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Original Article

Dynamic evaluation of serum atherogenic factors as a predictor of QT interval prolongation in patients with type 2 diabetes mellitus

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Abstract: Objective: To investigate the correlation between dynamic changes in serum atherogenic factors and QT interval prolongation in type 2 diabetes mellitus (T2DM) patients, and evaluate its clinical application value. Methods: A single-center retrospective analysis was conducted on 613 T2DM patients, who met the 2011 American Diabetes Association criteria, at Nantong Hospital to Nanjing University of Chinese Medicine. Clinical data, atherogenic lipid profiles, inflammatory factors, and endothelial function indicators were collected. All patients underwent 12-lead electrocardiography to measure corrected QT interval (QTc) at baseline and after 12-month follow-up. Repeated measures ANOVA was used to compare indicator dynamics between patients with new-onset QT prolongation and non-prolongation groups, followed by multivariate logistic regression and ROC curve analyses. Results: During follow-up, 32 (5.2%) patients developed QT prolongation. Baseline diabetes duration, HbA1c, atherogenic lipid indices (e.g., TG/HDL-C ratio), hs-CRP, IL-6, ET-1 and vWF were significantly higher, while HDL-C and NO were lower in the prolongation group (all $P<0.05$). These factors correlated with QTc. Multivariate regression identified TG/HDL-C ratio, hs-CRP, ET-1 and IL-6 as independent risk factors, with TG/HDL-C ratio showing the highest risk. Combined detection of these indicators yielded superior predictive value for QT prolongation over single indicators ($P<0.05$). Conclusion: Abnormal atherogenic lipids, inflammatory factors and endothelial markers correlate with QT interval prolongation in T2DM. Combined detection of TG/HDL-C ratio, hs-CRP, IL-6 and ET-1 enhances the predictive efficacy for QT prolongation.

Keywords: Type 2 diabetes mellitus, serum atherogenic factors, QT prolongation, clinical application

Introduction

Type 2 diabetes mellitus (T2DM) is common among chronic metabolic diseases, and its incidence continues to increase rapidly, posing a threat to human health [1]. The main characteristics of T2DM include insulin resistance and β-cell dysfunction, which not only cause disturbances in glucose metabolism but are also often accompanied by hypertension and lipid metabolism disorders, even increasing the risk of cardiovascular diseases. Research by Kofod DH et al. explored arrhythmias and hypoglycemia in diabetic and non-diabetic patients and found that diabetic patients have a higher risk of arrhythmias, severely affecting their quality of life and prognosis [2]. The QT interval is an electrocardiogram index, and its prolongation is related to delayed ventricular repolarization, which can easily trigger arrhythmias, and has been confirmed as a risk factor for fatal arrhythmic events [3]. Patients with T2DM are in a state of chronic hyperglycemia, causing chronic inflammation and oxidative stress, which reduces cardiac electrophysiological stability, thereby increasing the incidence of QT interval prolongation. A meta-analysis found that prolonged corrected QT (QTc) interval is more prevalent in patients with T2DM compared to non-diabetic patients, further highlighting the impact of diabetes on cardiac electrophysiology [4]. However, in clinical practice, monitoring of QT interval prolongation mainly relies on standard 12-lead electrocardiograms. This morpho-

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logical examination has several limitations. First, it is a static assessment and cannot capture the dynamic fluctuations of electrophysiological status. Second, when it detects definite QT interval prolongation, the patient's cardiac electrophysiological instability has often progressed to a certain stage, missing the optimal early intervention window [5]. Therefore, exploring circulating biomarkers that can reflect the risk of myocardial repolarization abnormalities in T2DM patients earlier and more dynamically is crucial for achieving risk warning and stratified management.

It is noteworthy that the cardiovascular complications of T2DM are closely linked to the pathological process of atherosclerosis. AS is not merely a simple lipid deposition but a complex process involving lipid metabolism disorders, chronic inflammation activation, and vascular endothelial dysfunction. The bioactive substances released during these processes, known as "atherogenic factors", not only drive vascular lesions but recent studies also suggest that they may directly or indirectly influence the electrophysiological properties of cardiomyocytes [6]. This indicates that atherogenic factors may play a crucial role between metabolic disorders in T2DM and cardiac electrophysiological abnormalities. Currently, most studies focus only on cross-sectional associations of single lipid, inflammatory, or endothelial markers with the QT interval, lacking a systematic, dynamic, longitudinal assessment of multidimensional atherogenic factors to clarify their role in the occurrence and development of QT interval prolongation. Based on this, this study analyses the association between serum atherogenic factors and QT interval prolongation, aiming to provide new insights for early clinical identification of high-risk patients.

Materials and methods

Case selection

This study was a retrospective analysis, including 613 T2DM patients who visited the Nantong Hospital to Nanjing University of Chinese Medicine.

Inclusion criteria: (1) meeting the 2011 American Diabetes Association diagnostic criteria for T2DM, i.e. fasting blood glucose ≥7.0 mmol/L and/or 2-hour postprandial blood glucose ≥11.1 mmol/L [7]; (2) aged 18 to 80 years; (3) complete lipid metabolism profile tested.

