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Association Between Free Triiodothyronine and Carcinoembryonic Antigen Levels in Type 2 Diabetes Mellitus Patients

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Background: Thyroid dysfunction is more common in other endocrine disorders such as diabetes mellitus (DM). Carcinoembryonic antigen (CEA), a common tumor biomarker, is found elevated in patients with thyroid dysfunction. However, the relationship between thyroid hormone levels and CEA levels remains unclear.

Methods: In total, 663 patients with type 2 diabetes at the Tongzhou Branch of Dongzhimen Hospital were enrolled in this retrospective study. Data were collected from inpatient electronic files between December 2011 and December 2019. Laboratory indices were statistically analyzed using logistic regression and Spearman correlation analyses.

Results: In our study, total triiodothyronine (TT3), free triiodothyronine (FT3), serum albumin(ALB), total protein (TP), and triglyceride (TG) levels were significantly higher in the T2DM patients with normal values of CEA than T2DM patients who had abnormal values of CEA, whereas alkaline phosphatase (ALP), Glucose (GLU), and HbA1c levels were significantly increased in the T2DM patients with abnormal CEA level. Binary logistic regression analysis demonstrated that FT3, GLU, HbA1c, and TG levels remained as independent risk factors for CEA in patients with T2DM (β=−0.907, P =0.004; β =−1.009, P=0.004; β =0.090, P = 0001; β= 0.336, P <0.001; β= −0.293, P =0.009, resp). Spearman correlation analysis showed that CEA level was significantly positively correlated with HbA1c and GLU (r_s value: 0.265, P <0.001; r_s value: 0.270, P <0.001, resp.) and negatively correlated with FT3 and TG levels (r_s value: −0.139, P <0.001; r_s value: −0.103 P =0.008, resp). Furthermore, multivariate logistic regression analysis indicated that the FT3 quartiles were significantly associated with CEA levels before and after adjusting for confounding factors.

Conclusion: Our study determined that FT3 remained an independent risk factor for CEA in patients with T2DM and was significantly negatively correlated with CEA levels.

Keywords: retrospective study, free triiodothyronine, carcinoembryonic antigen, thyroid function, type 2 diabetes mellitus

Introduction

The thyroid gland is the largest endocrine organ that synthesizes thyroid hormones including thyroxine (T4) and triiodothyronine (T3) to regulate growth, metabolism, and other important physiological processes in the human body. Thyroid dysfunction including hyperthyroidism, hypothyroidism, euthyroid sick syndrome (also referred to as low T3, T4 syndrome), thyroid enlargement, or no symptoms is associated with diabetes mellitus (DM). The association between thyroid dysfunction and DM has become a focus of clinical trials. Thyroid dysfunction, especially hypothyroidism, has been shown to be more common in patients with DM than in the general population.[1] Previous studies have been reported that the incidence of thyroid dysfunction in T2DM ranges from 11% to 16.2%.[2,3] In addition, the levels of free triiodothyronine (FT3) and free thyroxine (FT4) have been proved to be the most clinically characterized with thyroid disorders.[4]

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Carcinoembryonic antigen (CEA), a common tumor biomarker, is predominantly elevated in colorectal cancer and also associated with adenocarcinomas of the pancreas, lungs, prostate, ovaries, breasts, and thyroid. CEA is a fetal glycoprotein located on the endoluminal side of the cell membrane of epithelial interstitial cells, which also mediates endothelial cell adhesion, spreading, proliferation, and migration, both in vivo and in vitro.[5] In addition, overexpression of CEA also appears in immune dysfunctions, including inflammatory bowel disease, pancreatitis, liver cirrhosis, endometriosis, hypothyroidism, chronic obstructive pulmonary disease, and smoking.[6] Although serum CEA is not a specific biomarker, it might be an indicator of systemic malfunction and helpful in assessing disease progression.

Serum CEA levels may be associated with thyroid function, and elevated CEA levels have been reported in several cases of low T3, T4 syndrome,[7] and hypothyroidism.[8–10] However, the relationship between thyroid hormone levels and CEA levels is still uncertain. In the present study, we investigated the correlation between CEA levels and thyroid function in patients with T2DM.

