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Diseases & Research

Correlation Between Serum Total Bile Acids and QTc Interval Prolongation in Non-ST Elevation Myocardial Infarction Patients

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Background: Many diseases with elevated total bile acids (TBA) concentrations have varying degrees of abnormal cardiac electrophysiological activity, such as prolonged corrected QT (QTc) interval. In non-ST elevation myocardial infarction (NSTEMI) patients, prolonged QTc interval indicate poor prognosis. Therefore, we surveyed the relationship between TBA and QTc prolongation in NSTEMI patients.
Methods: This retrospective analysis examined 328 individuals from Chinese population from January 2019 to January 2022. We used the median serum TBA concentration to divide the study population into two groups (Low-TBA: < 2.8 μmol/L; High-TBA ≥ 2.8 μmol/L). Logistic regression models were constructed to investigate the associations of serum TBA with QTc prolongation. Spearman correlation analyses were conducted to determine variables linked to TBA.
Results: The prevalence of QTc prolongation immediately upon admission in the NSTEMI patients was 11.89%, 16.27% in the Low-TBA group, 7.41% in High-TBA group. Low-TBA was an independent risk factor associated with QTc prolongation (OR 2.493, 95% CI 1.090-5.700, P = 0.030). Spearman correlation analyses showed linear negative correlations of TC, LDL-C and ApoB with TBA. The same tendency of leukocytes, neutrophils and neutrophil-to-lymphocyte ratio being inversely proportional to TBA was found.
Conclusion: Lower TBA was an independent risk factor associated with QTc prolongation. And TBA may affect cardiac electrical activity by affecting lipid metabolism and inflammation.
Keywords: QTc prolongation; Bile acids; NSTEMI; Correlation; Risk factors.

Introduction

Serum bile acids (BAs) affect the heart through a variety of mechanisms. Importantly, BAs can activate certain receptors on the myocardial membrane, such as Takeda G-protein-coupled receptor 5 and Farnesoid X Receptor, which are crucial in regulating cardiac glucose and lipid metabolism homeostasis[1]. In addition, BAs can alter the composition and structure of cardiomyocyte membranes, thus affecting the bioactivity of ion channels and certain receptors, ultimately changing the electrical activity of cardiomyocytes[2]. It is reported that in liver cirrhosis[3], nonalcoholic fatty liver disease[4] and cholestatic liver disease[5,6] serum total BAs (TBA) concentration is associated with abnormal cardiac electrical activity, especially QTc interval prolongation. QTc interval prolongation results from structural or functional abnormalities in ion channels and associated proteins involved in cardiac repolarization.

The prevalence of QTc prolongation in NSTEMI patients was 21.95%[7]. It was known that prolonged QTc interval can increase the risk of arrhythmia, especially Torsade de Pointes, which may lead to sudden cardiac death[8]. Prolonged QTc interval independently predicted adverse outcomes, including nonfatal acute myocardial infarction, percutaneous or surgical revascularization, and cardiac death after NSTEMI[9].

The exact mechanism of QTc interval prolongation in NSTMI patients remains undocumented. And there are only a few speculations at present, for instance, cardiac micronecrosis[10] and myocardial ischemia causing a time-dependent increase in extracellular K^+ concentration[11]. We conducted this research to explore factors associated with prolonged QTc interval using a cross-sectional approach.

Methods

Study Population

The data from patients with NSTEMI who were admitted from January 2019 to January 2022 I were retrospectively collected. NSTEMI was diagnosed according to the guidelines by the European Society of Cardiology[12]. Exclusion criteria included: (1) age < 18 years; (2) Old myocardial infarction; (3) Persistent atrial fibrillation, bundle branch block or congenital long QT syndrome; (4) After cardiac pacemaker implantation; (5) Taking medications that may cause prolonged QTc intervals (http://www.crediblemeds.org) or prescriptions for bile acid sequestrants; (6) Combined with chronic kidney disease(CKD) stage 4 or 5; (7) Combined with liver dysfunction or obstructive diseases of the biliary tract; (8) Combined with malignant tumors; (9) Combined with serious infectious diseases; (10) no serum TBA meas-

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urement or complete ECG data within 24 hours after admission. Ultimately, 328 patients were included in the current study (Fig. 1). Demographic, clinical, drug, hematologic, electrocardiographic, and angiographic data were extracted from the medical records. The study adhered to the Declaration of Helsinki.