Exclusion criteria: (1) history of type 1 diabetes, or positive for islet cell antibodies and/or insulin antibodies; (2) atrial fibrillation, atrial flutter, atrioventricular block, or bundle branch block; (3) heart valve disease, myocardial infarction, cardiac surgery; (4) taking drugs affecting the QT interval such as tricyclic antidepressants, electrolyte disorders, etc.; (5) major diseases such as chronic liver disease, chronic kidney disease, or malignant tumours; (6) excessive daily alcohol intake, more than 60 g for men and 40 g for women; (7) acute complications (such as diabetic ketoacidosis) or endocrine diseases affecting glucose metabolism (such as hyperthyroidism). This study strictly followed medical ethics principles, and the research protocol was approved by the Ethics Committee of the Nantong Hospital of Traditional Chinese Medicine. During the study, the provisions of the Declaration of Helsinki regarding the protection of participants' rights and privacy were strictly followed. Since this study was a retrospective study, informed consent was waived.

Data collection

Baseline data collection: Baseline data included body measurements (height, weight, blood pressure, etc.), diabetes duration, hypoglycemic treatment schemes, use of antihypertensive drugs, use of lipid-lowering drugs (such as statins and fibrates), smoking history, and alcohol consumption history.

Serological indicators detection and calculation: All enrolled patients maintained a light diet within three days of admission, and fasting venous blood was drawn from the elbow on the following morning. Lipid metabolism profiles were tested, including triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). In addition, inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and endothelial function indicators including endothelin-1 (ET-1), nitric oxide (NO), and von Willebrand factor (vWF) were measured. Serum atherogenic factors were calculated, including TG/HDL-C ratio, atherogenic index of plasma (AIP), non-high-density lipoprotein cholesterol (non-HDL-C), and apolipoprotein B to apolipoprotein A1 ratio (ApoB/ApoA1).

Measurement and evaluation of electrocardiographic repolarization parameters: A cardiologist, blinded to patient groups and serological

results, performed standard 12-lead electrocardiograms on all patients. The following electrocardiographic repolarization parameters were manually measured and calculated: QT interval (corrected to QTc interval using Bazett's formula), QT dispersion (QT dispersion, QTd), T peak to end interval (Tp-e) and Tp-e/QT ratio. A QTc interval >440 ms for males or >460 ms for females was defined as prolonged QT interval.

Outcome metrics and variable definitions

Primary outcomes: The dynamic changes in QTc interval from baseline to the end of follow-up and the incidence of new-onset QT interval prolongation.

Secondary outcomes: (1) Baseline clinical characteristics (e.g., age, gender, diabetes duration, BMI, HbA1c, blood pressure, smoking history, and lipid-lowering medication use); (2) Assessments of the levels and dynamic trends of atherogenic lipid profiles (TG, HDL-C, LDL-C, TC, TG/HDL-C ratio, atherogenic index of plasma [AIP], non-HDL-C, apolipoprotein B/apolipoprotein A1 [ApoB/ApoA1] ratio); (3) Evaluations of inflammatory and endothelial function indicators (hs-CRP, IL-6, TNF-α, endothelin-1 [ET-1], nitric oxide [NO], von Willebrand factor [vWF]) regarding their levels and dynamic changes; (4) Assessments of electrocardiographic repolarization parameters (QTc, QT dispersion [QTd], Tp-e interval, Tp-e/QT ratio) at baseline and during follow-up; (5) Correlation analysis between baseline serological indicators (e.g., TG/HDL-C ratio) and electrocardiographic parameters (e.g., baseline QTc); (6) Risk factors: Explore the risk factors leading to the prolongation of the QTc interval through a regression model. Given the limited number of outcome events, to reduce the risk of model overfitting, only variables with clear clinical significance were included in the multivariate analysis; (7) Assessment of the predictive value of indicators such as the TG/HDL-C ratio for new-onset QT prolongation during follow-up using receiver operating characteristic (ROC) curves.

Statistical methods

SPSS 26.0 and R software were used for data analysis. Count data were expressed as counts and percentages and were compared using the χ^2 test. Measurement data were expressed as mean ± standard deviation, with independent sample t-tests used to compare measurement data between the two groups. For serological indicators and electrocardiographic parameters at multiple time points during follow-up (baseline, 6 months, 12 months), repeated measures ANOVA was used for overall comparison. If there was a statistically significant interaction between "time" and "group", LSD method was performed to compare differences between the two groups at the same time point and within the same group at different time points. Pearson correlation and scatter plots were used to analyze the association between baseline serological indicators (TG/HDL-C, inflammatory factors, etc.) and baseline electrocardiographic parameters (QTc, QTd, etc.). Logistic regression was performed to analyze the risk factors for QT interval prolongation. A *P* value <0.05 was considered statistically significant. ROC curve analysis was used to evaluate the predictive value of each independent risk factor and their combined indicators for QT interval prolongation, and the area under the curve (AUC) was calculated. An AUC>0.7 indicates acceptable predictive value, while an AUC>0.8 indicates good predictive value.

Results

Comparison of baseline clinical characteristics

After 12 months of follow-up, among 613 T2DM patients with normal baseline QTc, 32 cases (5.2%) developed new QT interval prolongation (QT prolongation group), while 581 cases (94.8%) did not (non-prolongation group). Patients in the QT prolongation group had a longer duration of diabetes and higher HbA1c levels than those in the non-prolongation group (both P<0.05). However, there were no statistically significant differences between the two groups in age, gender distribution, body mass index (BMI), systolic and diastolic blood pressure, smoking history, or the proportion of lipid-lowering drug use (all P>0.05). This suggests that a longer duration of diabetes and poorer glycemic control may be potential risk factors for QT interval prolongation. See **Table 1**.