Materials and Methods

Subjects and Data

This study was approved by the Medical Ethics Committee of the Dongzhimen Hospital, Beijing University of Chinese Medicine. Since anonymized data were collected from inpatient electronic files in this retrospective study in accordance with China ethical guidelines, informed consent was not obtained. All participants aged ≥ 18 years, fasting plasma glucose (FPG) level ≥ 7.0 mmol/L, or oral glucose tolerance test ≥11.1 mmol/L, or Glycated hemoglobin typeA1c (HbA1c) ≥6.5% who were diagnosed with T2DM according to the guidelines for prevention and treatment of type 2 diabetes in China (2020)[11] from December 2011 to December 2019 at Tongzhou Branch of Dongzhimen Hospital were identified and included in the study (Figure 1). The exclusion criteria were incomplete clinical data, history of thyroid surgery, history of levothyroxine tablets or other antithyroid drugs, severe liver disease which referred to the values of liver enzyme such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), Gamma-glutamyl transpeptidase (GGT) exceeding three times the upper limit of normal range, renal failure referring to serum creatinine (Scr) over 133 μmol/L, infection, acute diabetic complications, hypoglycemia, and acid-base disturbance within 2 weeks.

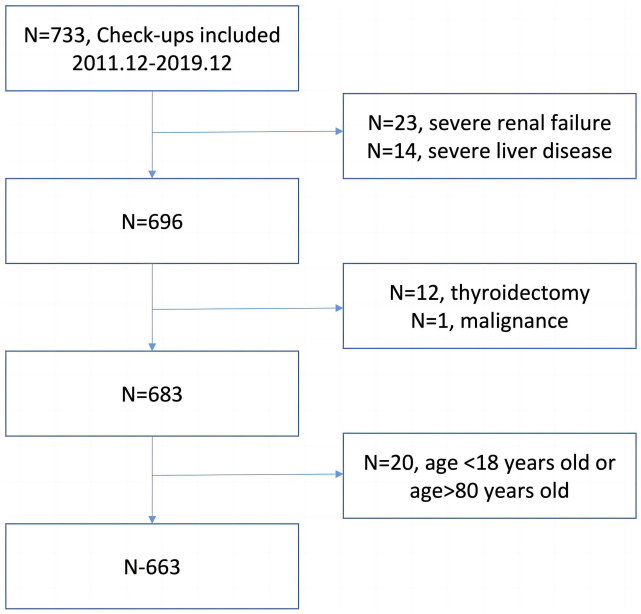

Figure 1 Flowchart of inclusion and exclusion criteria for the study.

Laboratory Assays

Blood was drawn after overnight fasting for at least 8h and analyzed immediately. HbA1c (%), FPG (mmol/L), TG (mmol/L), total cholesterol (TC, mmol/L), Scr (μmol/L), blood urea nitrogen (BUN, mmol/L), uric acid (UA, μmol/L), ALT (U/L), AST (U/L), ALB (g/L), TP (g/L), serum globulin (GLB, g/L), and ALP (U/L) levels were measured using an automatic biochemical analyzer (Beckman-DXC800, American). The thyroid function evaluation index including the free FT4 (normal reference range 0.59–1.25 ng/dL), free FT3 (normal reference range 2.14–4.21 pg/mL), serum thyroid stimulating hormone (TSH, normal reference range 0.56–5.91 μIU/mL), TT4 (normal reference range 5.44–11.85μg/dL), TT3 (normal reference range 0.66–1.61 ng/mL), CEA (normal reference range 0–5 ng/mL) were determined by automatic immune analyzer (Beckman-DXC800i, American).

Statistical Analysis

Normally distributed continuous variable TC was expressed as mean ± standard deviation (SD) and was calculated using the independent samples *t*-test to determine the differences. Other data in this study were skewed (Kolmogorov–Smirnov test: $p<0.1$ each) and would be expressed as median (interquartile range). Mann–Whitney *U*-tests were used to assess the differences in clinical characteristics between the CEA normal and abnormal groups. χ^2 tests were used for nonparametric variables. In the multivariate binary logistic regression analysis, predictors of abnormal CEA levels were selected based on both clinical and statistical significance. Based on the variables listed in Table 1 and our clinical experience, further we used binary logistic regression models to analyze the relationship between FT3 quartiles and CEA levels, with multivariable adjustment for age, gender, GLU, HbA1c, TG, TC, Scr, TP, ALB, GLB, and ALT. After conducting binary regression, only

