

Potential metabolic monitoring indicators of suicide attempts in first episode and drug naive young patients with major depressive disorder: a cross-sectional study

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Abstract

Backgrounds: Major depressive disorder is an ordinary mental disorder, suicide and physical health deterioration are two major sequelae. Some studies indicate that metabolic levels are associated with suicide attempt. Previous studies have focused on the relationship between suicide attempts and metabolism in elderly patients with MDD, while ignore the young people. The aim of this study is to find the potential relationship between suicide attempts and metabolism in young MDD patients to find a promising way to effectively prevent and ultimately reduce suicide in young MDD patients.

Methods: Cross-sectional design was employed in the study. 740 patients aged between 18 and 45 years old with MDD had been consecutively recruited in this study, 128 of whom had suicide attempts. Their serum samples which used to monitor fasting blood glucose, serum lipids as well as socio-demographic characteristics were collected. Besides, some clinical scales were also employed to measure symptoms of anxiety, depression and other conditions.

Results: This study indicated that compared with non-suicide attempters, suicide attempters in young patients with MDD showed higher levels of FBG, TC, LDL-C (all $p < 0.05$) and lower levels of HDL-C ($p < 0.001$). Further logistic regression analysis suggested that suicide attempts were associated with increased FBG with an odd ratio (OR) of 1.832, decreased HDL-C with an OR of 1.891 and obvious anxiety with an OR of 4.103.

Conclusions: suicide attempts in young patients with MDD may be predicted by metabolic levels in the future. And our findings suggested that the level of FBG and HDL-C can be promising biomarkers to predict the occurrence of this event.

Background

Major depressive disorder (MDD) is an ordinary mental disorder with a characteristic of insidious onset and a recurrent course. It mainly manifests as depressed, reduced interest, impaired concentration, insomnia or even intense suicidal ideation[1]. Among all the factors that lead to years lived with disability (YLD), mental disorders play a key role. However, approximately 40% of substantial disability and disease burden originates from two major sequelae of MDD: suicide as well as physical health deterioration[2]. It is obvious that there's a connection between suicide and MDD. Suicidal behavior is a global cause of injury and mortality, ranking as the fifteenth leading cause of death by WHO[3], which is sure to be the worst outcome of MDD[4].

Referring to risk factors for suicide attempt (SA), earlier studies have clarified, including occurrence of a major episode of depression[5], gender difference[6], age, education level, chronic diseases[7], the disturbance of metabolism[8], alcohol dependence[9], smoking[10] and so on. Although the concrete mechanisms are still unknown, speculations can be based on the foundation of these. According to the data from WHO in 2017, about 800,000 people commit suicide worldwide. Among the age groups, the incidence of suicide in youth is higher. On the basis of the definition of WHO, people who aged between

18-45 are considered as young people. Besides, throughout the lifespan the rapidest growth in the death number of suicide takes place between early period of adolescence and young adulthood[11]. Young people are the backbone of a nation, thus suicidal attempts among youth warrant social concerns.

Metabolic levels are likely to have a bidirectional relationship with psychological distress [12] and are also associated with suicidal attempts. The relationship between metabolism and suicide attempts has been discussed in many studies. For instance, a community-based cohort study showed that metabolic abnormalities are correlated with suicide[13].The study focused on the community and the objects of the study are all older than 30 years old with no specific mental health diseases. It could be better if they also focused on other different health care systems or more specific people. Therefore, this study didn't comprehensively analyze the relationship between metabolic levels and suicide in the condition of specific diseases, like MDD. However, it gave inspirations that there indeed existed correlation between metabolism and suicide. Another research revealed that lower serum cholesterol and triglyceride levels were found in the bipolar disorder men with suicide attempts in comparison to those without suicide attempts [8].However, Jalal Shakeri et al. expressed their opinions in the study that in patients with bipolar disorder aged from 21 to 60 , the incidence of suicide attempt was associated with higher cholesterol values[14].Both studies concentrated on the correlation between the serum cholesterol and suicide in the bipolar disorder patients, but drew the different conclusions. Even though, several other studies also held the view that low cholesterol increases suicidal risk[15-17].Thus, it is interesting to probe into the distinction and relation. Except serum cholesterol, the level of blood glucose makes a difference to the incidence of suicide as well. A pilot study suggested that abnormal glucose metabolism may reflect biological changes ahead or concomitant with suicide[18]. Diabetes mellitus with depression showed higher past rate of suicide attempts [19].What's more, a cohort study about investigating the risk factors for future suicide found that diabetes rather than raised blood glucose impinge on suicide[20].However, due to the low incidence of metabolic diseases in young people, most studies have ignored this group, and we speculate that abnormal metabolism in patients with depression, although not up to the disease standard, may also have an impact on suicidal behavior[21].

