Association Between Tryptase and Macrovascular Complications in Type 2 Diabetes Mellitus: A Ten-Year Follow-up Post-print Study

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Abstract

Background Diabetic macrovascular complications are common complications of diabetes mellitus with high prevalence and significant harm. However, the pathogenesis remains unclear. Inflammatory response and oxidative stress have consistently been research hotspots in its pathogenesis, and it has been established that multiple inflammatory mediators are involved in the occurrence and development of diabetes mellitus complicated with macrovascular disease. However, whether tryptase, as an important inflammatory mediator, is associated with the pathogenesis of type 2 diabetes mellitus complicated with macrovascular disease has rarely been reported.

Objective To analyze serum tryptase levels in patients with type 2 diabetes mellitus complicated with macrovascular disease, and to conduct a non-interventional follow-up of individuals diagnosed with newly diagnosed diabetes mellitus through oral glucose tolerance test (OGTT), repeat the investigation after 10 years, screen out populations with type 2 diabetes mellitus complicated with macrovascular disease and type 2 diabetes mellitus, and explore the baseline serum tryptase levels in populations with different outcomes and the influencing factors for the outcome of diabetic macrovascular complications.

Methods Using cluster random sampling method, 4,000 residents from Xicao, Dashanping, and Longmatan communities in Luzhou city were selected as study subjects from April to November 2011, undergoing physical examination, questionnaire collection, and biochemical tests. From these, healthy individuals were randomly selected as the normal control group (NG group, n=30), newly diagnosed type 2 diabetes mellitus patients as the type 2 diabetes mellitus group (B-T2DM group, n=30), and type 2 diabetes mellitus patients complicated with macrovascular disease as the type 2 diabetes mellitus complicated with macrovascular disease group (B-T2DM+CVD group, n=30). A 10-year non-interventional follow-up was conducted on 331 newly diagnosed diabetes

mellitus patients from the baseline survey, and the investigation was repeated from April to November 2021, randomly screening out the type 2 diabetes mellitus group (R-T2DM group, n=30) and the type 2 diabetes mellitus complicated with macrovascular disease group (R-T2DM+CVD group, n=26).

Results At baseline survey, there were statistically significant differences among different groups in fasting plasma glucose (FPG), OGTT 2-hour glucose, glycated hemoglobin (HbA1c), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), BMI, and tryptase levels (P<0.05). Specifically, the B-T2DM group had higher FPG, OGTT 2-hour glucose, HbA1c, TG, BMI, and tryptase levels than the NG group; the B-T2DM+CVD group had higher FPG, OGTT 2-hour glucose, HbA1c, and tryptase levels than both the B-T2DM and NG groups, and higher TG and BMI than the NG group (P<0.05). Tryptase was positively correlated with FPG, OGTT 2-hour glucose, HbA1c, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), BMI, and waist-to-hip ratio (WHR) (r values were 0.226, 0.296, 0.185, 0.272, 0.213, 0.245, and 0.278, respectively), and negatively correlated with HDL-C (r value was -0.209) (P<0.05). Univariate Logistic regression analysis showed that tryptase was a risk factor for type 2 diabetes mellitus complicated with macrovascular disease (OR=1.832, 95%CI=1.015~3.308), but multivariate Logistic regression analysis showed that tryptase was not an influencing factor for type 2 diabetes mellitus complicated with macrovascular disease (P>0.05). After 10 years of follow-up, 26 out of 331 diabetes mellitus patients transitioned to type 2 diabetes mellitus complicated with macrovascular disease. The R-T2DM+CVD group had higher baseline OGTT 2-hour glucose and HBA1C than the R-T2DM group (P<0.05), while there was no statistically significant difference in baseline tryptase between the two groups (P>0.05). Univariate Logistic regression analysis identified OGTT 2-hour glucose (OR=1.205, 95%CI=1.001~1.451) and HBA1C (OR=1.699, 95%CI=1.009~2.863) as influencing factors for transitioning to type 2 diabetes mellitus complicated with macrovascular disease (P<0.05), while multivariate Logistic regression analysis showed that OGTT 2-hour glucose (OR=1.118, 95%CI=0.867~1.441), HbA1c (OR=1.331, 95%CI=0.664~2.795), and tryptase (OR=1.003, 95%CI=0.513~1.961) were not risk factors for transitioning to type 2 diabetes mellitus complicated with macrovascular disease (P>0.05).