Electrocardiogram (ECG) for Measurement of the QTc Interval

Twelve-lead surface ECGs were recorded immediately upon admission. All ECGs were performed by cardiologists on an electrocardiograph (ECG-1350P, NIHON KOHDEN, Japan) with automatic sampling mode. Parameters were automatically measured by electrocardiograph. All tracings were examined by two independent investigators, and a consensus was attained in instances of disagreement. QTc was corrected by the Framingham formula [QTc = QT + 154 × (1 − 60/HR)] according to the recommendation by the American Heart Association[13]. QTc ≥ 450 ms for males and QTc ≥ 460 ms for females were defined as prolonged QTc[13].

Coronary Angiography (CAG) for Measurement of the Severity of Coronary Lesions

The CAG reports were evaluated by at least two experienced interventional cardiologists, Following that, Gensini scores (GS) were evaluated by summing the product of the scores reflecting the degree of vascular stenosis and the corresponding vascular weight values[14].

Laboratory Examinations

Patients received standard laboratory examinations for cardiovascular diseases prior to CAG. All laboratory tests were conducted using standard techniques. Serum fasting TBA was quantified using an enzymatic cycling method using reagents (Pureauto S TBA, SEKISUI MEDICAL CO., LTD.) on a Hitachi Chemistry Analyzer 7,600 according to the protocols. Quality control procedures were executed in accordance with the established protocols, and the coefficients of variation were all ≤ 5%.

Statistical Analysis

Statistical analysis was conducted utilizing SPSS 25.0, while graphs drawn using GraphPad Prism 9.0. Quantitative variables were presented as the mean ± standard deviation (SD) if normally distributed or median interquartile range (IQR) otherwise. Categorical variables were expressed as the number (percentage). The median TBA concentration of 2.8 μmol/L was utilized as the criterion for categorization among all patients. Participants were categorized into two groups: Low-TBA (≤ 2.8 μmol/L) and High-TBA (≥ 2.8 μmol/L). T-test or the non-parametric Mann–Whitney U-test were employed for quantitative variables as appropriate. A Pearson's Chi-square or Fisher's exact test was performed to compare qualitative data. Uni-and multivariable logistic regression analyses were utilized to identify clinical parameters associated with QTc prolongation. Spearman correlation analyses were conducted to determine variables linked to TBA. The significance level was set at $P < 0.05$ (2-tailed).

Results

Baseline data

The patients' clinical and biochemical characteristics are represented in Table 1. There were no significant differences in age, gender, hypertension, diabetes, Smoker, CK-MB, hs-cTnT, potassium, calcium, and gensini scores between the two groups.

