


# Cognitive Impairment and Related Factors Among Middle-Aged and Elderly Patients with Type 2 Diabetes from a Bio-Psycho-Social Perspective


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**Objective:** This study investigated the biomedical, psychological, and social behavior risk factors for cognitive impairment in middle-aged and elderly patients with type 2 diabetes mellitus (T2DM).

**Methods:** This cross-sectional study included 240 patients with T2DM. A questionnaire was used to collect demographic and disease-related data on patients, and the Self-rating Depression Scale (SDS), Diabetes Self-care Scale (DSCS), and Social Support Rating Scale (SSRS) were used to assess patients' depression status, self-management behavior, and social support, respectively. The Chinese version of the Montreal Cognitive Assessment (MoCA) was used to evaluate cognitive function, with a score <26 set as the threshold for cognitive impairment.

**Results:** The prevalence of cognitive dysfunction in middle-aged and elderly patients with T2DM was 52.5%. Multivariate logistic regression analysis showed that older age, a history of hypoglycemia within 1 month, and depression were independent risk factors for cognitive impairment. Education for >12 years, urban living, and a higher total score on the DSCS were independent protective factors against cognitive impairment.

**Conclusion:** T2DM patients with high risk of cognitive impairment can be identified early from the bio-psycho-social perspective. Patients with T2DM who are older, less educated, living in rural areas, have hypoglycemia history, and have poor self-management of diabetes are at increased risk of cognitive impairment. Closer monitoring of patients with hypoglycemia, early detection of depression, and improving patients' self-management capacity can prevent cognitive impairment in middle-aged and elderly patients with T2DM.

**Keywords:** type 2 diabetes mellitus, cognitive impairment, depression, self-care, social support

## Introduction

Type 2 diabetes mellitus (T2DM) is a common metabolic disease characterized by chronic hyperglycemia. It is estimated that about 9.3% (463 million) of the adult population worldwide suffers from diabetes, with T2DM accounting for 90% of cases.<sup>1</sup> T2DM is often associated with organ damage and dysfunction including cardiovascular disease, blindness, nerve damage, and renal failure that can lead to disability or death.<sup>2</sup>

Recent studies have shown that T2DM increases the risk of cognitive impairment in middle-aged and elderly people.<sup>3,4</sup> About 10–20% of patients with T2DM experience mild cognitive impairment (MCI).<sup>5,6</sup> T2DM also accelerates the

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progression of MCI to dementia,<sup>7,8</sup> which can diminish the quality of life and prognosis of patients. Cognitive impairment is one of the serious complications of T2DM, but it is often easy to be ignored. There are no standardized recommendations on the prevention and treatment of T2DM cognitive impairment. In addition, the impairment of cognitive function is difficult to reverse.<sup>9</sup> Therefore, the early prevention of cognitive impairment is particularly important. Taking measures to delay the progress of cognitive impairment in MCI stage is the key measure to prevent its transformation to dementia.

The mechanism of type 2 diabetes affecting cognitive function is not yet clear. However, many studies have reported different risk factors, including long duration of diabetes, obesity,<sup>10</sup> physical inactivity, age,<sup>11</sup> depression,<sup>12</sup> lack of social support,<sup>13,14</sup> unstable blood glucose level,<sup>15,16</sup> elevated level of inflammatory markers,<sup>17</sup> and other diagnostic markers.<sup>18</sup> Some studies have reported the protective effects of being married and living in the city<sup>19</sup> on cognitive function in type 2 diabetic patients. And other studies have specifically explored the close relationship between cognitive function and self-management behavior.<sup>20,21</sup>

So far, the study on the influencing factors of cognitive function in T2DM patients is still limited, mainly focusing on biomedical factors, and many risk factors have also been evaluated separately. In this study, we investigated the status of cognitive function in middle-aged and elderly T2DM patients, and explored the effects of general information, self-management behavior, depression and social support on cognitive function in T2DM patients. To explore the risk factors of cognitive impairment in middle-aged and elderly T2DM patients from the biomedical, psychological, and social behavioral perspective. Furthermore, professional cognitive function assessment needs to be led by specialists and takes a long time. It is almost impossible to arrange professional evaluations for all T2DM patients. Therefore, we aim to provide clinicians and diabetes specialist nurses with a quick way to identify high-risk patients with cognitive impairment, so as to promote early assessment and intervention of cognitive impairment in T2DM patients and improve their health outcomes.