Taking a panoramic view of the studies, we find that researches on the relationship between metabolic levels and suicide attempts in patients with MDD are rare or merely emphasizes on the one side. For example, Ji Hyun Baek et al. suggested that in MDD patients , the serum lipids levels are associated with suicide attempts[22]. Hannu Koponen et al. indicated that glucose disturbances and lipid metabolism commonly exist in the groups of patients with depression aged 35 years and older [23],their results could be better if the subjects of depression are further subdivided according to the degrees. Since of all the age groups, the incidence of suicide in youth is higher. However, most related studies either concentrated on the whole crowd nor on the middle-aged and elderly, while ignore the group of youth. The group of youth is worthy of attention, for they are pillars of the society. Due to the pressure of life and other factors, more and more young people are subjected to depression, some ignore at first and then develop into MDD and finally commit suicide. Previous studies inspired us that there were potential links between metabolic levels and suicide attempts in patients with MDD. So we speculated that the relationship between metabolic levels and suicide attempts in young patients with MDD can also be found.

Therefore, we pay attention to this special groups, by systematically analyzing the correlation between metabolic levels and suicide attempts in patients with MDD aged 18-45 so as to find biomarkers to intervene when suicide ideation is in its infancy in the earlier life in MDD patients.

Methods

Study design

Cross-sectional design was employed in the study. The aim of this study is to find the potential relationship between SA and metabolism in young MDD patients to find a promising way to effectively prevent and ultimately reduce suicide in young MDD patients.

Subjects

According to the inclusion and exclusion criteria, this study had consecutively recruited 740 MDD patients, 128 of whom had suicide attempts before. The inclusion criteria were (1) ethnic Han, aged from 18 to 45 years; (2) conformed to the MDD criteria on DSM-IV ; (3) the score of the 17-item Hamilton Rating Scale for Depression (HAMD) reached 24 or greater and depressive symptoms were the first episode when enrolled; (4) not contacted with any antidepressants or antipsychotics before. And the exclusion criteria were (1) a psychiatric diagnosis except MDD; (2) people who had labile or severe physical conditions, for example, epilepsy, liver or kidney diseases, diabetes, heart diseases and so on; (3) people who were in pregnancy or breastfeeding; (4) with drugs addition and alcohol dependence; (5) those who refused to take part in. The cross-sectional was adopted in the study. And as for those who agreed to participate were inquired about the medical histories carefully and then underwent a systematic physical examination as well as the laboratory inspection.

Social demography and clinical measures collection and evaluation

Socio-demographic characteristics are made up of age, course of disease, age of onset, gender, cultural degree, marital status, body mass index (BMI). As for the MDD patients who used to have suicide attempts, their information about suicide attempts were required to be further learned about and collected.

17-item Hamilton depression rating scale (HAMD) was used in the research in order to quantify the severity of depression in subjects. The ratings on HAMD are confirmed by a semi-structured clinical interview with a maximum score of 52[24]. The standard for evaluation included: ≤ 7 means not depressed; ≥ 8 means depressed; ≤ 17 means mild to moderate depressive symptom; and ≥ 24 means severe depression[25]. The demarcation point of 24 is used to distinguish whether the patient is MDD or not.

In addition, Hamilton anxiety rating scale (HAMA) was employed to comprehensively measure the severity of perceived anxiety symptoms. All the items are rated on the 5-point scale, with a basic numeric

scoring of 0 (not present) to 4 (severe). The total score of HAMA is 56[26]. If the final score reaches or exceeds 21, the patient is considered having obvious anxiety symptoms.