Table 1 Characteristics of Subjects Stratified According to Abnormal-CEA or Normal CEA

Variables	Normal group (n=593)	Abnormal group (n=70)	Z/t/ χ2 values	P values
Gender				
Male, n (%)	336(56.7)	47 (67.1)	2.820	0.089
Female, n (%)	257(43.3)	23(32.9)		
Age (years)	57(48,66)	60(51.5,68)	−1.293	0.196
ALT	19.0(14.0,28.0)	17.0(14.0,28.5)	−0.780	0.436
AST	19.0(16.0,24.0)	18.0(15.0,22.5)	−1.149	0.251
GGT	25.0(18.0,37.0)	23.0(18.5,30.0)	−0.640	0.522
ALP	66.0(56.0,80.5)	74.5(62.0,87.0)	−3.106	0.002
T2DM course	8.0(3.0,14.0)	10.0(2.0,14.5)	−0.058	0.953
TT3 (ng/mL)	0.85(0.74,0.98)	0.78 (0.67,0.88)	−3.466	0.001
FT3 (pg/mL)	3.01(2.75,3.26)	2.81(2.61,3.05)	−3.565	<0.001
TSH (μIU/mL)	1.61(1.09,2.44)	1.56(0.96,2.67)	−0.153	0.878
TT4 (μg/dL)	8.25(7.24,9.15)	8.39(7.28,9.40)	−0.456	0.648
FT4 (ng/dL)	0.92(0.84,1.03)	0.98(0.86,1.11)	−1.899	0.058
TP	64.0(60.9,67.65)	61.8(57.6,66.25)	−2.740	0.006
ALB	37.3(34.95,39.9)	35.6(32.85,38.35)	−3.076	0.002
SCR (μmol/L)	61.0(51.0,73.0)	60.0(48.0,80.0)	−0.009	0.993
BUN (mmol/L)	4.80(3.90,5.80)	5.15(3.70,6.95)	−1.590	0.112
UA (μmol/L)	287.0(241.5,350.5)	284.5(211.0,346.5)	−0.798	0.425
GLU (mmol/L)	9.00(7.05,12.2)	13.90(10.55,18.1)	−6.951	<0.001
GLB (mmol/L)	26.45(24.2,29.35)	27.3(22.25,31.25)	−0.157	0.875
TC (mmol/L)	4.50±1.06	4.43±1.14	−0.525	0.600
TG (mmol/L)	1.74(1.19,2.67)	1.35(0.88,2.17)	−2.637	0.008
HbA1c (%)	8.76(7.53,10.16)	10.85(9.37,12.06)	−6.823	<0.001

Abbreviations; CEA: Carcinoembryonic antigen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transpeptidase, ALP: Alkaline phosphatase, TT3: Total triiodothyronine, FT3: Free triiodothyronine, TSH: Thyroid stimulating hormone, TT4: Total thyroxine, FT4: Free thyroxine, TP: Total protein, ALB: Serum albumin, SCR: Serum creatinine, BUN: Blood urea nitrogen, UA: Uric acid, GLU: Glucose, GLB: Globulin, TC: Total cholesterol, TG: Triglyceride, HBA1C: Glycated hemoglobin typeA1c.

FT3, GLU, HbA1c, TG, and gender were retained in the model, while the others were excluded. Spearman correlation analysis was used to evaluate the correlation between CEA levels and the clinical data. The predictors of abnormal CEA levels included gender and FT3, GLU, HbA1c, and TG levels. Data were analyzed using SPSS software (Statistical Package for the Social Sciences, version 25.0, Chicago). Statistical significance was set at $P < 0.05$.

Results

General Data and Correlation Analysis

The clinical characteristics of the patients are summarized in Table 1. The present study included 633 patients with T2DM (593 patients in the normal CEA group and 70 patients in the abnormal CEA group). In our study, TT3, FT3, ALB, TP, and TG levels were significantly higher in the normal CEA group than in the abnormal CEA group, whereas ALP, GLU, and HbA1c levels were significantly increased in the abnormal CEA group. However, gender and TSH, TT4, and FT4 levels had no significant difference between the two groups.

Independent Factor Analysis of CEA Group

Binary logistic regression analysis demonstrated that FT3 (β =−1.009, P=0.004), GLU (β =0.090, P = 0001), HbA1c (β= 0.336, P <0.001), TG (β= −0.293, P =0.009), and gender (β =−0.907, P =0.004) were risk factors for CEA in T2DM patients (Table 2). Conversely, TT3 did not affect CEA levels (Table 2).