Conclusion Serum tryptase levels were higher in type 2 diabetes mellitus complicated with macrovascular disease than in the type 2 diabetes mellitus group and normal group; serum tryptase level was positively correlated with FPG, OGTT 2-hour glucose, HbA1c, TC, LDL-C, BMI, and WHR, and negatively correlated with HDL-C; tryptase was a risk factor for type 2 diabetes mellitus complicated with macrovascular disease, but this effect disappeared after adjusting for FPG, OGTT 2-hour glucose, and HbA1c; tryptase may have no effect on the outcome of type 2 diabetes mellitus complicated with macrovascular disease.

Full Text

Title and Authorship

Relationship between Tryptase and Type 2 Diabetes Mellitus with Macrovascular Complications: A Ten-Year Follow-up Study

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Abstract

Background: Diabetic macrovascular complications represent prevalent and severe consequences of diabetes mellitus, characterized by high morbidity and significant clinical impact. While the precise pathogenesis remains undefined, inflammation and oxidative stress have long been recognized as key pathogenic mechanisms. Multiple inflammatory mediators are known to contribute to the development and progression of diabetes-associated macrovascular disease. However, the involvement of tryptase—an important inflammatory mediator—in the pathogenesis of type 2 diabetes with macrovascular complications has rarely been reported.

Objective: This study analyzed serum tryptase levels in patients with type 2 diabetes mellitus complicated by macrovascular disease. We conducted a non-interventional ten-year follow-up of patients newly diagnosed with diabetes via oral glucose tolerance test (OGTT) and performed a repeated survey to identify individuals who developed type 2 diabetes with macrovascular complications versus those with type 2 diabetes alone. We aimed to explore baseline serum tryptase levels across different outcome groups and investigate factors influencing the progression of diabetic macrovascular complications.

Methods: Using cluster random sampling, we selected 4,000 residents from three communities in Luzhou (Xicao, Dashanping, and Longmatan) between April and November 2011 for physical examinations, questionnaire surveys, and biochemical testing. From this cohort, we randomly established three groups: healthy individuals as normal controls (NG group, n=30), newly diagnosed type 2 diabetes patients as the baseline T2DM group (B-T2DM group, n=30), and type 2 diabetes patients with macrovascular disease as the baseline T2DM+CVD group (B-T2DM+CVD group, n=30). Among 331 patients newly diagnosed with diabetes at baseline, we conducted a ten-year non-interventional follow-up and performed a repeated survey between April and November 2021, randomly selecting a follow-up T2DM group (R-T2DM group, n=30) and a follow-up T2DM+CVD group (R-T2DM+CVD group, n=26).

Results: At baseline, statistically significant differences were observed among groups in fasting plasma glucose (FPG), OGTT 2-hour glucose, glycated hemoglobin (HbA1c), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), body mass index (BMI), and tryptase levels ($P<0.05$). The B-T2DM group exhibited higher FPG, OGTT 2-hour glucose, HbA1c, TG, BMI, and tryptase levels compared to the NG group. The B-T2DM+CVD group showed higher FPG, OGTT 2-hour glucose, HbA1c, and tryptase levels than both the B-T2DM and NG groups, along with higher TG and BMI than the NG group ($P<0.05$). Correlation analysis revealed that tryptase was positively correlated with FPG, OGTT 2-hour glucose, HbA1c, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), BMI, and waist-to-hip ratio (WHR) ($r=0.226$, 0.296, 0.185, 0.272, 0.213, 0.245, 0.278) and negatively correlated with HDL-C ($r=-0.209$) ($P<0.05$). Univariate logistic regression identified tryptase as a risk factor for T2DM+CVD (OR=1.832, 95%CI=1.015-3.308), but multivariate analysis showed it was not an independent influencing factor ($P>0.05$).