Comparison of lipid profiles

Although all patients had normal QTc intervals at baseline, multiple atherogenic lipid indicators were generally higher in the QT prolongation group than in the non-prolongation group

Table 1. Comparison of baseline clinical characteristics

Indicator	QT prolongation group (n=32)	Non-prolongation group (n=581)	Statistical value	*P*
Age (years)	61.08±10.92	58.35±8.41	t=1.757	0.079
Gender (male), n (%)	18 (56.25%)	312 (53.70%)	X^2=0.079	0.778
Course of diabetes (years)	11.50±3.82	9.87±4.10	t=2.197	0.028
Body mass Index (kg/m^2)	26.15±2.85	25.20±3.12	t=1.684	0.092
HbA1c (%)	8.65±1.08	7.55±1.12	t=5.419	<0.001
Systolic blood pressure (mmHg)	138.20±14.85	133.75±15.36	t=1.598	0.111
Diastolic blood pressure (mmHg)	83.45±8.92	81.20±9.15	t=1.356	0.176
Smoking history, n (%)	12 (37.50%)	208 (35.80%)	X^2=0.038	0.845
Use lipid-lowering drugs, n (%)	10 (31.25%)	175 (30.12%)	X^2=0.018	0.892

Table 2. Comparison of lipid factors

Indicator	Group	Baseline (0 months)	6-months	12-months	Interaction effect *P* value
TG (mmol/L)	QT prolongation group (n=32)	2.85±0.73	3.10±0.80	3.35±0.88	<0.001
	Non-prolongation group (n=581)	2.20±0.55	2.15±0.53	2.12±0.52	
HDL-C (mmol/L)	QT prolongation group (n=32)	0.92±0.18	0.89±0.17	0.86±0.16	<0.001
	Non-prolongation group (n=581)	1.08±0.20	1.09±0.20	1.10±0.21	
LDL-C (mmol/L)	QT prolongation group (n=32)	3.05±0.65	3.10±0.67	3.15±0.70	0.085
	Non-prolongation group (n=581)	2.70±0.60	2.68±0.59	2.65±0.58	
TC (mmol/L)	QT prolongation group (n=32)	4.95±0.85	5.00±0.87	5.05±0.90	0.124
	Non-prolongation group (n=581)	4.60±0.78	4.58±0.77	4.55±0.76	
TG/HDL-C ratio	QT prolongation group (n=32)	3.42±1.05	3.70±1.15	4.00±1.25	<0.001
	Non-prolongation group (n=581)	2.15±0.70	2.10±0.68	2.05±0.65	
AIP	QT prolongation group (n=32)	0.53±0.16	0.56±0.17	0.59±0.18	<0.001
	Non-prolongation group (n=581)	0.32±0.12	0.31±0.11	0.30±0.11	
Non-HDL-C (mmol/L)	QT prolongation group (n=32)	4.03±0.80	4.11±0.83	4.19±0.87	<0.018
	Non-prolongation group (n=581)	3.52±0.72	3.49±0.71	3.45±0.70	
ApoB/ApoA1 ratio	QT prolongation group (n=32)	0.98±0.22	1.02±0.23	1.06±0.25	0.026
	Non-prolongation group (n=581)	0.80±0.18	0.79±0.17	0.78±0.17	

Note: TC: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, and LDL-C: low-density lipoprotein cholesterol, ApoB/ApoA1: apolipoprotein B to apolipoprotein A1 ratio, AIP: atherogenic index of plasma.

at enrolment. During the 12-month follow-up, the QT prolongation group exhibited higher TG, TG/HDL-C ratio, and AIP, but lower HDL-C, non-HDL-C and ApoB/ApoA1 (all P<0.05). In contrast, the indicators in the non-prolongation group remained relatively stable and within the ideal range. However, although TC and LDL-C showed mild fluctuations during the follow-up period, the time × group interaction effect did not reach statistical significance (P>0.05), suggesting that the correlation between their dynamic changes and the prolongation of QT interval was limited. Post hoc tests further clarified that at baseline, 6 months, and 12 months, the levels of the above abnormal lipid indicators in the QT prolongation group were significantly higher than those in the non-prolongation group (all P<0.05). See **Table 2**.

Comparison of inflammation and endothelial function

At baseline, patients in the QT prolongation group had higher levels of inflammatory and endothelial injury markers than those in the non-prolongation group. During follow-up, levels of hs-CRP, IL-6, TNF-α, ET-1, and vWF continued to rise in the QT prolongation group, while NO levels decreased, indicating a continuous aggravation of inflammation and endothelial

Table 3. Comparison of inflammation and endothelial function indicators ($\bar{x}\pm s$)