## Materials and Methods

### Study Design and Participants

This cross-sectional study included 240 patients with T2DM who were recruited at the Department of

Endocrinology and Metabolism, the Third Affiliated Hospital of Sun Yat-sen University, from September 2019 to February 2020. All participants were eligible if they were aged 45 years or older, diagnosed with T2DM, and had diabetes for longer than 3 months. Participants were excluded if they were diagnosed with organic brain diseases; abused drugs; had mental or neurologic diseases or communication disorders; or had serious infections, cancer, or other serious diseases.

After the participants signed the informed consent form, we collected general information and performed the cognitive assessment. The participants also completed related questionnaires.

### Main Variables

We collected patient data from the bio-psycho-social perspective. The biomedical dimension included sociodemographic and disease factors; the psychological dimension included depression; and the social behavior dimension included self-management behavior and social support.

Baseline data included the following.

1. Sociodemographic factors: Age, sex, education level, place of residence, occupational status, smoking, drinking, and diabetes education.
2. Disease factors: Body mass index; diabetes course; history of hypoglycemia; diabetes treatment; hypertension; diabetes complications (cardiovascular diseases, peripheral vascular disease, peripheral neuropathy, diabetic nephropathy, and diabetic retinopathy); blood glucose (glycated hemoglobin [HbA1c] and fasting blood glucose); blood lipids (total cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein); liver function (aspartate aminotransferase and alanine aminotransferase [ALT]); and renal function (blood urea nitrogen, creatinine).
3. Psychological factors: Self-Rating Depression Scale (SDS), which was compiled by Zung in 1965 and revised by Wang et al, consists of 20 items for a total of 80 points, with a score of 53 points set as the threshold for depression. A score of less than 53 means no depression.<sup>22,23</sup> SDS has good reliability and validity and can accurately reflect the subjective depression of self-raters in the previous week.<sup>24</sup>
4. Self-management factors: The Diabetes Self-care Scale (DSCS), which was compiled by Hurley and

revised by Wang et al from Taiwan, has good internal consistency (Cronbach alpha = 0.87).<sup>25</sup> The scale has 26 items, including 6 dimensions (diet management, blood glucose monitoring, foot care, exercise, medication according to doctor's orders, and prevention and treatment of high and low blood sugar, with a higher score representing better self-management behavior).<sup>26</sup>

5. Social support factors: Social Support Rating Scale (SSRS) was developed by Shuiyuan Xiao in 1986 and revised in 1990.<sup>27</sup> The 10-item scale consists of 3 dimensions (subjective support, objective support, and support utilization, with a higher score representing better self-management behavior). The scale has presented great validity and reliability in Chinese population.<sup>28,29</sup>

## Cognitive Assessment

Cognitive impairment was evaluated with the Chinese version of the Montreal Cognitive Assessment (MoCA), which has been validated in previous studies and takes into account the cultural and socioeconomic conditions of the Chinese population so that all question items can be easily understood and answered.<sup>30–32</sup> The Chinese version of MoCA has good criterion-related validity (Pearson correlation coefficient MoCA vs MMSE = 0.933) and reliable internal consistency (Cronbach alpha = 0.818), consistent with the original version (Pearson correlation coefficient MoCA vs MMSE = 0.87 and Cronbach alpha = 0.83).<sup>32</sup> The test has 12 question items, with the total score ranging from 0 to 30. Each item was assigned 1 point for a correct answer and 0 points for incorrect or unknown answers. If the participant had  $\leq 12$  years of education, 1 point was added to the overall MoCA score. An overall score  $< 26$  indicated cognitive impairment.

## Statistical Analysis

We used SPSS v21.0 software (IBM, Armonk, NY, USA) for data analysis. Normally distributed continuous data are described as mean and standard deviation, with the independent *t*-test used for intergroup comparisons. Discrete data are described as frequency, composition ratio, or percentage, and the chi-squared and Mann–Whitney *U*-tests were used for intergroup comparisons. Variables with  $p < 0.1$  in these tests were input into the multivariate logistic regression model to identify predictors of cognitive impairment. All findings from the regression modeling

are reported as odds ratio with 95% confidence interval. All significant *P* values ( $P < 0.05$ ) were 2-tailed.

