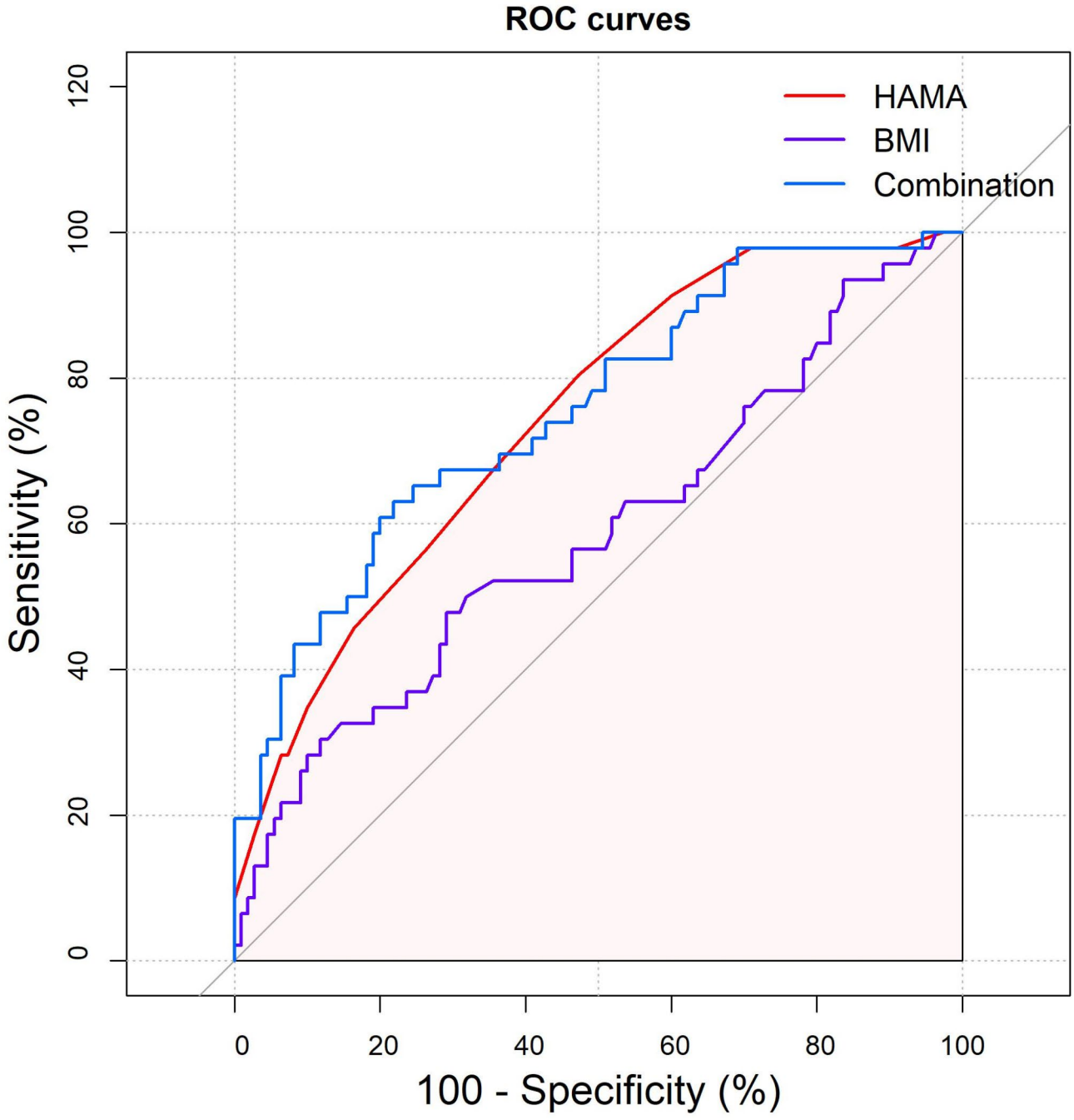

Fig. 2 The ROC curve of logistic regression prediction model for SAs in FEDN MDD patients with comorbid MetS (male). The area under the curve of HAMD score, BMI, and the combination of these two factors were 0.74, 0.59, 0.76, respectively

that gender was not an influencing factor for SAs in FEDN MDD patients with MetS. However, different influencing factors of SAs in FEDN MDD patients with comorbid MetS in different gender groups were found in this study. Finally, the ROC curves by combining all influencing factors by gender demonstrated good performance and model accuracy.