Indicator	Group	Baseline (0 months)	6-months	12-months	Interaction effect *P* value
hs-CRP (mg/L)	QT prolongation group (n=32)	4.85±1.62	5.25±1.75	5.70±1.90	0.021
	Non-prolongation group (n=581)	2.80±1.10	2.75±1.05	2.70±1.00	
IL-6 (pg/mL)	QT prolongation group (n=32)	8.42±2.51	9.00±2.70	9.65±2.95	<0.001
	Non-prolongation group (n=581)	5.76±1.88	5.70±1.85	5.65±1.80	
TNF-α (pg/mL)	QT prolongation group (n=32)	12.65±3.74	13.50±4.00	14.50±4.30	<0.001
	Non-prolongation group (n=581)	8.21±2.35	8.15±2.30	8.10±2.25	
ET-1 (pg/mL)	QT prolongation group (n=32)	85.36±16.28	90.50±17.50	95.75±18.80	<0.001
	Non-prolongation group (n=581)	65.15±13.47	64.80±13.20	64.40±12.90	
NO (μmol/L)	QT prolongation group (n=32)	48.72±11.35	45.80±10.80	42.90±10.20	<0.001
	Non-prolongation group (n=581)	62.93±13.42	63.20±13.50	63.50±13.60	
vWF (%)	QT prolongation group (n=32)	155.38±28.64	162.40±30.80	170.80±33.50	<0.001
	Non-prolongation group (n=581)	125.75±22.19	124.20±21.80	122.50±21.30	

Note: hs-CRP: C-reactive protein, IL-6: interleukin-6, and TNF-α: tumor necrosis factor-α, ET-1: endothelin-1, NO: nitric oxide, and vWF: von Willebrand factor.

Table 4. Comparison of electrocardiogram parameters ($\bar{x}\pm s$)

Indicator	Group	Baseline (0 months)	6-months	12-months	Interaction effect *P* value
QTc (ms)	QT prolongation group (n=32)	437.5±8.5	441.2±9.8	455.8±12.5	<0.001
	Non-prolongation group (n=581)	420.8±8.2	421.5±8.5	422.1±8.8	
QTd (ms)	QT prolongation group (n=32)	42.5±6.8	48.2±8.0	56.8±10.3	<0.001
	Non-prolongation group (n=581)	36.8±5.5	37.1±5.7	36.5±5.3	
Tp-e (ms)	QT prolongation group (n=32)	108.5±10.8	115.8±12.5	122.6±14.2	<0.001
	Non-prolongation group (n=581)	95.8±9.5	96.2±9.7	95.5±9.3	
Tp-e/QT ratio	QT prolongation group (n=32)	0.251±0.028	0.262±0.030	0.269±0.032	<0.001
	Non-prolongation group (n=581)	0.228±0.024	0.228±0.025	0.226±0.023	

Note: QTc (corrected to QTc using Bazett's formula), QTd: QT dispersion, Tp-e: T-peak to T-end interval.

injury (all P<0.05). In contrast, the non-prolongation group remained relatively stable. The interaction effect between time and grouping was also significant (all P<0.05). See **Table 3**.

Comparison of electrocardiographic parameters

At baseline, the QTc of both groups was within the normal range. Over the follow-up period, repolarization parameters including QTc, QTd, Tp-e, and Tp-e/QT ratio exhibited a progressive deterioration in patients with QT interval prolongation, accompanied by a gradual elevation in electrical instability. Notably, some patients in this group were diagnosed with QT interval prolongation at the 12-month follow-up time point. In contrast, all repolarization parameters in the non-prolongation group remained within the normal reference range with only minor, stable fluctuations. The interaction effects of all electrocardiographic parameters were statistically significant (all P<0.05). See **Table 4**.

Correlation analysis

Pearson correlation showed that in terms of lipid profile, AIP and TG/HDL-C ratio, ApoB/ApoA1 ratio were positively correlated with QTc (all r>0, P<0.05), while HDL-C was negatively correlated with QTc (r<0, P<0.05). In terms of inflammation and endothelial function, TNF-α, hs-CRP, and IL-6 were positively correlated with QTc (all r>0, P<0.05), and endothelial function indicators ET-1 and vWF were also positively correlated with QTc (r>0, P<0.05). In addition, the correlations between TG, TC, LDL-C, non-HDL-C and QTc intervals did not reach statisti-

Table 5. Correlation analysis of lipid profile, inflammation and endothelial function indicators with electrocardiogram parameters

Indicator	Statistical value	QTc	QTd	Tp-e	Tp-e/QT ratio
TG (mmol/L)	*R*	0.073	0.040	0.074	0.038
	P	0.071	0.317	0.069	0.344
HDL-C (mmol/L)	*R*	-0.087	-0.084	-0.024	0.021
	P	0.031	0.037	0.559	0.605
LDL-C (mmol/L)	*R*	-0.01	-0.01	0.071	0.041
	P	0.799	0.797	0.079	0.312
TC	*R*	0.01	0.04	0.008	0.043
	P	0.803	0.317	0.847	0.286
TG/HDL-C ratio	*R*	0.107	0.106	0.071	0.123
	P	0.008	0.009	0.077	0.002
AIP	*R*	0.150	0.111	0.103	0.096
	P	<0.001	0.006	0.011	0.017
Non-HDL-C	*R*	0.052	0.014	0.059	0.042
	P	0.196	0.725	0.143	0.299
ApoB/ApoA1 ratio	*R*	0.087	0.064	0.116	0.021
	P	0.032	0.116	0.004	0.598
hs-CRP	*R*	0.144	0.084	0.127	0.067
	P	<0.001	0.037	0.002	0.096
IL-6	*R*	0.126	0.021	0.033	0.063
	P	0.002	0.607	0.416	0.116
TNF-α	*R*	0.169	0.065	0.192	0.085
	P	<0.001	0.11	<0.001	0.035
ET-1	*R*	0.201	0.067	0.105	0.042
	P	<0.001	0.097	0.009	0.295
NO	*R*	-0.047	-0.031	-0.111	-0.065
	P	0.243	0.445	0.006	0.109
vWF	*R*	0.140	0.105	0.095	-0.042
	P	<0.001	0.009	0.019	0.294

Note: TC: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, ApoB/ApoA1: apolipoprotein B to apolipoprotein A1 ratio, AIP: atherogenic index of plasma, hs-CRP: C-reactive protein, IL-6: interleukin-6, and TNF-α: tumor necrosis factor-α, ET-1: L endothelin-1, NO: nitric oxide, vWF: von Willebrand factor.

cal significance (P>0.05), suggesting a weak linear correlation. See **Table 5** and **Figure 1**.