The Correlation Factor Analysis of the CEA Group

Spearman correlation analysis showed that CEA had a significant positive correlation with HbA1c and GLU levels (r_s value: 0.265, P <0.001; r_s value: 0.270, P <0.001, respectively). In addition, there was a significant negative correlation between CEA, FT3, and TG, while the correlations were statistically weak (r_s value: −0.139, P <0.001; r_s value: −0.103, P =0.008, respectively), as shown in Table 3. However, the CEA group did not exhibit any correlation with the other thyroid function evaluation indices (Figure 2).

Table 2 Binary Logistic Regression Analysis of Predictors of CEA Group

Items	*β* values	Wald values	*P* values	OR	95% CI
FT3	−1.009	8.147	0.004	0.364	0.182~0.729
GLU	0.090	10.984	0.001	1.094	1.037~1.154
HBA1C	0.336	19.958	<0.001	1.399	1.207~1.621
TG	−0.293	6.781	0.009	0.746	0.598~0.930
Gender	−0.907	8.222	0.004	0.404	0.217~0.750

Table 3 Correlation Between CEA Levels and Predictors

Variable	r_s values	P values
FT3	−0.139	<0.001
Gender	−0.065	0.093
HBA1C	0.265	<0.001
GLU	0.270	<0.001
TG	−0.103	0.008

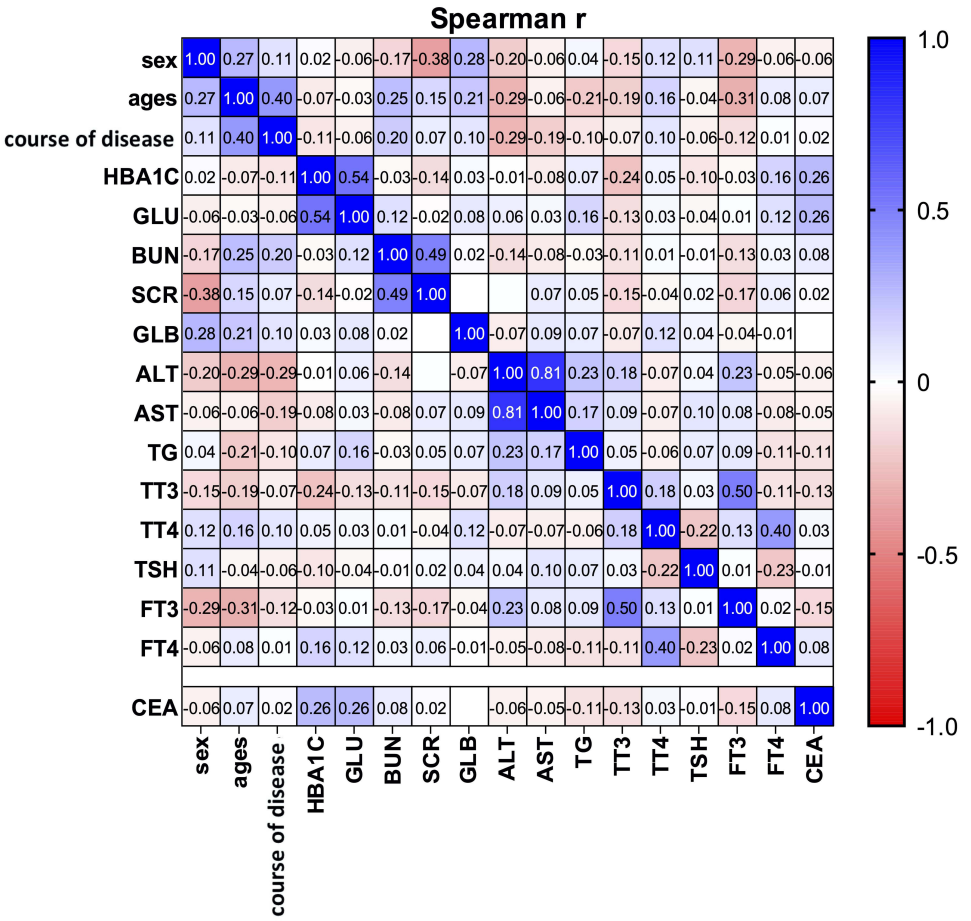

Figure 2 Correlations between continuous variables and correlation coefficients (Blue represents a positive correlation, red represents a negative correlation, and the darker the color, the greater the correlation coefficient). As shown in Figure 2, the negative correlation between CEA and FT3 is visually evident.