After ten years of follow-up, 26 of the 331 diabetic patients progressed to T2DM+CVD. The R-T2DM+CVD group had significantly higher baseline OGTT 2-hour glucose and HbA1c than the R-T2DM group ($P<0.05$), while baseline tryptase levels did not differ significantly between groups ($P>0.05$). Univariate logistic regression identified OGTT 2-hour glucose (OR=1.205, 95%CI=1.001-1.451) and HbA1c (OR=1.699, 95%CI=1.009-2.863) as influencing factors for progression to T2DM+CVD ($P<0.05$). However, multivariate analysis revealed that OGTT 2-hour glucose (OR=1.118, 95%CI=0.867-1.441), HbA1c (OR=1.331, 95%CI=0.664-2.795), and tryptase (OR=1.003, 95%CI=0.513-1.961) were not independent risk factors for progression ($P>0.05$).

Conclusions: Serum tryptase levels are elevated in patients with type 2 diabetes and macrovascular disease compared to those with diabetes alone and healthy controls. Tryptase correlates positively with FPG, OGTT 2-hour glucose, HbA1c, TC, LDL-C, BMI, and WHR, and negatively with HDL-C. While tryptase appears to be a risk factor for T2DM+CVD, this association disappears after adjusting for glycemic parameters. Tryptase likely does not influence the progression of macrovascular complications in type 2 diabetes.

Keywords: Diabetes mellitus, type 2; Coronary vessels; Cholesterol, HDL; Cholesterol, LDL; Tryptases

Introduction

Diabetic macrovascular complications represent a common and serious health concern for patients with diabetes. These complications develop insidiously and are often irreversible once established. Although the pathogenesis of diabetic chronic complications remains incompletely understood, research has implicated hyperglycemia, lipid accumulation, oxidative stress, inflammatory responses, and insulin resistance in their development and progression [1]. Inflammation

and oxidative stress have been particularly active areas of investigation, with multiple inflammatory mediators—including interleukin-6 (IL-6) and C-reactive protein (CRP)—confirmed to participate in the pathogenesis of diabetes with macrovascular disease [2].

Tryptase, an endopeptidase released by mast cell degranulation, serves as an important inflammatory mediator with diverse biological functions. It promotes inflammatory factor aggregation and release, activates mast cells, and participates in apoptosis, neovascularization, and extracellular matrix remodeling [3-4]. Current research has established associations between tryptase and chronic kidney disease, chronic sinusitis, allergic diseases [5-7], as well as atherosclerosis [8-9]—the primary pathological basis of diabetic macrovascular disease. This suggests tryptase may contribute to the development and progression of diabetic macrovascular complications, though relevant studies are scarce.

To address this gap, we measured serum tryptase levels in normal controls, newly diagnosed type 2 diabetes patients, and type 2 diabetes patients with macrovascular disease identified from the 2011 Luzhou Diabetes Epidemiology Survey. We conducted a ten-year non-interventional follow-up of patients diagnosed with new-onset diabetes via OGTT and performed a repeated survey to investigate baseline tryptase levels across different outcome groups and identify factors influencing the progression of diabetic macrovascular complications.

Methods

Study Design and Participants

Baseline Survey: We employed cluster random sampling to recruit 4,000 residents from three Luzhou communities (Xicao, Dashanping, and Longmatan) between April and November 2011. Participants underwent physical examinations, questionnaire surveys, and biochemical testing. From this cohort, we randomly selected healthy individuals as normal controls (NG group, n=30), newly diagnosed type 2 diabetes patients as the baseline T2DM group (B-T2DM group, n=30), and type 2 diabetes patients with macrovascular disease as the baseline T2DM+CVD group (B-T2DM+CVD group, n=30).

Follow-up Survey: We conducted a ten-year non-interventional follow-up of 331 patients newly diagnosed with diabetes at baseline. Inclusion criteria were: (1) age $ $40 years; (2) residence in the community for $ $5 years; (3) voluntary participation with completion of follow-up examinations, questionnaires, and biochemical tests; and (4) good general health. Exclusion criteria included limited activities of daily living, selective withdrawal during the survey period, or refusal to participate in follow-up investigations. Between April and November 2021, we performed a repeated field survey and randomly selected a follow-up T2DM group (R-T2DM group, n=30) and a follow-up T2DM+CVD group (R-T2DM+CVD group, n=26).

Group Definitions

B-T2DM Group: (1) Patients with newly diagnosed type 2 diabetes; (2) No history of coronary heart disease, cerebral infarction, or peripheral macrovascular disease.