Multivariate logistic regression analysis

The aforementioned univariate analysis showed that multiple lipid, inflammation and endothelial function indicators were associated with prolonged QT interval. The statistically significant variables were further included in the multivariate Logistic regression model. Multivariate logistic regression analysis revealed that when lipid factors, inflammatory factors, and endothelial factors were included in the multivariate logistic regression model, TG/HDL-C ratio, hs-CRP, ET-1, and IL-6 were identified as risk factors for QT interval prolongation, with the TG/HDL-C ratio exhibiting the strongest risk. TNF-α, AIP and the ApoB/ApoA1 ratio were associated with prolonged QT interval in the univariate analysis, but did not reach statistical significance after adjusting for other variables in the multivariate model and were not identified as independent risk factors. See **Table 6**.

Predictive value of baseline serum factors for QT prolongation

ROC analysis showed that the TG/HDL-C ratio, hs-CRP, and ET-1 had high predictive value for QT interval prolongation, with AUCs of 0.835, 0.845, and 0.826, respectively. IL-6 (AUC= 0.804) also demonstrated good predictive ability. The predictive performance was further

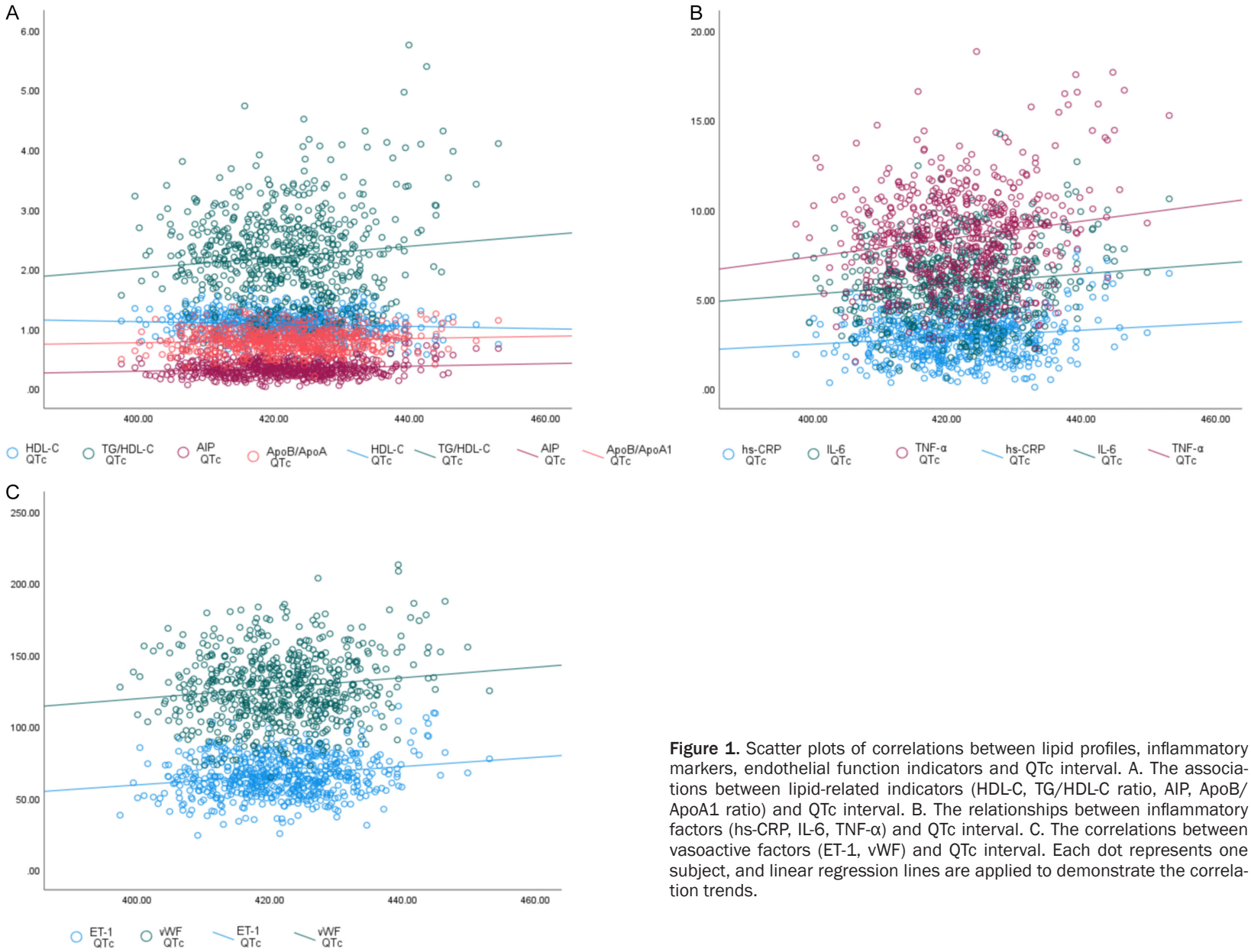

Figure 1. Scatter plots of correlations between lipid profiles, inflammatory markers, endothelial function indicators and QTc interval. A. The associations between lipid-related indicators (HDL-C, TG/HDL-C ratio, AIP, ApoB/ApoA1 ratio) and QTc interval. B. The relationships between inflammatory factors (hs-CRP, IL-6, TNF-α) and QTc interval. C. The correlations between vasoactive factors (ET-1, vWF) and QTc interval. Each dot represents one subject, and linear regression lines are applied to demonstrate the correlation trends.