The Association Between FT3 Quartiles and CEA Group

Furthermore, we investigated the association between FT3 quartiles and CEA levels by using binary logistic regression models. The quartile regression could present that the changing trend of the influence of CEA on the FT3 at different quantile points. As shown in Table 4, compared with those in the highest quartile, the OR (95% CIs) were 3.37(1.54, 7.38), 2.37(1.04, 5.40), and 1.62(0.68, 3.85) for Q1-Q3 for incident abnormal CEA in FT3 (P for trend= 0.008 in model 1). After adjusting for age, gender, GLU, and HbA1c, the incidence of abnormal CEA levels was significantly increased in lower quartiles compared to the highest quartile (OR, 95% CIs: 3.69, 3.58, 2.09; P for trend< 0.001 in Model 2). Additionally, after adjusting for TC, TG, Scr, TP, ALB, GLB, and ALT, the

Table 4 Association Between FT3 and CEA Group in All the Participants

	Quartiles of FT3				
	Quartiles 1	**Quartiles 2**	**Quartiles 3**	**Quartiles 4**	**P for trend**
Cases/participants	28/173	19/159	14/165	9/166	
Model 1	3.37(1.54,7.38)	2.37(1.04,5.40)	1.62(0.68,3.85)	1.0	0.008
Model 2	3.69(1.58,8.62)	3.58(1.50,8.56)	2.09(0.85,5.16)	1.0	<0.001
Model 3	3.35(1.43,7.88)	3.35(1.39,8.08)	1.71(0.67,4.36)	1.0	<0.001

Notes: Model 1, unadjusted. Model 2, adjusted for age, gender, GLU, and HbA1c levels. Model 3, further adjusted for TG, TC, Scr, TP, ALB, GLB, and ALT levels.

incidence of abnormal CEA across–Q1-Q3 in FT3 increased significantly (OR, 95% CIs: 3.35, 3.35, 1.71; P for trend< 0.001 in Model 3). Multivariate logistic regression analysis indicated that FT3 level was significantly associated with CEA level before and after adjusting for confounding factors.

Discussion

Epidemiologic evidence suggests that diabetes increases the relative risk of cancer in the liver, pancreas, endometrium, colon and rectum, breast, and bladder.[12]

Elevated levels of tumor markers such as CEA and CA199 have been shown to correlate with diabetic pancreatic cancer.[13] CEA has been reported to exhibit significantly higher serum levels in diabetic patients compared with non-diabetic subjects.[14] Meanwhile Chung S demonstrated that CEA levels were positively associated with HbA1c levels in patients with diabetes but not in prediabetic patients and normal individuals.[15] In this retrospective study, serum CEA levels were positively correlated with HbA1c and GLU in the patients with T2DM. HbA1c and GLU could reflect the glycemic control status of patients with diabetes, since HbA1c represents the overall glucose content over the last 2–3 months and GLU is another key monitoring indicator. Hospitalized patients with diabetes usually have high blood glucose levels. Abnormal CEA elevation in inpatients with diabetes presented positive relation with poor hyperglycemia controlled.[16] We found significant higher HbA1c (range of 9.37 to 12.06%) and GLU (range of 10.55 to 18.1 mmol/L) in T2DM patients with abnormal CEA. Some studies have also indicated that poor glycemic control is an independent risk factor for CEA in patients with diabetes.[17] In our study, GLU and HbA1c remained risk factors for CEA levels in patients with T2DM. As a result, there was a positive relationship between CEA levels and glycemic status, which is consistent with the findings of this study.