The Positive and Negative Syndrome Scale (PANSS) was employed to assess the presence or absence of mental symptoms and the severity of each symptom. On the basis of the level of psychopathology, each item is scored on a 7-point scale. Those whose final scores reach or exceed 15 are defined as having psychotic symptoms in this study[27, 28].

Requests of the staff

At least two qualified psychiatrists who have had a good training on the use of HAMD, HAMA and PANSS scales were needed in the study. After the training, the correlation coefficient of inter-raters on these scales was more than 0.8. Above all, they were completely unaware of the patient's condition before the test.

Measure standards of suicide attempts

Suicide attempts are defined that the person who had suicidal thoughts and committed suicide, but for various reasons, he failed and was saved. By carefully enquiring the patients of whether patients have attempted suicide in their lifetime, if they answered yes and then the person was regarded as suicide attempters. After that, for suicide attempters, further questions were required to see the frequency, way and concrete date of the suicide attempts. If they answered uncertainly or unclearly, complementary information was gained by asking their family members, relatives or friends.

Collection and detection of serum samples and others

Overnight fasting blood samples of the patients were collected by the nurses and then delivered to the hospital's laboratory center to be measured by a chemiluminescence immunoassay using Cobas E610 (Roche, Basel, Switzerland). The serum indexes required included fasting blood-glucose (FBG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG). The normal range was between 3.90-6.10 mmol/L for FBG, less than 5.17mmol/L for TC, 1.04-2.07 mmol/L for HDL-C, less than 3.10mmol/L for LDL-C and 0.56-1.69 mmol/L for TG. Besides, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also monitored.

Statistical analysis

Socio-demographic data and clinical characteristics between participants with and without suicide attempts were analyzed by employing one-way analysis of variance (ANOVA) and Chi-squared test. In addition, the binary logistic regression analysis was utilized to analyze the factors associated with suicide attempts in young MDD patients. And then Pearson correlation analysis was used to explore the potential correlations between the serum indicators and clinical variables. Bonferroni corrections were used to adjust for multiple testing. All tests were two-sided with a p value of 0.05. The correlation

intensity was quantified by coefficient value, odds ratio (OR) and 95% confidence interval (CI). Data analysis was conducted by using SPSS version 25.0.

Results

Table 1 compares the socio-demographics, clinical characteristics and metabolic indicators between MDD patients with and without suicide attempts. Among all the MDD patients, 128 of 740 (17.3%) met the inclusion criteria as suicide attempters and the remain 612 (82.7%) were recognized as non-suicide attempters. Compared with non-suicide attempters, suicide attempters had relatively higher serum levels in FBG, TC, LDL-C, while lower level in HDL-C (all $p < 0.05$). Besides, young MDD patients with SA also showed differences in the course of disease, the scores of HAMD, HAMA, PANSS, and the blood pressure compared with those without SA (all $p < 0.05$).

Further binary logistic regression analysis (Table 2) indicated that in young MDD patients, suicide attempts were related to increased FBG with an odd ratio (OR) of 1.832 (95% CI: 1.071–3.133; $df = 1$, $p < 0.05$), decreased HDL-C with an OR of 1.891 (95% CI: 1.207–2.962; $df = 1$, $p < 0.01$) and obvious anxiety with an OR of 4.103 (95% CI: 2.515–6.692; $df = 1$, $p < 0.001$).

In addition, Pearson correlation analysis showed that there existed correlations between the level of FBG and the following parameters: depression ($r=0.282, df=740, p<0.001$), positive symptom ($r=0.149, df=740, p<0.001$), anxiety ($r=0.091, df=740, p=0.013$); correlations also existed in the level of TC and depression ($r=0.563, df=740, p<0.001$), positive symptom ($r=0.215, df=740, p<0.001$), anxiety ($r=0.277, df=740, p<0.001$). Besides, LDL-C was associated with depression ($r=0.365, df=740, p<0.001$), positive symptom ($r=0.122, df=740, p<0.001$), anxiety ($r=0.193, df=740, p<0.001$) and HDL-C was associated with depression ($r=-0.168, df=740, p<0.001$), positive symptom ($r=-0.117, df=740, p=0.001$), anxiety ($r=-0.086, df=740, p=0.019$) (Table 3). Except the difference between FBG and anxiety, HDL-C and anxiety, all significant differences had passed the Bonferroni corrections (Bonferroni corrected $p < 0.05/12=0.0041$).