Table 6. Risk Factors for prolonged QT interval

Indicator	β	Standard error	Wald	*P*	*OR*	95% CI
Constant	-69.424	21.012	10.917	0.001	0.000	
TG/HDL-C ratio	5.481	2.026	7.315	0.007	239.995	4.522-12735.855
AIP	13.375	7.112	3.536	0.060	643456.475	2.068-71.895
ApoB/ApoA1 ratio	7.322	4.145	3.120	0.077	1512.507	1.060-1.479
hs-CRP	2.501	0.905	7.631	0.006	12.193	1.101-4.986
IL-6	0.851	0.385	4.881	0.027	2.343	0.568-728825266801.098
TNF-α	0.421	0.314	1.797	0.180	1.523	0.448-5102529.022
ET-1	0.225	0.085	7.008	0.008	1.252	0.823-2.817
vWF	0.009	0.024	0.127	0.721	1.009	0.962-1.058

Note: TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, hs-CRP: C-reactive protein, IL-6: interleukin-6, ApoB/ApoA1: apolipoprotein B to apolipoprotein A1 ratio, AIP: atherogenic index of plasma, TNF-α: tumor necrosis factor-α, ET-1: endothelin-1, vWF: von Willebrand factor.

Table 7. ROC analysis of the predictive value of baseline serum factors for QT prolongation

Indicator	AUC	Standard error	P	95% CI	Sensitivity (%)	Specificity (%)
TG/HDL-C ratio	0.835	0.040	<0.001	0.757-0.913	78.1	76.3
hs-CRP	0.845	0.040	<0.001	0.755-0.898	81.2	74.0
IL-6	0.804	0.041	<0.001	0.723-0.885	74.6	71.8
ET-1	0.826	0.037	<0.001	0.651-0.845	76.9	73.2
Joint	0.896	0.026	<0.001	0.844-0.947	85.4	82.1

Note: TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, hs-CRP: C-reactive protein, IL-6: interleukin-6, ET-1: endothelin-1.

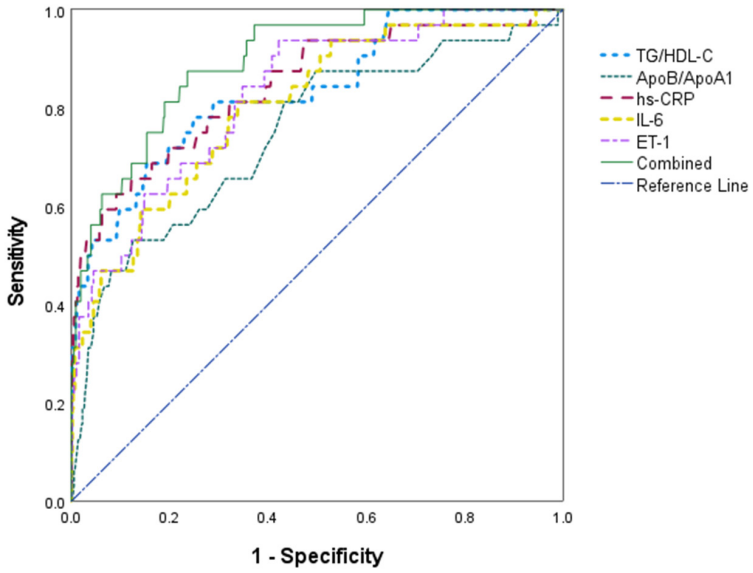

Figure 2. ROC analysis for predictive value of baseline serum factors in QT interval prolongation.

enhanced when combining these indicators, with an AUC of 0.896 (95% CI: 0.844-0.947), superior to a single indicator (P<0.05). The optimal cut-off value was determined based on the Youden index. The sensitivity of the TG/HDL-C ratio in predicting QT interval prolongation was 78.1%, and the specificity was 76.3%. The sensitivity of hs-CRP was 81.2% and the specificity was 74.0%. The sensitivity of IL-6 was 74.6% and the specificity was 71.8%. The sensitivity of ET-1 was 76.9% and the specificity was 73.2%. The sensitivity of the combined model was 85.4% and the specificity was 82.1%, achieving the best balance between sensitivity and specificity. See **Table 7** and **Figure 2**.

Construction, validation, and performance evaluation of the predictive model

Based on the four independent risk factors for QT interval prolongation determined by multivariate logistic regression analysis (TG/HDL-C ratio, hs-CRP, ET-1, and IL-6), this study developed a nomogram model to predict the risk of QT interval prolongation in patients with T2DM (**Figure 3**).