## Results

Baseline characteristics of the participants with and without cognitive impairment are shown in Table 1. The average age of the participants was  $61.15 \pm 8.15$  years; 127 (52.9%) were middle-aged and 113 (47.1%) were elderly. The majority (64.6%) were male, and 82.5% lived in cities, and 53.3% had had diabetes for more than 10 years. A total of 60 participants had a history of hypoglycemia within 1 month and 79.2% had HbA1c  $\geq 7\%$ , with poor blood glucose control. The average MoCA score was  $24.72 \pm 3.64$ ; 126 (52.5%) patients with a MoCA score  $< 26$  were classified as having cognitive impairment.

In the biomedical dimension, participants with cognitive impairment were older, less educated, and more likely to live in rural areas and be unemployed than those with normal cognition. In terms of disease factors, participants with cognitive impairment had a longer course of diabetes, history of hypoglycemia within 1 month, high blood pressure, elevated HbA1c, and lower ALT. In the psychological dimension, 39 participants were determined to be depressed; participants with cognitive impairment had higher SDS scores. In the social behavior and self-management dimensions, participants with cognitive impairment had lower total scores on the DSCS and SSRS and lower scores on each dimension of these tests than those with normal cognition.

The results of the multivariate logistic regression analysis showed that older age, a history of hypoglycemia within 1 month, and depression were independent risk factors for cognitive impairment. Having  $> 12$  years of education, urban living, and a higher total score on the DSCS were independent factors that protected against cognitive impairment. Professional status, diabetes course, combined hypertension, HbA1c, ALT, and SSRS score were not associated with cognitive impairment in the multivariate model (Table 2).

## Discussion

In this study, we found that middle-aged and elderly patients with T2DM had high rates of cognitive dysfunction, which may be related to the use of only one instrument (MoCA) for evaluation. We also found older age, a history of hypoglycemia, and depression were independent risk factors for cognitive impairment whereas

**Table 1** Sociodemographic, Disease, Psychological, Self-Management, and Social Support Factors at Baseline Stratified by Cognitive Impairment

Variable	Total (n=240)	Cognitive Impairment (n = 126)	No Cognitive Impairment (n = 114)	P value <sup>a</sup>
N (%)	240	126 (52.5)	114 (47.5)	–
MoCA score	24.72±3.64	21.83±2.54	27.92±1.10	<0.001
<b>Sociodemographic factors</b>				
Age (years)	61.15±8.15	63.52±8.80	58.54±6.47	<0.001*
~45	127 (52.9)	52 (41.3)	75 (65.8)	<0.001*
~60	113 (47.1)	74 (58.7)	39 (34.2)	–
Sex				
Male	155 (64.6)	77 (61.1)	78 (68.4)	0.237
Female	85 (35.4)	49 (38.9)	36 (31.6)	–
Education (years)				
≤12	165 (68.8)	106 (84.1)	59 (51.8)	<0.001*
>12	75 (31.3)	20 (15.9)	55 (48.2)	–
Place of residence				
Rural	42 (17.5)	37 (29.4)	5 (4.4)	<0.001*
Urban	198 (82.5)	89 (70.6)	109 (95.6)	–
Professional status				
On-job	98 (40.8)	41 (32.5)	57 (50.0)	0.006*
Unemployed or retired	142 (59.2)	85 (67.5)	57 (50.0)	–
Smoking				
Yes	90 (37.5)	43 (34.1)	47 (41.2)	0.256
No	150 (62.5)	83 (65.9)	67 (58.8)	–
Drinking				
Yes	32 (13.3)	18 (14.3)	14 (12.3)	0.648
No	208 (86.7)	108 (85.7)	100 (87.7)	–
Received diabetes education				
Yes	104 (43.4)	51 (40.5)	53 (46.5)	0.348
No	136 (56.7)	75 (59.5)	61 (53.5)	–
<b>Disease factors</b>				
BMI (kg/m <sup>2</sup> )	24.57±2.68	24.52±2.65	24.61±2.73	0.518
<18.5	10 (4.2)	7 (5.6)	3 (2.6)	0.111
~18.5	95 (39.6)	46 (36.5)	49 (43.0)	–
~24	110 (45.8)	64 (50.8)	46 (40.4)	–
~28	25 (10.4)	9 (7.1)	16 (14.0)	–
Diabetes course (years)	10.00 (5.00, 14.00)	10.00 (5.00, 15.00)	8.00 (5.00, 12.00)	0.005*
<10	112 (46.7)	45 (35.7)	67 (58.8)	<0.001*
≥10	128 (53.3)	81 (64.3)	47 (41.2)	–
Hypoglycemia in 1 month				
Yes	60 (25.0)	39 (31.0)	21 (18.4)	0.025*
No	180 (75.0)	87 (69.0)	93 (81.6)	–
Diabetes treatment				
Lifestyle only	8 (3.3)	2 (1.6)	6 (5.3)	0.050