Table 1 Socio-demographics, clinical characteristics and metabolic indicators between patients with and without suicide attempts

Variable	MDD without SA (n=612)		MDD with SA (n=128)		F/X ²	P
Age, mean (SD), y	22.68	4.09	22.98	3.765	0.610	0.435
Course of disease, mean (SD), m	4.58	2.99	5.54	3.85	9.710	0.002**
Gender						
Male, n (%)	236	38.6	51	39.8		
Female, n (%)	376	61.4	77	60.2		
Cultural degree						
Junior high school education level, n (%)	29	4.8	13	10.2		
Senior high school education level, n (%)	300	49.0	55	43.0		
University education level, n (%)	240	39.2	50	39.0		
Postgraduate education level, n (%)	43	7.0	10	7.8		
Marital status						
Single	384	62.7	86	67.2		
Married	228	37.3	42	32.8		
HAMD, mean (SD)	29.71	2.84	32.08	2.75	74.600	0.000***
HAMA, mean (SD)	20.03	3.10	23.20	3.47	105.711	0.000***
Obvious anxiety (HAMA ≥ 21), n (%)	270	44.1	102	79.7	740	0.000***
PANSS, mean (SD)	8.32	3.59	10.60	5.92	32.949	0.000***
Psychotic symptoms (PANSS ≥15)	43	7.02	24	18.75	6.643	0.012*
BMI, mean (SD), kg/m ²	24.31	1.87	24.14	2.75	0.694	0.405
SBP, mean (SD), mmHg	111.82	9.19	119.42	12.57	62.909	0.000***
DBP, mean (SD), mmHg	72.98	5.81	76.63	7.01	38.651	0.000***
FBG, mean (SD), mmol/L	5.32	0.61	5.61	0.70	23.145	0.000***
Increase (FBG > 6.1mmol/L), n (%)	66	10.8	29	22.7	13.334	0.000***

TC, mean (SD), mmol/L	5.00	1.07	5.80	1.14	57.461	0.000***
Increase (TC > 5.17mmol/L), n (%)	149	24.3	62	48.4	30.142	0.000***
HDL-C, mean (SD), mmol/L	1.25	0.28	1.12	0.31	20.920	0.000***
Decrease (HDL-C <1.04mmol/L), n (%)	147	24.0	55	43.0	19.153	0.000***
LDL-C, mean (SD), mmol/L	2.84	0.86	3.17	1.01	14.378	0.000***
Increase (LDL-C >3.10mmol/L), n (%)	222	36.3	70	54.7	15.024	0.000***
TG, mean (SD), mmol/L	2.12	0.97	2.25	1.05	1.756	0.185
Increase (TG >1.69mmol/L), n (%)	368	60.0	79	61.7	0.112	0.738

Note: MDD without SA = major depressive disorder without suicide attempts; MDD with SA = major depressive disorder with suicide attempts; HAMD = Hamilton depression rating scale, HAMA = Hamilton anxiety rating scale; PANSS= The Positive and Negative Syndrome Scale; BMI = body mass index; SBP= systolic blood pressure; DBP= diastolic blood pressure; FBG=fasting blood glucose; TC= total cholesterol; HDL-C= high-density lipoprotein cholesterol; LDL-C= low-density lipoprotein cholesterol; TG= triglyceride. *p < 0.05; **p < 0.01; ***p < 0.001.

Table 2 Logistic regression for factors associated with suicide attempts in MDD patients

Variable	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI for EXP(B)	
							Lower	Upper
Psychotic symptom	0.456	0.297	2.362	1	0.124	1.578	0.882	2.825
Obvious anxiety	1.412	0.250	31.968	1	0.000***	4.103	2.515	6.692
FBG increase	0.605	0.274	4.890	1	0.027*	1.832	1.071	3.133
TC increase	0.316	0.254	1.540	1	0.215	1.371	0.833	2.258
HDL-C decrease	0.637	0.229	7.740	1	0.005**	1.891	1.207	2.962
TG increase	-0.323	0.222	2.119	1	0.145	0.724	0.468	1.119
LDL-C increase	0.192	0.238	0.650	1	0.420	1.211	0.760	1.930