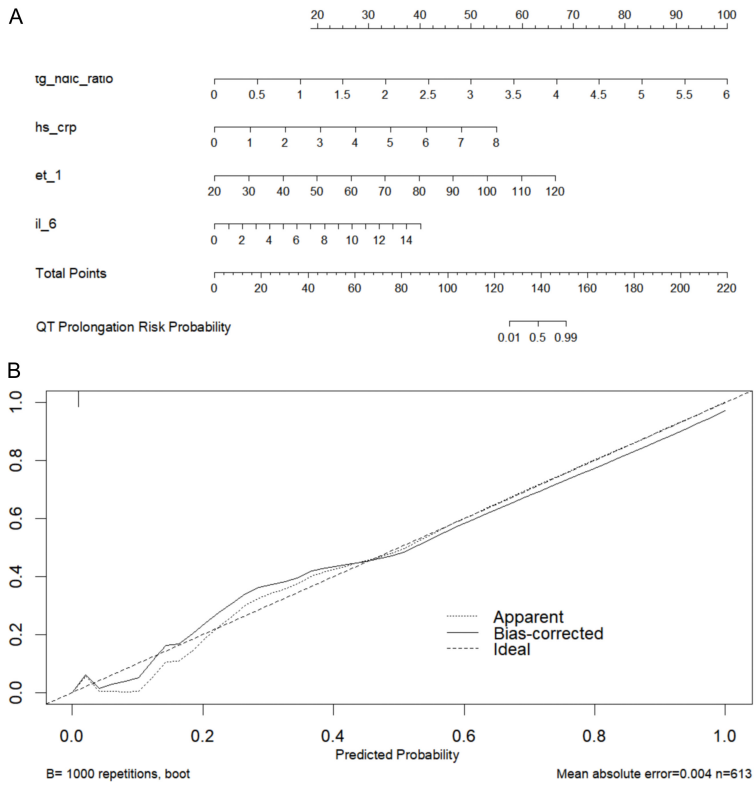

Figure 3. Nomogram and calibration curve for qt prolongation prediction based on serum factors. A. Nomogram of the prediction model for QT prolongation. B. Calibration curve of the prediction model for QT interval prolongation.

The model converted the regression coefficients of each indicator into an intuitive scoring scale, with the total score corresponding to the probability of QT prolongation. To validate the model, internal validation was performed using the Bootstrap method (1,000 repeated samplings). The calibration curve showed that the probabilities predicted by the nomogram were in close agreement with both the actual observed frequencies and the ideal reference curve, thereby verifying the satisfactory calibration performance of the model (**Figure 3**).

Discussion

T2DM is a common metabolic disease, and its cardiovascular complications are significant factors affecting patient prognosis and increasing mortality and disability rates [8, 9]. Prolongation of the QT interval is a manifestation of abnormal cardiac electrical activity, with a higher incidence in the T2DM population than in the general population, and is associated with an increased risk of arrhythmias and sudden cardiac death from cardiac causes [10, 11]. However, current detection of QT interval prolongation mainly relies on electrocardiography, and by the time it is detected, patients often already have a certain degree of cardiac electrophysiological abnormalities, with insufficient early prediction and identification capability and a lack of sensitive predictive indicators [12]. The results of this study showed that after 12 months of follow-up, among 613 T2DM patients with normal baseline QTc, 32 patients (5.2%) developed new QT interval prolongation. Notably, these patients already exhibited a longer duration of diabetes, higher HbA1c levels, and characteristic atherogenic lipid profiles, inflammation activation, and endothelial dysfunction at baseline. This suggests that QT interval prolongation is not an isolated phenomenon but occurs on the basis of multiple pathophysiological conditions including metabolic disorders, chronic inflammation, and vascular dysfunction.

Specifically, in terms of lipid metabolism, patients in the QT prolongation group exhibited typical atherogenic characteristics: high TG, low HDL-C, significantly elevated TG/HDL-C ratio, AIP, and ApoB/ApoA1 ratio. Dyslipidemia is closely associated with lipid metabolism imbalance, where the elevated ApoB/ApoA1 ratio indicates an imbalance between anti-atherogenic and pro-atherogenic lipoproteins in the prolongation group, and the increased TG and non-HDL-C reflect a relative accumulation of very low-density lipoproteins and their remnants in the QT prolongation group; while low HDL-C indicates a reduction in antioxidant capacity and endothelial protective function, suggesting these patients may have relatively more severe vascular wall lipid deposition [13-15]. Li et al. found that some abnormal changes in atherogenic factors not only directly promote the formation of atherosclerotic plaques but also encourage lipid deposition within car-

diomyocytes, reducing ion channel function through inflammation and oxidative stress, increasing thus prolonging the QT interval [16]. Moreover, high levels of free fatty acids can directly damage cardiomyocyte membranes, affecting ion channel function closely related to the repolarization process, lengthening the action potential duration and causing QT interval prolongation. In terms of inflammation and endothelial damage, patients in the QT prolongation group had significantly elevated levels of inflammatory factors such as hs-CRP, IL-6, and TNF-α, accompanied by increased ET-1 and decreased NO, which is largely consistent with the findings of Nunes JPS et al. The underlying reason is that elevated inflammatory cytokines like TNF-α and IL-6 are associated with inflammatory responses; chronic inflammation activates the NF-κB pathway, increases adhesion molecules, exacerbates endothelial dysfunction, and directly affects cardiomyocytes, thereby delaying action potential repolarization and prolonging the QT interval [17]. Furthermore, inflammation and lipid metabolism disorders may interact to form a vicious cycle, jointly aggravating myocardial matrix deterioration and prolonging the QT interval [18]. Moreover, endothelial function is closely linked to cardiomyocyte injury; endothelial dysfunction affects coronary microcirculatory perfusion, leads to local myocardial ischemia, induces myocardial fibrosis, and impacts the conduction of electrical excitation [19]. Among endothelial function indicators, ET-1 is a potent vasoconstrictor that promotes vascular smooth muscle proliferation, impairs endothelium-dependent vasodilation, and acts on endothelin receptors on cardiomyocytes, reducing repolarization potassium current and prolonging the QT interval. vWF is associated with platelet activation and worsening endothelial cell damage, thus relating to cardiac electrical abnormalities. Reduced NO results in decreased vasodilation capacity, exacerbates microcirculatory disturbance, and increases the risk of myocardial ischemia [20].