(Continued)

Table I (Continued).

Variable	Total (n=240)	Cognitive Impairment (n = 126)	No Cognitive Impairment (n = 114)	P value <sup>a</sup>
Oral hypoglycemic drugs	131 (54.6)	63 (50.0)	68 (59.6)	–
Insulin	49 (20.4)	33 (26.2)	16 (14.0)	–
Oral hypoglycemic drugs+insulin	52 (21.7)	28 (22.2)	24 (21.1)	–
Hypertension				
Yes	135 (56.3)	82 (65.1)	53 (46.5)	0.008
No	104 (43.4)	43 (34.1)	61 (53.5)	–
Cardiovascular disease				
Yes	42 (17.5)	21 (16.7)	21 (18.4)	0.721
No	198 (82.5)	105 (83.3)	93 (81.6)	–
Peripheral vascular disease				
Yes	150 (62.5)	76 (60.3)	74 (64.9)	0.463
No	90 (37.5)	50 (39.7)	40 (35.1)	–
Peripheral neuropathy				
Yes	108 (45.0)	55 (43.7)	53 (46.5)	0.659
No	132 (55.0)	71 (56.3)	61 (53.5)	–
Diabetic nephropathy				
Yes	69 (28.8)	34 (27.0)	35 (30.7)	0.525
No	171 (71.3)	92 (73.0)	79 (69.3)	–
Diabetic retinopathy				
Yes	46 (19.2)	25 (19.8)	21 (18.4)	0.780
No	194 (80.8)	101 (80.2)	93 (81.6)	–
HbA1c (%) ^	8.75±1.99	9.09±2.18	8.37±1.69	0.005*
<7	50 (20.8)	22 (17.5)	28 (24.6)	0.176
≥7	190 (79.2)	104 (82.5)	86 (75.4)	–
FPG (mmol/l)	8.31±2.65	8.44±2.79	8.16±2.49	0.420
TC (mmol/l)	4.68±1.08	4.57±1.10	4.80±1.06	0.103
TG (mmol/l)	1.56 (1.11, 2.20)	1.56 (1.02, 2.14)	1.59 (1.17, 2.62)	0.092
HDL (mmol/l)	1.01±0.24	1.03±0.27	1.00±0.21	0.436
LDL (mmol/l)	3.05±1.00	2.95±1.02	3.15±0.98	0.112
AST (U/l)	19.00 (17.00, 26.00)	18.50 (16.75, 26.00)	19.00 (17.00, 26.00)	0.846
ALT (U/l) #	21.00 (16.00, 33.00)	19.50 (15.00, 27.0)	23.00 (17.00, 36.00)	0.002*
≤35	184 (76.7)	101 (80.2)	83 (72.8)	0.179
>35	56 (23.3)	25 (19.8)	31 (27.2)	–
BUN (mmol/l)	5.93±2.24	6.00±2.71	5.86±1.57	0.649
Cr (μmol/l)	70.00 (60.00, 83.00)	71.50 (61.75, 83.50)	66.00 (59.00, 79.00)	0.079
<b>Psychological factors</b>				
SDS score	35.33±10.37	37.94±11.87	32.43±7.45	<0.001*
≥53 points	39 (16.3)	32 (25.4)	7 (6.1)	<0.001*
<53 points	201 (83.8)	94 (74.6)	107 (93.9)	–

(Continued)