Note: FBG=fasting blood glucose; TC= total cholesterol; HDL-C= high-density lipoprotein cholesterol; TG= triglyceride; LDL-C= low-density lipoprotein cholesterol. * p < 0.05; **p < 0.01; ***p < 0.001

Table 3 Inter-corrections between some serum variables and clinical variables

variables	depression		positive symptom		anxiety	
	r	p	r	p	r	p
FBG	0.282	0.000***	0.149	0.000***	0.091	0.013***
TC	0.563	0.000***	0.215	0.000***	0.277	0.000***
HDL-C	-0.168	0.000***	-0.117	0.001 **	-0.086	0.019 *
LDL-C	0.365	0.000***	0.122	0.001 **	-0.193	0.000 ***

Note: FBG=fasting blood glucose; TC= total cholesterol; HDL-C= high-density lipoprotein cholesterol; LDL-C= low-density lipoprotein cholesterol. * p < 0.05; **p < 0.01; ***p < 0.001

Discussion

As far as we are concerned, our study for the first time put the emphasis on exploring the relationship between metabolic levels and suicide attempts among young patients who were in first episode and drug naive with MDD aged from 18-45. The sample size of this study was relatively large. The study aimed to find the potential relationship between SA and metabolic levels in young MDD patients to find a promising way to effectively prevent and ultimately reduce suicide in young MDD patients.

In general, this study found that in young MDD patients, suicide attempts have something to do with relatively high level of FBG, TC, LDL-C in serum, low level of HDL-C as well as high level of blood pressure, which may be promising biomarkers for evaluating suicidal attempts in patients with MDD. After binary logistic regression analysis, it suggested that elevated levels of FBG, decreased levels of HDL-C and the condition of obvious anxiety were regarded as independent risk factors for SA in young MDD patients.

As is suggested in this study that high level of FBG in serum is associated with suicide risk in MDD patients aged from 18-45, which is in accordance with the previous studies to a certain extent. Koponen revealed in his research that higher level of blood glucose for the OGTT at baseline and 2 hours were found in depression patients with suicide attempt compared to those without suicide attempt[23]. Other studies also showed the relationship between high level of blood glucose and suicide[20, 29]. Batty et al. found that raised fasting blood glucose increases the risk of suicide in their 14 years follow-up studies. And Ko et al. implicated that elevated level of fasting plasma glucose may lead to suicidal risk as well. One possible mechanism may be that glucose is a ubiquitous source of energy, which can provide energy to human brain cells. And some psychological processes like self-control and regulation of emotions are associated with the supply of glucose in the brain cells[30]. Elevated peripheric blood glucose can reflect the signs of intracellular glucose deficiency from the side. When the brain cells lack for glucose, the dysregulation of emotions may occur, which can lead to aggressive impulses, pessimism and impulsivity.

Hyperglycemia is a decrease in the ability of cells to absorb circulating glucose due to insulin deficiency or insulin resistance. It may explain why Diabetes mellitus combined with depression showed higher past rate of suicide attempts. Morbid blood glucose metabolism can greatly aggravate the risks of suicide attempts. Even though, we speculate that fluctuant blood glucose in normal range, especially elevated, can also influence the brain cells take in glucose, which can also increase the risks of suicide attempts. Moreover, we found that there existed correlations between the level of FBG and depression, anxiety and psychotic symptoms. Generated suicidal ideation can be further amplified when depression worsens[31]. Furthermore, Wanqiu Yang et al. suggested that anxiety deteriorated the depression and in MDD patients increased the rate of suicide attempts[32]. Elevated glucose levels are associated with mood disorders[33], thus we suggested that the changes of FBG can also indirectly increase the risks of SA by aggravating the degree of anxiety, depression and psychotic symptoms, especially when FBG increased.