According to our study, the proportion of MetS in FEDN MDD patients was 34.4%, similar to previous studies. For instance, a meta-analysis based on 5531 depressed individuals indicated the prevalence of MetS in people with MDD was 30.5% (95% CI 26.3–35.1), and when these individuals were compared with age- and gender-matched control groups, individuals with MDD had a higher MetS prevalence [18]. Furthermore, our results showed that the proportion of MetS in female patients with FEDN MDD was higher than those in male individuals (38.5% vs. 26.5%). However, the prevalence of

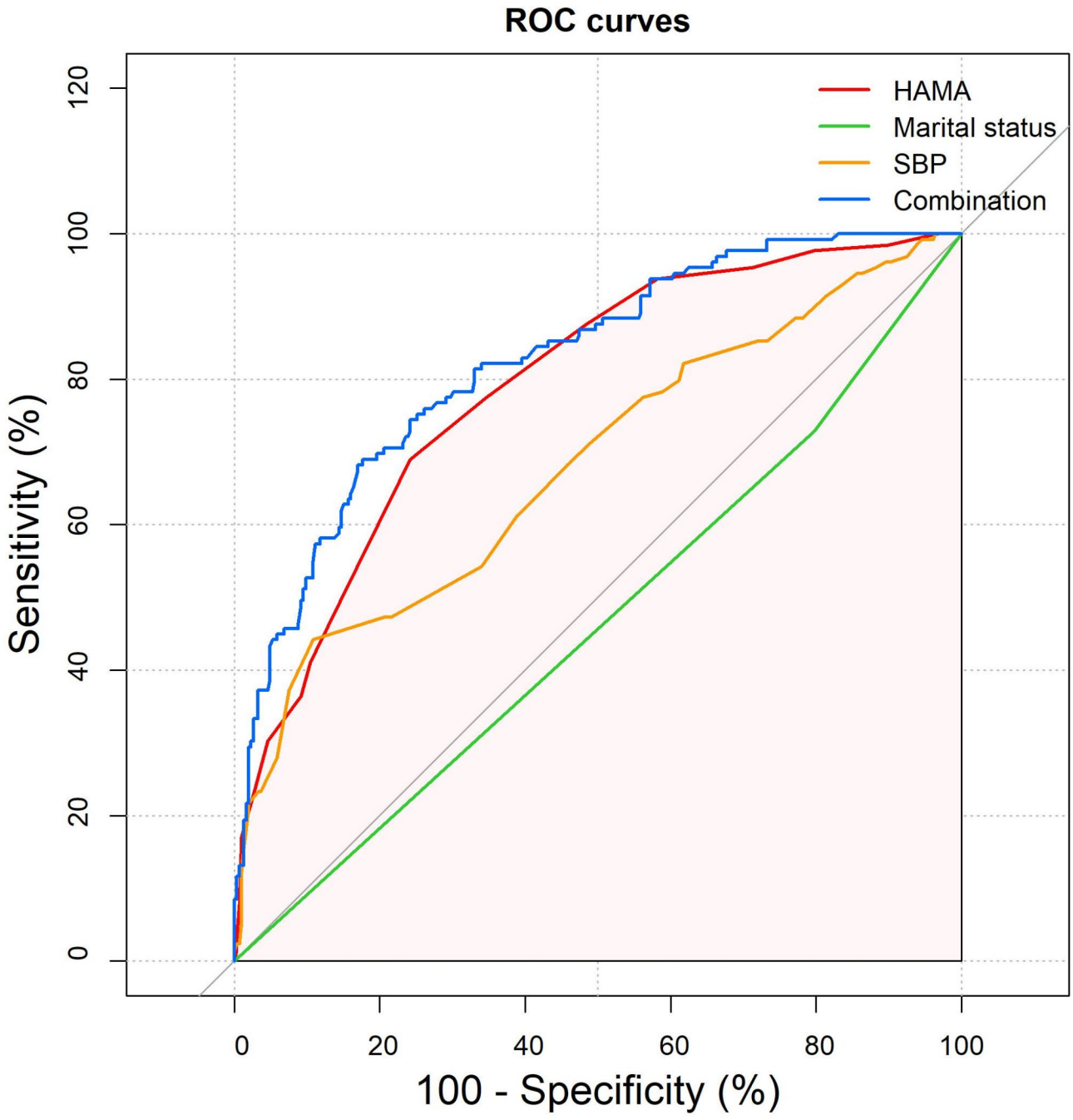

Fig. 3 The ROC curve of logistic regression prediction model for SAs in FEDN MDD patients with comorbid MetS (female). The area under the curve of HAMD score, marital status, SBP and the combination of these two factors were 0.79, 0.47, 0.68, 0.82, respectively. Notes: ROC: Receiver operating characteristics; FEDN: first-episode and drug naïve; MDD: major depressive disorder; MetS: metabolic syndrome; SAs: Suicide attempts; HAMA: Hamilton Anxiety Scale; BMI: Body mass index; SBP: Systolic blood pressure

MetS in patients with MDD by gender is controversial. Indeed, some researchers have found that the prevalence of MetS in female MDD patients is higher than that of males [36]. However, other researchers have found that male MDD patients have higher prevalence of Mets than female patients [37]. It is worth noting that the diagnostic criteria of MetS used between studies were different. One study found that, for the same study sample, the prevalence of International Diabetes Federation (IDF) -defined MetS in females was slightly higher than male group (30.3% vs. 29.0%), but the prevalence was 26.8% in men and 25.0% in women by the revised NCEP-ATP-III definition in 2005 [23]. Moreover, the prevalence of the MetS increased with age, especially among women. Another

study also found the prevalence of MetS increased with the age for both genders. The prevalence of MetS in male patients was higher than female patients under 60 years old, but this phenomenon was reversed in patients over 60 years old [38]. Given these lingering questions, additional longitudinal studies are needed.