B-T2DM+CVD Group: (1) Patients with established type 2 diabetes; (2) Those with angina symptoms, myocardial infarction history with ECG changes, or confirmed diagnosis by coronary angiography; patients with hemiplegia or other focal neurological symptoms with ischemic changes confirmed by cranial CT or MRI; patients with intermittent claudication, rest pain, and possible ischemic foot ulcers or gangrene with confirmed peripheral atherosclerotic ischemia or occlusion by vascular ultrasound (medical records, laboratory reports, or discharge summaries were required during field surveys). Due to questionnaire design limitations, patients with type 2 diabetes and carotid artery plaques were not included.

R-T2DM Group: (1) Patients with newly diagnosed type 2 diabetes at baseline; (2) No history of coronary heart disease, cerebral infarction, or peripheral macrovascular disease at baseline or during follow-up.

R-T2DM+CVD Group: (1) Patients with newly diagnosed type 2 diabetes at baseline; (2) No macrovascular disease history at baseline but development of such conditions during follow-up (medical documentation was required).

Exclusion Criteria for All Groups: (1) Other diabetes types (type 1, secondary, or gestational diabetes); (2) Presence of diabetic nephropathy or retinopathy; (3) Stress conditions, autoimmune diseases, allergic diseases, or malignancies.

Data Collection and Laboratory Measurements

Baseline Survey: (1) Questionnaires collected demographic information including sex and age; (2) Physical examinations measured height, weight, blood pressure, waist and hip circumference; (3) Laboratory tests: residents without diabetes history underwent OGTT, while those with known diabetes consumed 100 g of steamed bread without sugar.

OGTT Procedure: 75 g of anhydrous glucose was dissolved in 200 mL warm water and consumed within 5 minutes. Venous blood samples were collected before and 2 hours after glucose administration (with only small amounts of water permitted and no other food consumed during this period) to measure fasting and 2-hour glucose levels. We also measured HbA1c and lipid profiles [including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)]. All blood samples were sent to internationally standardized laboratories for analysis. Approximately 5 mL of fasting blood was collected in vacuum coagulation-promoting tubes, centrifuged at 3,000 r/min for 5 minutes, and the supernatant was transferred to 0.5 mL EP tubes and stored at -80°C until use. Glucose was measured

by glucose oxidase method, HbA1c by high-performance liquid chromatography, and serum tryptase using a human mast cell tryptase (MCT) enzyme-linked immunosorbent assay kit from Shanghai Xitang Biological Technology Co., Ltd., with detection by double-antibody sandwich ELISA.

Diagnostic Criteria

Diabetes: FPG $ $7.0 mmol/L and/or OGTT 2-hour glucose $ $11.1 mmol/L.

Impaired Glucose Regulation (IGR): (1) Impaired fasting glucose (IFG): FPG 6.1–6.9 mmol/L and OGTT 2-hour glucose <7.8 mmol/L; (2) Impaired glucose tolerance (IGT): FPG <6.1 mmol/L and OGTT 2-hour glucose 7.8–11.1 mmol/L; (3) IFG+IGT: FPG 6.1–6.9 mmol/L and OGTT 2-hour glucose 7.8–11.1 mmol/L.

Normal Glucose Tolerance (NGT): FPG <6.1 mmol/L and/or OGTT 2-hour glucose <7.8 mmol/L.

Quality Control

All survey personnel received relevant training, and we implemented quality control measures for laboratory measurement techniques. Pilot surveys were conducted to ensure a 100% qualification rate.

Statistical Analysis

Survey data were double-entered and verified using Epidata 3.0 software, with statistical analyses performed using SPSS 21.0. Normally distributed continuous variables were expressed as mean ± standard deviation, with inter-group comparisons using ANOVA and pairwise comparisons using LSD-t tests. Non-normally distributed continuous variables were expressed as medians, with TG undergoing natural logarithm transformation before analysis. Categorical variables were compared using ^{2} tests. Binary logistic regression analysis was used to identify factors influencing diabetic macrovascular complications. Statistical significance was defined as $P<0.05$.