**Table I** (Continued).

Variable	Total (n=240)	Cognitive Impairment (n = 126)	No Cognitive Impairment (n = 114)	P value <sup>a</sup>
<b>Self-management factors</b>				
DSCS score	86.66±17.79	79.80±17.77	94.24±14.48	<0.001*
Exercise score	12.68±4.95	11.34±4.63	14.16±4.90	<0.001*
Diet management score	21.05±6.02	20.10±6.20	22.11±5.65	0.009*
Medication management score	13.90±2.28	13.73±2.55	14.09±1.93	0.219
Blood glucose monitoring score	9.48±3.49	8.21±2.84	10.89±3.61	<0.001*
Foot care score	17.48±5.29	15.52±5.61	19.64±3.92	<0.001*
High and low blood sugar prevention and treatment score	12.32±2.90	11.41±3.04	13.32±2.36	<0.001*
<b>Social factors</b>				
SSRS score	41.60±5.30	39.70±4.97	43.70±4.86	<0.001*
Objective support score	10.53±1.90	9.86±1.57	11.28±1.95	<0.001*
Subjective support score	24.59±3.61	23.44±3.66	25.84±3.12	<0.001*
Support utilization score	6.60±1.71	6.38±1.81	6.84±1.57	0.037*

**Notes:** <sup>a</sup>Chi-squared test for categorical variables, Student's *t*-test and Mann–Whitney *U*-test for continuous variables; <sup>†</sup>Targets for comprehensive control of type 2 diabetes; <sup>#</sup>Normal laboratory limit; \**P* < 0.05.

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; DSCS, Diabetes Self-care Scale; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein; MoCA, Montreal Cognitive Assessment; SDS, Self-Rating Depression Scale; SSRS, Social Support Rating Scale; TC, total cholesterol; TG, triglyceride.

a higher education level, urban life, and better self-management were independent protective factors.

Our assumption was that biomedical and psychological factors and social behaviors all influence cognitive function. In the biomedical dimension, T2DM patients who were older, less educated, lived in rural areas, and had a history of hypoglycemia were at greater risk of cognitive impairment. This is in agreement with previous studies that have reported older age as a risk factor for cognitive impairment.<sup>33,34</sup> Cognitive function declines with age; this is accelerated and is exacerbated in patients with diabetes compared to those without diabetes.<sup>35</sup> Cognitive dysfunction in patients with T2DM was found to be 2.5 times more common in patients between 66 and 80 years of age than in those in the 40–60 age group.<sup>36</sup> This may be attributable to the emergence of vascular changes and neurodegeneration in the brain with aging.<sup>37</sup>

Education level and place of residence have been shown to impact cognitive function.<sup>19,38</sup> The results of a 21-year cohort study showed that people with a higher education level and who engaged in mental activities had a lower risk of cognitive impairment in old age,<sup>39</sup> possibly because regular stimulation of neurons preserves their functioning over a long period of time. One study of 2017 elderly people reported a higher prevalence of cognitive impairment in

rural residents.<sup>40</sup> This may be because compared to life in an urban setting, rural living is more monotonous with less information and stimulation from the outside world.

The relationship between hypoglycemia and cognitive impairment in T2DM patients is controversial. Some studies have shown that hypoglycemia in patients with T2DM leads to impaired brain function and an increased rate of cognitive decline.<sup>41,42</sup> However, others have reported no association between the risk of hypoglycemia and a decline in cognitive function or quality of life.<sup>34,43</sup> The inclusion of the participants' history of hypoglycemia into the regression model in our study underscored the importance of preventing this condition in the treatment of diabetes; safer treatments should be prescribed based on individual cases and health education concerning hypoglycemia is needed for patients. Meanwhile, clinicians should be aware of the increased risk of cognitive decline in patients with a history of hypoglycemia.