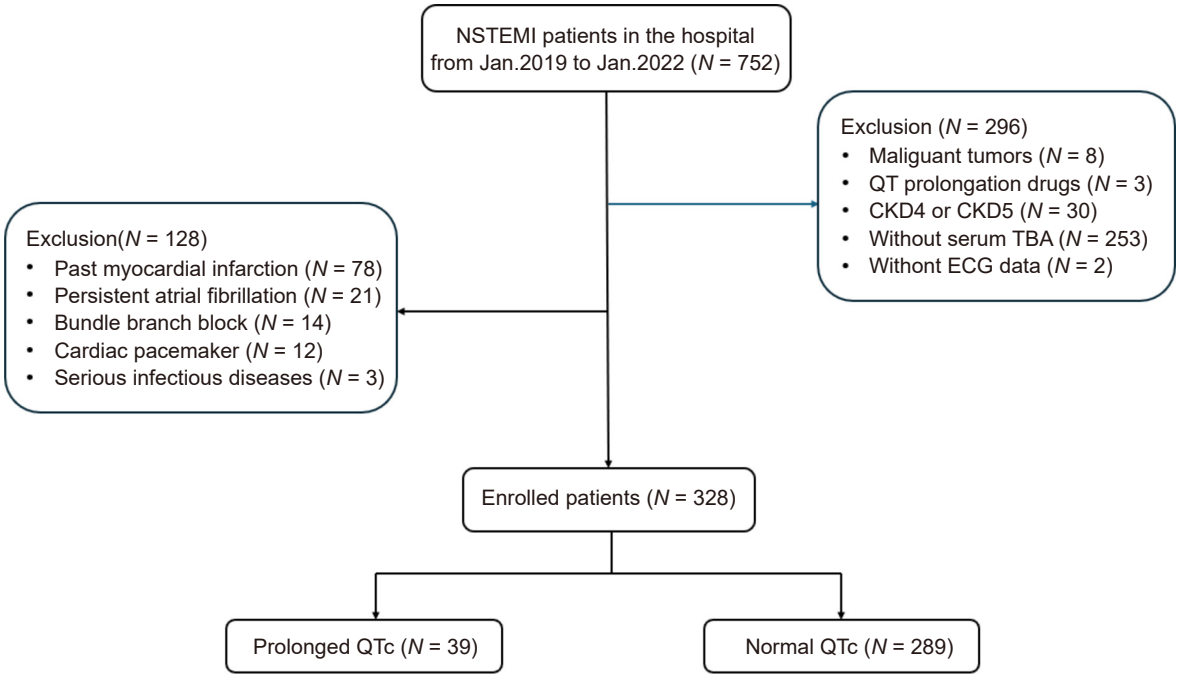

Fig. 1. Flow diagram of the patients.

Table 1. Demographic and clinical parameters of the study population.

Parameters	Low-TBA (n = 166)	High-TBA (n = 162)	*P*-value
Age (years)	59.66 ± 11.95	60.78 ± 11.31	0.384
Sex/Male	128(77.11%)	124(76.54%)	0.903
Hypertension	97(58.43)	99(61.11)	0.621
Diabetes	47(28.31)	51(31.48)	0.531
Smoker	99(59.64)	81(50.00)	0.079
EF (%)	63(54-69)	63(53-69)	0.903
Heart rate (bpm)	69(61-80)	71(63-80)	0.331
PR (ms)	157(147-177)	161(144-174)	0.827
QRS (ms)	101(94-107)	99(93-107)	0.455
QT (ms)	398(378-430)	394(376-420)	0.092
QTc (ms)	420(404-439)	420(401-432)	0.189
QTc prolongation	27(16.27%)	12(7.41%)	0.013
CK-MB (U/L)	25.55(13.98-48.13)	19.00(11.48-44.75)	0.093
CRP (mg/L)	3.72(1.99-9.71)	4.04(1.62-9.64)	0.550
hs- cTnT (ug/L)	0.42(0.07-0.96)	0.34(0.10-0.89)	0.546
LDL-C (mmol/L)	2.36(1.81-2.92)	2.18(1.72-2.71)	0.108
K (mmol/L)	3.96(3.67-4.28)	3.95(3.68-4.20)	0.643
Ca (mmol/L)	2.26(2.18-2.35)	2.28(2.18-2.37)	0.515
WBC (109/L)	7.64(6.08-9.56)	7.16(5.97-8.79)	0.031
ALT (U/L)	25.00(19.00-41.25)	28.00(18.00-39.25)	0.948
eGFR (mL/min/1.73 m^2)	99.62(88.78-108.27)	99.55(89.42-107.84)	0.857
PTA (%)	98.36 ± 16.74	95.42 ± 18.31	0.149
Gensini scores	62(43-97)	65(44-92)	0.984

EF: ejection fraction; CRP: C-reactive protein; hs-cTnT: high-sensitivity cardiac troponin T; LDL-C: low density lipoprotein- cholesterol; WBC: white blood cell count; K: potassium; Ca: calcium; ALT: alanine transaminase; PTA: prothrombin activity; eGFR: estimate glomerular filtration rate.

Compared with High-TBA group, Low-TBA patients displayed higher levels of white blood cell count. As expected, the prevalence of QTc prolongation in the Low-TBA group was 16.27% (27/166), which was significantly higher than that in the High-TBA group 7.41% (12/162).