Results

Baseline Characteristics Across Groups

At baseline, significant differences were observed among groups in FPG, OGTT 2-hour glucose, HbA1c, TG, HDL-C, BMI, and tryptase levels ($P<0.05$). The B-T2DM group exhibited higher FPG, OGTT 2-hour glucose, HbA1c, TG, BMI, and tryptase levels compared to the NG group. The B-T2DM+CVD group showed higher FPG, OGTT 2-hour glucose, HbA1c, and tryptase levels than both the B-T2DM and NG groups, and higher TG and BMI than the NG group ($P<0.05$) .

Correlation Between Tryptase and Baseline Indicators

Correlation analysis demonstrated that tryptase was positively correlated with FPG, OGTT 2-hour glucose, HbA1c, TC, LDL-C, BMI, and WHR (r=0.226, 0.296, 0.185, 0.272, 0.213, 0.245, 0.278) and negatively correlated with HDL-C (r=-0.209) (P<0.05). No linear correlations were found with TG, systolic blood pressure (SBP), or diastolic blood pressure (DBP) (P>0.05) .

Risk Factors for Type 2 Diabetes with Macrovascular Disease

Using the presence of T2DM+CVD as the dependent variable and FPG, OGTT 2-hour glucose, HbA1c, tryptase, TG, BMI, and other continuous variables (entered as measured values) as independent variables, univariate logistic regression analysis identified FPG (OR=1.955, 95%CI=1.395-2.740), OGTT 2-hour glucose (OR=1.222, 95%CI=1.097-1.361), HbA1c (OR=2.127, 95%CI=1.390-3.256), and tryptase (OR=1.832, 95%CI=1.015-3.308) as influencing factors (P<0.05) . However, multivariate logistic regression analysis showed that FPG, OGTT 2-hour glucose, HbA1c, and tryptase were not independent predictors of T2DM+CVD .

Comparison of Baseline Characteristics by Outcome

After ten years of follow-up, 26 of the 331 diabetic patients progressed to T2DM+CVD. The R-T2DM+CVD group had significantly higher baseline OGTT 2-hour glucose and HbA1c than the R-T2DM group (P<0.05). No significant differences were observed between groups in baseline sex, age, FPG, TC, TG, LDL-C, HDL-C, SBP, DBP, WHR, BMI, or tryptase levels (P>0.05) .

Predictors of Macrovascular Disease Progression

Using progression to T2DM+CVD as the dependent variable and baseline FPG, OGTT 2-hour glucose, HbA1c, tryptase, TG, BMI, and other parameters (entered as measured values) as independent variables, univariate logistic regression identified OGTT 2-hour glucose (B=0.187, SE=0.095, Wald ^{2}=3.882, OR=1.205, 95%CI=1.001-1.451, P=0.049) and HbA1c (B=0.530, SE=0.266, Wald ^{2}=3.972, OR=1.699, 95%CI=1.009-2.863, P=0.046) as influencing factors for progression (P<0.05). Multivariate logistic regression revealed that OGTT 2-hour glucose, HbA1c, and tryptase were not independent risk factors for progression to T2DM+CVD (P>0.05) .

Discussion

Our findings demonstrate that at baseline, the B-T2DM group had significantly higher FPG, OGTT 2-hour glucose, HbA1c, TG, BMI, and tryptase levels than the NG group, while the B-T2DM+CVD group exhibited even higher FPG, OGTT 2-hour glucose, HbA1c, and tryptase levels compared to both other

groups. However, multivariate logistic regression analysis indicated that FPG, OGTT 2-hour glucose, HbA1c, and tryptase were not independent influencing factors for T2DM+CVD.