Our study also revealed that in MDD patients with suicide attempts who aged from 18-45 had higher value of TC and LDL, which is inconsistent with some studies. For example, Segoviano-Mendoza et al. discovered that in Northern Mexico, MDD patients associated with suicide attempts showed lower level of cholesterol compared with healthy people[17]. The difference may occurred by the regional disparities and the ways of comparison was different from us. What's more, Papadopoulou et al. suggested that psychiatric patients who were used to have suicidal attempts showed lower TC than normal people[34]. However, the sample size of the study was relatively small and the objects of study didn't concentered to one specific disease, like MDD. Interestingly, Bartoli et al. showed in his research that serum cholesterol had nothing to do with suicide attempts[15]. The participants in this study included patients who had taken antipsychotics and / or antidepressants before, and drugs can have an effect on serum cholesterol levels as well as lead to confounding factors of the results. Besides, the average ages of the objects in this study are relatively high. However, some other studies drew another conclusion. For instance, Brunner et al. suggested that serum cholesterol and suicide had a positive association[35]. According to 2010 Korean National Health and Nutrition Examination Survey, Sun-Mi Kim et al. found that people with suicidal ideation had relatively higher TC than those without suicidal ideation[36]. Nevertheless, this study put the emphasis on the relationship between metabolic syndrome and suicidal ideation in adolescents and adults, which didn't make a study on the specific people with MDD. Even though, we can also get inspired that the level of cholesterol may be different in different groups or conditions. Our study focused on the young people, the possible hypothesis may be that the life style has changed due to the improvement of living standards , afterwards more and more young people are susceptible to the diets or other factors that may influence the level of serum lipids. Besides, previous studies made researches more on the westerners, while our study focused on Chinese. This may be the source of difference. In short, the level of TC and LDL-C remained controversial to some extent, but maybe the level of HDL-C can be used to predict suicide attempts in young MDD patients. Because our study revealed that a decreased level of HDL-C was regarded as a risk factor of suicide attempts in young patients with MDD. And we found that there existed relationship between the level of HDL-C and anxiety, depression and psychotic symptoms. Buydens-Branchey et al. indicated that low HDL-C was associated

with reduced 5-HT function[37].When 5-HT function reduced, it can aggravate the degree of depression and increase the risks of suicide behaviors.

The current study we did had several limitations. Firstly, the cross-sectional design made causal relationship between metabolic levels and suicide attempts in young MDD patients seem hard to be drawn. Therefore, the longitudinal study should be considered in future studies in order to study the causality better. Secondly, some other social demography factors that may influence the results were not included in the study. For instance, the condition of drinking or smoking, economic condition and so on. Thirdly, only certain age groups were studied, future studies will be done in other age ranges.

Conclusions

Identifying strong and accurate risk factors is a promising way to effectively prevent and ultimately reduce suicide in young MDD patients. Our studies concluded that in young MDD patients with suicide attempts, the levels of metabolism were quite different from those without SA. Among the metabolic indicators, we indicated the level of FBG and HDL-C were promising biomarkers, especially elevated FBG and decreased HDL-C. The results are important for clinical practice, because some changes in serum or psychiatric symptoms can predict certain development trend of suicide attempts in young MDD patients. Even though, more researches are still needed to clarify the intrinsic relationships between metabolism and suicide attempts in young MDD patients, because some results are different from previous studies which may be affected by some potential factors.

Abbreviations

MDD: Major Depressive Disorder; YLD: Years Lived with Disability; SA: Suicide Attempt; HAMD: Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale; PANSS: The Positive and Negative Syndrome Scale; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FBG: Fasting Blood Glucose; TC: Total Cholesterol; HDL-C: High-density Lipoprotein Cholesterol; LDL-C: Low-density Lipoprotein Cholesterol; TG: Triglyceride.

Declarations

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Ethics approval and consent to participate

This study was conducted at the psychiatric clinic department in a general hospital in Taiyuan, Shanxi province, China. And the study was authorized by the Institutional Review Board (IRB) of the First Clinical Medical College, Shanxi Medical University. All patients had signed the informed consent and were

informed of having rights to make up their mind or refuse to participate or quit anytime. 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.

Availability of data and materials

Data can be gained from the corresponding author.

Competing interests

None.

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Authors' contributions

ZK, ZSY, ZXY, TW and WW participated in the research design. SX, CJU, ZYY, FKL and ZXY collected and analyzed the data. ZXY, TW and WW helped conduct the analysis with constructive discussions. ZK, ZSY, SX, CJU, ZYY, FKL, ZXY, TW and WW contributed to the writing of the manuscript. All authors had read and approved the final manuscript.

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