TBA was Associated with QTc Prolongation

Out of 328 individuals, 39 were diagnosed with QTc prolongation. The incidence of QTc prolongation in the NSTEMI patients immediately upon admission was 11.89% (Table2). Patients with QTc prolongation were older than those without, and female percentage was significantly higher in patients with QTc prolongation. Moreover, serum levels of TC, HDL, LDL were higher in patients with QTc prolongation than in non- QTc prolongation patients, whereas patients with QTc prolongation exhibited lower FT3, Hb, ALT, TBil, eGFR levels. The median serum TBA level in the 39 NSTEMI patients with QTc prolongation [2.10 μmol/L (range 0.60–27.00 μmol/L)] was significantly lower than that in the 289 NSTEMI patients without QTc prolongation [3.00 μmol/L (range 0.30–23.2 μmol/L), $P = 0.008$]. Accordingly, the percentage of Low-TBA was higher in patients exhibiting QTc prolongation compared to those without.

After univariate logistic regression selection, 12 variables were associated with QTc prolongation, including age, sex, hs- cTnT, TC, HDL, LDL, FT3, Hb, ALB, groups of TBA, TBil and eGFR (Table 3). Due to the strong connection between TC and LDL ($P < 0.001$), only one variable was included in the multivariate logistic regression analysis, with LDL selected for further examination based on its superior Area Under Curve (AUC). Incorporation of these 11 variables into a multivariate logistic regression model, analysis revealed that female, LDL and Low-TBA were independent risk factors associated with QTc prolongation, while FT3 was an independent protective factor associated with QTc prolongation, as shown in Table 3.

Subgroup Analyses Validated the Relationship of TBA and QTc Prolongation

Thereafter, adjusted subgroup analyses of the QTc prolongation were a performed according to important variables, namely sex, hypertension, diabetes, smoking and higher GS (over the median of 63.50 in all patients). The TBA concentration (divided by the median of 2.80 μmol/L) was treated as a dichotomous variable.

Table 2. Characteristics of patients with prolonged QTc and normal QTc.

Variables	QTc Prolongation (n = 39)	Non-QTc Prolongation (n = 289)	*P*-value
Age (years)	64.92 ± 11.31	59.57 ± 11.55	0.007
Sex/Female	21(53.85%)	55(19.03%)	< 0.001
Hypertension	22(56.41%)	174(60.21%)	0.650
Diabetes	12(30.77%)	86(29.75%)	0.908
CK-MB (U/L)	27.80(12.00-59.00)	20.50(12.00-47.00)	0.564
hs- cTnT (ug/L)	0.59(0.11-1.46)	0.34(0.09-0.88)	0.131
TC (mmol/L)	4.23(3.83-4.96)	3.76(3.18-4.37)	0.001
TG (mmol/L)	1.43(1.26-1.76)	1.42(1.03-1.87)	0.610
HDL-C (mmol/L)	0.98(0.85-1.18)	0.90(0.79-1.03)	0.010
LDL-C (mmol/L)	2.64(2.20-3.43)	2.16(1.72-2.75)	< 0.001
HbA1c (%)	5.75(5.40-6.13)	5.80(5.50-6.80)	0.253
Hcy (μmol/L)	16.85(11.70-24.80)	17.40(13.40-24.50)	0.634
FT3 (pmol/L)	4.12(3.48-4.87)	4.53(3.87-5.25)	0.021
K (mmol/L)	3.87(3.38-4.19)	3.96(3.73-4.24)	0.106
Ca (mmol/L)	2.22(2.14-2.31)	2.27(2.19-2.36)	0.082
Mg (mmol/L)	0.98(0.93-1.03)	0.99(0.91-1.06)	0.939
Hb (g/L)	133(119-146)	140(130-152)	0.010
PLT (10^9/L)	224.08±76.21	212.17±66.60	0.304
WBC (10^9/L)	7.44(5.33-9.21)	7.51(6.09-9.09)	0.661
ALT (U/L)	21(16-29)	28(19-42)	0.006
ALB (g/L)	37.40(34.90-39.50)	38.60(36.15-40.90)	0.059
TBA (μmol/L)	2.10(1.50-3.30)	3.00(1.90-5.00)	0.008
Low-TBA	27(69.23)	139(48.10)	0.013
TBil (μmol/L)	10.80(8.60-15.50)	13.50(9.70-17.68)	0.042
eGFR (mL/min/1.73m^2)	93.25(80.33-102.42)	99.96(89.75-108.45)	0.021
Gensini scores	68.00(47.00-92.00)	63.00(43.00-95.50)	0.711