There was a significant difference in SAs between FEDN MDD patients with and without comorbid MetS, where FEDN MDD patients with comorbid MetS were more likely to suffer from SAs than those without MetS in our study. This result appeared in all patients, whether as a whole or divided by gender. Likewise, Isomaa et al. found that people with MetS had higher mortality than those without MetS according to the WHO definition [39]. The high rate of suicide and mortality in patients with MetS may be related for many reasons. It has been reported that MetS is significantly associated with a variety of diseases, such as cardiovascular disease, type 2 diabetes and dementia, which could reduce the quality of life and significantly increase the economic burden of patients [40]. They also found that MetS was strongly associated with an unhealthy lifestyle, for example, junk diet, physical inactivity and poor physical fitness. However, there are few related studies on MDD patients with comorbid MetS. Therefore, it is necessary to explore the differences and influencing factors between individuals with or without SAs in depressed patients with comorbid MetS.

Previous studies have consistently shown that the severity of depression, anxiety and psychotic symptoms in MDD patients increased suicidal behavior. Hoertel et al. found that the severity of depression independently predicted SAs in patients with MDD [41]. Zhou et al. found that MDD patients with anxiety symptoms had a much higher incidence of SAs than those MDD patients without anxiety symptoms [42]. Leo et al. found that PANSS positive subscale score was higher among veterans with SAs compared to those without SAs [43]. We also found that both male and female patients with SAs had a higher level of HAMD, HAMA and PANSS positive subscale scores than patients without SAs in the MetS subgroup. Moreover, our results showed that the severity of HAMA was an influencing factor of SAs in both male and female patients. The HAMA scale was known as a valid and reliable indicator of the severity of anxiety in depressed patients [44]. Another meta-analysis also have demonstrated that patients with anxiety disorders had more suicidal behaviors, including SI and SAs, and complete suicide more frequently than those without anxiety disorders [45]. Furthermore, Hawton et al. reported that anxiety was a risk factor for SAs in MDD [46]. Therefore, it is essential for the prevention of SAs to evaluate and monitor the severity of depression, anxiety and psychotic symptoms, especially the severity of anxiety, among FEDN patients with comorbid MetS regularly.

In terms of the components of MetS, influencing factors of SAs in FEDN MDD patients with MetS differed by gender. BMI was negatively associated with SAs in male FEDN MDD patients with MetS in our study. It has been reported that an increased suicide mortality rate was associated with weight loss [47, 48]. Another study found that obese people were less likely to commit suicide than people of low or normal weight likewise [49]. Moreover, one study based on 18,784 male subjects over 38 years showed that obesity and unexplained weight loss were associated with an elevated suicide risk [50]. Female suicide attempters in FEDN MDD patients with comorbid MetS had higher level of blood pressure (including SBP and DBP) than non-suicide attempters in our study. Similarly, Liu et al. also found suicide attempters had higher level of SBP and DBP than non-suicide attempters [51]. After further analysis, we found that SBP was an influencing factor of female subjects. Mental health has an impact on the relationship between suicide and hypertension. Previous study found MDD combined with hypertension had additional adverse impact on physical function and quality of life of patients [52]. Depression in hypertensive patients was associated with poorer health status, including lower quality of life, increased medical sources, lower rate of treatment compliance, and even increased mortality [53–56]. Moreover, it has been reported nearly 20% of people with hypertension had SI [57], which would be more common in hypertensive patients with depression. Additionally, there were many risk factors, such as estrogen, for the development of vascular diseases in female [58]. This will lead to a higher rate and severity in female depression with hypertension which alarm us that we must attach great importance to depression patients with hypertension, especially among female population.

Gender differences in suicide behavior among depressed patients with comorbid MetS are still controversial. Fang et al. found that male gender was a risk factor for SI in patients with MDD, while other researcher found that female patients with MDD had higher rates of SI than male patients [59, 60]. Another study found that male MDD patients had higher rates of completed suicide [61], but the rates for SAs of male MDD patients was lower than that of female patients [62]. Our study revealed that although gender was not an influencing factor for SAs in FEDN MDD patients with MetS, the influencing factors for SAs in male and female groups were different. The severity of HAMA and BMI were influencing factors of male suicide attempters in FEDN MDD patients with comorbid MetS while the severity of HAMA, marital status and SBP were influencing factors of female patients. Furthermore, the ROC curves,

demonstrating the combination all influencing factors by gender, showed good performance and model accuracy, which may help quickly identify potential suicide risks among different genders in clinical practice. In a word, clinicians should not only give individualized diagnosis and treatment to patients of different genders, but also have a holistic view of the disease in clinical work.