Previous studies have shown that thyroid dysfunction is associated with T2DM, especially a high risk of T2DM, correlating with elevated TSH and decreased FT3 and FT4 levels.[18] Female gender, central obesity, duration of DM, and diabetic kidney disease have been reported to be risk factors for thyroid dysfunction in T2DM.[19] Interestingly, our results also revealed that CEA levels were significantly associated with thyroid function in T2DM patients. Many case reports have indicated that elevated serum CEA levels are associated with low serum T3 and T4 levels or high serum TSH concentrations.[7,20] One study that included 149 patients with various thyroid diseases showed that elevated CEA levels had significant relation with the duration of hypothyroidism.[10] It was also suggested that there was an inverse correlation between circulating CEA and T4 levels. However, our study indicated that serum TT3 and FT3 levels were significantly decreased in the abnormal-level CEA group of T2DM patients, while TSH, TT4, and FT4 levels were not significantly different between the normal and abnormal CEA groups. FT3 also remained an independent risk factor for CEA in patients with T2DM and was significantly negatively correlated with CEA levels. The incidence of abnormal CEA levels was significantly related to the FT3 quartiles before and after adjusting for confounding factors. CEA levels were negatively associated with FT3 levels in patients with T2DM. A reduction in FT3 has been attributed to multiple events, including malnutrition, acute and chronic diseases. Decrease of serum FT3 also represents the severity of disorder and is associated with prognosis. In addition, CEA referred to an indicator of systemic malfunction and helpful in assessing disease progression. Therefore, correlation between increase of CEA level and decrease of FT3 in T2DM might be reflect the severity of disease progresses.

TSH is regulated by the hypothalamic-pituitary axis and stimulates thyroid follicular cells to release a large quantity of T4 and small amount of T3. T4 and T3 also exert a negative feedback on TSH levels, especially T3, which is the predominant inhibitor of TSH secretion. Approximately 20% of T3, the active form of thyroid hormone, originates from thyroid secretion, and the majority is produced by peripheral conversion from T4. T3 acts on target tissues by binding to thyroid receptors in the nuclei of target cells.[21] FT3, the biologically active unbound free form, accounts for only a small percentage of circulating T3. FT3 is one of the most clinically relevant markers for evaluating thyroid disorders. FT3 decreases as the severity of disease progresses. Previous studies have shown that FT3 is closely associated with inflammatory factors in thyroid dysfunction and many chronic diseases such as insulin resistance,[22] end-stage renal disease,[23] and chronic heart failure.[24] In patients with DM, CRP levels are negatively correlated with FT3 concentration.[25] A recent cross-sectional study indicated that FT3 is inversely related to the inflammatory marker IL-6

in T2DM patients.[26] Data from IL-6 knockout mice support the role of IL-6 in thyroid dysfunction, especially the reduction in plasma T3 levels compared with wild-type mice.[27]

Many clinical studies have demonstrated the association of CEA with inflammatory markers, including IL-6, C-reactive protein, and neutrophil/lymphocyte ratio in chronic diseases.[28–31] CEA causes activation of Kupffer cells via binding to the CEA receptor, resulting in the production of inflammatory cytokines including IL-1α, IL-1β, IL-6, IL-10, and tumor necrosis factor (TNF-α).[32,33] Cytokines play a vital role in the immune system and directly target thyroid follicular cells via invasion during the pathogenesis of thyroid diseases.[34] It has been reported that the inflammatory cytokines TNF-α, IL-6 were significantly elevated in autoimmune thyroid disease, and thyroid dysfunction.[22] Therefore, we inferred that the underlying mechanism of the correlation between CEA and FT3 in T2DM patients might be attributed to inflammation.

At last, the representativeness of this study is limited due to the insufficient sample size. Notwithstanding its limitation, the present study indicated that FT3 remained an independent risk factor for CEA in patients with T2DM and was significantly negatively correlated with CEA levels. Next, we will conduct a multi-dimensional study of CEA to evaluate the predictive value of low FT3, and further explore the internal mechanism between CEA and FT3 in T2DM through experiments.

Data Sharing Statement

The data that support this study are available from the corresponding author only upon reasonable request, once the study has been published.

Ethics Approval and Consent to Participate

This retrospective study was approved by the Medical Ethics Committee of Dongzhimen Hospital, Beijing University of Chinese Medicine (2021DZMEC-038-02). The requirement for consent to participate was waived by the Medical Ethics Committee of the Dongzhimen Hospital, Beijing University of Chinese Medicine. This study was conducted in accordance with the principles of the Declaration of Helsinki.

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Author Contributions

Jingxin Zhou and Can Cao contributed to the work equally and share first authorship. Lili Wu and Juan Miao are co-corresponding authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest regarding the publication of this paper.

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