In the psychological dimension, depression was a risk factor for cognitive impairment in patients with T2DM. This is consistent with previous reports that individuals with comorbid T2DM and depression had a higher risk of cognitive impairment than those with either condition alone.<sup>44,45</sup> Depression has been shown to promote the progression of MCI to dementia<sup>38</sup> and can lead to poor

**Table 2** Multivariate Logistic Regression Analysis of Cognitive Impairment in Patients with Type 2 Diabetes

Variable	$\beta$	SE	Wals $\chi^2$	OR	95% CI	P
Age	0.121	0.024	25.272	1.128	1.076–1.182	<0.001
Education >12 years	-1.325	0.392	11.435	0.266	0.123–0.573	0.001
Living in urban area	-2.031	0.603	11.325	0.131	0.040–0.428	0.001
Hypoglycemia in 1 month	1.022	0.412	6.151	2.778	1.239–6.230	0.013
Depression	0.655	0.561	1.363	1.925	0.641–5.782	0.243
DSCS score	-0.059	0.011	28.442	0.942	0.922–0.963	<0.001
Constant	0.072	1.674	0.002	1.075		0.966

**Abbreviations:** CI, confidence interval; DSCS, Diabetes Self-care Scale; OR, odds ratio; SE, standard error.

blood glucose control and blood vessel and nerve damage, resulting in cognitive impairment. Thus, more attention should be paid to the mental health of patients with T2DM, and those exhibiting negative emotions or depressive tendencies should receive timely and appropriate treatment.

In the social behavior dimension, better self-management ability was a protective factor against cognitive impairment. This is in accordance with an earlier study in which cognitive impairment in patients with diabetes was found to be linked to poor medication management and glucose self-monitoring.<sup>21</sup> The exercise and diet dimensions of self-management behavior are closely related to cognitive impairment.<sup>20</sup> T2DM patients with good self-management also have more stable blood glucose, which may reduce the toxic effect of hyperglycemia on the central nervous system. Exercise directly excites the cerebral cortex, which could help to maintain nerve cells and synaptic function.

In the present study, the scores of each dimension of DSCs showed that “blood glucose monitoring” was at a low level; “Exercise”, “diet management”, “foot care”, “high and low blood sugar prevention and treatment” were at a medium level; “Medication management” was at a high level. It was suggested that the self blood glucose monitoring behavior of the participants in this study was not ideal. We should pay attention to the guidance and education of self blood glucose monitoring to help the patients master the correct knowledge and technology; Strengthen life guidance and formulate individualized exercise and diet programs; Emphasize the relationship between self-management and cognitive impairment. We also found that over half of the patients reported that they had not received comprehensive education on diabetes; in order to mitigate the risk of developing cognitive deficits, T2DM patients should be educated about diabetes and self-management behaviors.

In this study, we considered the comprehensive impact of factors of different dimensions on patients, and determined the risk factors for cognitive impairment in patients with T2DM, and emphasized the importance of long-term rational control of blood glucose, mood pleasure and good self-management. Our findings help clinicians or diabetes specialist nurses quickly identify T2DM patients with high risk of cognitive impairment and provide evidence for cognitive function screening in T2DM patients. High risk patients will benefit from more targeted lifestyle interventions, such as exercise, diet, hypoglycemia health education and stress reduction,<sup>46,47</sup> which will help to prevent and delay the decline of cognitive function in T2DM patients. A limitation of our study was the cross-sectional design, which made it difficult to establish a causal relationship between specific risk factors and cognitive impairment; additionally, as there were no healthy middle-aged and elderly as a control group, we were unable to determine the precise relationship between diabetes and cognitive function. We will continue to follow up the participants in this study and at the same time expand the sample size in order to obtain more conclusive results.

## Conclusions

We investigated the risk factors for cognitive impairment in 240 middle-aged and elderly patients with T2DM by assessing their cognitive function and influencing factors through questionnaires, along with depression status, self-management behavior, and social support. Patients with T2DM who are older, less educated, living in rural areas, have hypoglycemia history, and have poor self-management of diabetes are at increased risk of cognitive impairment; controlling hypoglycemia, detecting and treating depression as early as possible, and improving self-management capabilities are important for preventing cognitive decline in this group. Our study provides a basis for medical care personnel to early identify T2DM patients with high risk of cognitive impairment and carry out follow-up cognitive function screening, and provides

theoretical support for the formulation of prevention and intervention measures for T2DM patients with cognitive impairment.

## Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

## Ethical Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Medical Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University.

## Consent

The patients provided written informed consent for participation in this study.

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. Weiran Xu and Xiling Hu contributed equally to this work.

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## Disclosure

The authors report no conflicts of interest in this work.

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