It can be seen that QT interval prolongation in T2DM patients is related to atherogenic dyslipidemia, inflammation, and endothelial dysfunction, and these mechanisms may form a vicious cycle, further increasing cardiovascular risk. This study confirmed through multivariate logistic regression analysis that the TG/HDL-C ratio, hs-CRP, ET-1, and IL-6 are independent risk factors for QT interval prolongation. This may be because the TG/HDL-C ratio is closely related not only to lipid metabolism disorders and excessive free fatty acids but also comprehensively reflects the inhibition of potassium channel function required for myocardial repolarization and the prolongation of the action potential duration due to lipid metabolism abnormalities, directly affecting QT prolongation [21]. Additionally, an elevated TG/HDL-C ratio is associated with insulin resistance and can also stimulate systemic inflammation, damaging endothelial function, thereby showing a higher impact on QT interval prolongation. ROC analysis showed that the TG/HDL-C ratio, hs-CRP, and ET-1 have high predictive value for QT interval prolongation, and IL-6 also demonstrated good predictive ability. The predictive efficiency was further improved when these indicators were combined. In addition, based on the four independent risk factors for QT interval prolongation identified by multivariate Logistic regression analysis, this study constructed a nomogram model to predict the risk of QT interval prolongation in T2DM patients. Internal validation using the Bootstrap method (1,000 repeated samplings) showed that the calibration curve indicated a close fit between the predicted probability by the nomogram and the actual observed frequency with the ideal curve, demonstrating good calibration of the model.

The present study has several limitations that warrant consideration. First, as a single-center observational study, despite rigorous efforts to control for potential confounding factors, the influence of unmeasured variables (e.g., genetic background or neurological function status) cannot be completely ruled out. Thus, the conclusions drawn herein reflected an associative relationship rather than a definitive causal link. Second, the 12-month follow-up duration was relatively short, and the number of endpoint events (i.e., QT interval prolongation) was limited. This may lead to unstable risk estimates (such as the OR for the TG/HDL-C ratio) and hinder the ability to evaluate the long-term predictive value of these factors for hard clinical endpoints including cardiac arrhythmias or sudden cardiac death. Third, manual measurement of the QT interval may introduce minor measurement errors, which could have a marginal impact on the accuracy of the results. Additionally, the study focused solely on serum

biomarkers without incorporating complementary approaches such as cardiac imaging techniques, which limited the in-depth exploration of the underlying pathophysiological mechanisms.

Future research should address these limitations through multicenter, large-sample, long-term cohort studies to validate the proposed predictive model and extend outcome measures to clinically meaningful hard endpoints (e.g., symptomatic arrhythmias and sudden cardiac death), thereby clarifying the model's true utility in the primary prevention of cardiovascular events. Furthermore, future investigations could integrate multidimensional data modalities, such as cardiac magnetic resonance imaging, whole-genome sequencing, and 24-hour dynamic electrocardiogram monitoring. In parallel, animal models or in vitro cellular experiments are needed to elucidate how dysregulated lipid profiles and elevated inflammatory factors contribute to QT interval prolongation via specific molecular pathways (e.g., oxidative stress, endoplasmic reticulum stress, or mitochondrial dysfunction), thus unraveling the underlying mechanisms at both the molecular and electrophysiological levels. A more translationally relevant direction would be to design interventional studies based on this risk stratification model. Targeted intensive lipid-lowering, anti-inflammatory, or endothelial function-improving therapies could be administered to high-risk individuals identified by the model, to verify whether early intervention can effectively mitigate the risk of QT interval prolongation and malignant cardiovascular events, and ultimately translate risk stratification into tangible clinical benefits.

It should also be noted that the lipid, inflammatory, and endothelial function indicators included in the multivariate logistic regression model exhibit a certain degree of multicollinearity. Combined with the relatively small number of QT prolongation events, this may have led to unstable OR values and wide 95% CIs for some variables. Nevertheless, this is a common statistical phenomenon in regression analyses with sparse endpoint events, and it does not affect the statistical significance (*P* values) or the direction of effect of the identified variables, nor does it alter the main conclusions of the present study. In addition, given that this study only adopted internal validation, there is a risk that the predictive performance of this nomogram model may be overestimated. In the next step of research, further validation through an external cohort is still needed before it can be used in clinical practice.

In conclusion, in T2DM patients, abnormal levels of atherogenic lipid profiles, inflammatory factors, and endothelial function markers are associated with QT interval prolongation. Among these factors, the TG/HDL-C ratio, hs-CRP, IL-6, and ET-1 serve as important independent risk factors. Combined detection of these biomarkers can significantly improve the predictive efficacy for QT interval prolongation in this patient population.

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Disclosure of conflict of interest

None.

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