Limitations

There are some limitations of this study that should be noted. First, this is a case-control design study and cannot draw any causal conclusion. Thus, the controversial questions mentioned above need to be explored by further longitudinal studies. Second, since all our participants were patients with FEDN MDD, it was not possible to exclude potential patients with bipolar disorders, which is indeed one of the methodological limitations of this study. We should have followed these patients for 3–6 months to exclude patients with bipolar disorder. Third, in this study, we asked each subject the following question: "Have you ever attempted suicide in your lifetime?" If yes, the subject was taken as a suicide attempter. If this attempt occurred far before the current depressive episode, it indicates that the patient might have suffered another depressive episode so that he/she could not be diagnosed as the first-onset depressive episode. In future studies, we should compensate for this limitation by asking patients another question: "Have you recently attempted suicide after having MDD? Fourth, considering the diagnosis of MDD, we did not use any diagnostic tools such as the Structured Clinical Interview for DSM-5 Disorders (SCID-5) or the MINI-International Neuropsychiatric Interview (M.I.N.I), which should be remedied in future studies. Fifth, the psychotic symptoms of MDD patients are different from those of schizophrenia patients. The PANSS was designed for patients with psychosis, especially schizophrenia. We should have used more suitable scales to assess psychotic symptoms in MDD patients, such as the HDRS items of "feelings of guilt", "hypochondriasis" and "insight" or the psychotic disorder scale in the M.I.N.I., which will be remedied in future studies. Additionally, we did not use a specialized structured assessment tool, such as the Beck Scale for Suicide Ideation (BSSI), or the Columbia-Suicide Severity Rating Scale (C-SSRS) to assess the severity of SAs, and therefore need to examine the association between relevant factors and the severity of suicidal behaviors in future studies. Finally, despite the large sample size of 1718 outpatients with MDD, this study was conducted in the outpatient department of a general hospital and all recruited patients were Han people. Therefore, our findings in this study may not be representative, and cannot be generalized to other populations, such as inpatients, community patients, outpatients in psychiatric hospitals and other population with different ethnic and clinical backgrounds.

Conclusion

In summary, there were significant differences in the distribution of SAs and gender between FEDN MDD patients with or without comorbid MetS. In the MetS subgroup, although gender was not an influencing factor for SAs in FEDN MDD patients with MetS, clinical characteristics and influencing factors of those subjects with SAs differed in different gender groups. HAMA score was an influencing factor for all individuals with SAs. However, marital status and SBP were associated with SAs in female subjects while only BMI was associated with SA in male subjects. This underscores the importance of providing gender-specific interventions and screening protocols for suicide attempters among FEDN MDD patients with comorbid MetS. This has the potential to enhance suicide prevention efforts and improve the management of MetS in psychiatric settings.

Abbreviations

Ads	Antidepressant
BMI	Body mass index
BSSI	Beck Scale for Suicide Ideation
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
FBG	Fasting blood glucose
FEDN	First-episode and drug naïve
HAMA	Hamilton Anxiety Scale
HAMD	Hamilton Depression Scale
HDL-C	High-density lipoprotein cholesterol
IDF	International Diabetes Federation
IRB	Institutional Review Board
MDD	Major depressive disorder
MetS	Metabolic syndrome
M.I.N.I	MINI-International Neuropsychiatric Interview
NCEP- ATP	National Cholesterol Education Program-Third Adult Treatment Panel
OR	Odds Ratio
PANSS	Positive and Negative Syndrome Scale
ROC	Receiver Operating Characteristics
SAs	Suicide attempts
SBP	Systolic blood pressure
SCID-5	Structured Clinical Interview for DSM-5 Disorders
SI	Suicidal ideation
TG	Triglycerides

Supplementary Information

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Supplementary Material 1

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Author contributions

P.S. and YY.H. wrote the main manuscript text and performed the analyses; H.Y. and XH.W. collect the data; J.C. provided language help and writing assistance; XY.Z. and YR.F. designed the study. All authors have reviewed and approved

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Data availability
The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Declarations
The manuscript has been read and approved by all the authors, that the requirements for authorship as stated by the journal have been met, and that each author believes that the manuscript represents honest work.

Ethics approval and consent to participate
This study was approved by the Institutional Review Board (IRB) of the First Hospital of Shanxi Medical University. After the study procedures were explained to the participants, written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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