Patients with type 2 diabetes face substantially increased mortality risk from macrovascular disease, with atherosclerosis as the primary pathological basis. Atherosclerosis is characterized by chronic inflammatory responses and the formation of macrophage-derived foam cells in the arterial intima. Tryptase is closely associated with atherosclerosis [10], potentially through several mechanisms: (1) **Atherosclerosis initiation and progression:** Yeong et al. [11] demonstrated that tryptase promotes foam cell formation in macrophages by suppressing LXRalpha activation. Ramalho et al. [12] found that tryptase participates in foam cell formation and maintenance by degrading high-density lipoprotein 3 (HDL3), impairing reverse cholesterol transport, and promoting cholesterol accumulation in the arterial intima. Additionally, tryptase can damage vascular endothelial cells and induce apoptosis [13], and activate matrix metalloproteinases (MMP)-1, -2, and -3 [14] to facilitate atherosclerosis initiation and progression. (2) **Increasing plaque vulnerability:** Vulnerable plaques are characterized by thin fibrous caps, large lipid cores, and substantial inflammatory cell infiltration. Tryptase can reduce fibrous cap thickness and compromise plaque stability by directly and indirectly degrading extracellular matrix components (such as gelatin, denatured type I collagen, fibrinogen, intact type VI collagen microfibrils, and fibronectin), potentially leading to plaque rupture. Furthermore, tryptase induces expression of interleukin-8 and monocyte chemoattractant protein-1 (MCP-1) in vascular walls, promoting inflammatory cell infiltration in atherosclerotic plaques and increasing plaque vulnerability [14-15]. Studies have also shown that serum tryptase is higher in patients with acute myocardial infarction compared to those with unstable or stable angina, and significantly higher than in individuals without coronary artery disease, suggesting that serum tryptase may serve as an independent biomarker of plaque stability with predictive value for cardiovascular events [16-18]. Ramalho et al. [12] observed in 44 autopsy cases that higher densities of tryptase and chymase correlated with more severe atherosclerotic plaque damage. Xiang et al. [17] demonstrated that tryptase participates in abdominal aortic aneurysm development through mechanisms involving smooth muscle cell apoptosis, inflammatory factor infiltration, cysteinyl cathepsin expression, and vascular remodeling. Additionally, mast cell tryptase inhibitors have been shown to delay atherosclerosis progression and may have therapeutic potential [19].

Our correlation analysis revealed associations between tryptase and multiple cardiometabolic risk factors, including positive correlations with FPG, OGTT 2-hour glucose, HbA1c, TC, LDL-C, BMI, and WHR, and a negative correlation with HDL-C. These findings suggest that beyond its direct role in atherosclerosis, tryptase may influence diabetic macrovascular disease progression by affecting established risk factors. Hyperglycemia, dyslipidemia, and obesity—particularly central obesity—are well-known risk factors for diabetic macrovascular disease.

Tryptase may impact disease development through oxidative stress, increased insulin resistance, and secretion of adipokines [20]. Vitte et al. [21] measured serum tryptase in 4,915 Swedish individuals aged 50–64 years and found higher levels in diabetic versus non-diabetic patients. Similarly, Shi et al. [22] and Yabut et al. [23] reported associations between mast cell tryptase and these risk factors, consistent with our findings.

The UK Prospective Diabetes Study (UKPDS) identified elevated LDL-C, reduced HDL-C, increased HbA1c, higher diastolic blood pressure, and smoking as sequential risk factors for coronary artery disease in type 2 diabetes [24]. In our study, comparison of baseline characteristics between outcome groups revealed statistically significant differences only in OGTT 2-hour glucose and HbA1c, though the R-T2DM+CVD group showed trends toward higher age, FPG, TC, TG, LDL-C, SBP, DBP, WHR, and BMI, and lower HDL-C compared to the R-T2DM group. Multivariate logistic regression identified OGTT 2-hour glucose and HbA1c as risk factors for progression to T2DM+CVD, while other indicators showed no significant differences. These findings may reflect insufficient sample size or the possibility that the R-T2DM group already had subclinical atherosclerosis at baseline despite lacking overt macrovascular disease symptoms.

In summary, tryptase—a major mast cell protease with diverse biological functions—shows a relationship with type 2 diabetes complicated by macrovascular disease. Mast cell tryptase inhibitors may represent a novel therapeutic strategy for preventing and treating diabetic macrovascular complications. However, this study has limitations, including failure to account for smoking, alcohol consumption, medications, and disease duration, as well as a relatively small sample size that may limit generalizability. Future research should expand sample sizes and extend follow-up duration.

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Author Contributions

ZHAO Ya was primarily responsible for study conception, design, implementation, data collection and analysis, statistical processing, figure and table preparation, and manuscript writing, with overall responsibility for the article. WAN Qin was primarily responsible for quality control and review, with overall responsibility and supervision of the article.

Conflict of Interest

The authors declare no conflict of interest.

Additional Information

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Ethical Approval: This study was authorized by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University (Approval No. 2014-52), with informed consent obtained from all participants.

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