CK-MB: creatine kinase isoenzymes; hs-cTnT: high-sensitivity cardiac troponin T; TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein- cholesterol; LDL-C: low density lipoprotein- cholesterol; HbA1c: glycosylated hemoglobin A1c; Hcy: homocysteine; FT3: triiodothyronine; K: potassium;Ca:calcium; Mg: magnesium; WBC: white blood cell count; PLT: platelet count; Hb: hemoglobin; ALT: alanine transaminase; ALB: albumin; TBA: total bile acids; TBil: total bilirubin; eGFR: estimate glomerular filtration rate.

As shown in Fig. 2, lower TBA were associated with prolonged QTc interval in the subgroups of male patients, without hypertension patients, without diabetes patients and without higher GS patients, while no significant relationship was found in other subgroups. Whether or not smoking, no significant relationship was found between TBA groups and QTc prolongation.

Serum TBA Concentration was Associated with Serum Lipid and Inflammatory Markers

Spearman correlation analyses revealed linear negative correlations of TC, LDL-C and ApoB with TBA. The same tendency of leukocytes, neutrophils and neutrophil-to-lymphocyte ratio being inversely proportional to TBA was found (Table 4). Nonetheless, no significant relationships were observed between the TBA concentration and the levels of C-reactive protein, monocytes or lymphocytes.

Discussion

Previous studies have indicated an association between the QTc interval and myocardial micronecrosis in NSTEMI patients[15,16], and prolonged QTc interval identified as an independent risk factor for poor prognosis in this population[7,9,17]. Interestingly, we found that the prevalence of QTc prolongation of NSTEMI patients with lower serum TBA concentration was significantly higher than their counterparts with higher serum TBA concentration. Consistent with our research, several studies have proved that BAs can affect the electrical activity of cardiomyocytes[18,19].

We found that low TBA is an independent risk factor associated with QTc prolongation in NSTEMI patients. In earlier research, elevated serum TBA levels have been demonstrated to be associated with QTc prolongation. However, it should be noted that most of these studies were conducted in patients with intrahepatic cholestasis of pregnancy[20] or liver diseases[21,22], where

Table 3. Identification of the independent factors for QTc prolongation.

Variables	Univariate Logistic Regression		Multivariate Logistic Regression	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.043(1.011-1.076)	0.008		
Female vs male	4.964(2.478-9.943)	< 0.001	4.488(2.028-9.935)	< 0.001
Hypertension	1.169(0.595-2.297)	0.650		
Diabetes	1.049(0.508-2.167)	0.897		
CK-MB	1.003(0.998-1.008)	0.181		
hs- cTnT	1.278(1.011-1.616)	0.040		
TC	1.886(1.356-2.625)	< 0.001		
TG	0.977(0.697-1.370)	0.892		
HDL-C	10.128(2.052-49.986)	0.004		
LDL-C	2.152(1.466-3.158)	< 0.001	1.860(1.216-2.846)	0.004
HbA1c	0.940(0.736-1.200)	0.618		
Hcy	0.996(0.964-1.029)	0.799		
FT3	0.628(0.433-0.910)	0.014	0.640(0.420-0.974)	0.037
K	0.501(0.239-1.050)	0.067		
Ca	0.294(0.048-1.797)	0.185		
Mg	1.625(0.067-39.694)	0.766		
Hb	0.976(0.959-0.993)	0.006		
PLT	1.003(0.998-1.007)	0.303		
WBC	0.973(0.859-1.102)	0.662		
ALT	0.997(0.990-1.005)	0.488		
ALB	0.905(0.825-0.992)	0.034		
Low-TBA vs High TBA	2.428(1.184-4.979)	0.015	2.493(1.090-5.700)	0.030
TBil	0.937(0.883-0.995)	0.035		
eGFR	0.979(0.963-0.996)	0.013		
Gensini scores	1.000(0.991-1.010)	0.974		

EF: ejection fraction; CK-MB: creatine kinase isoenzymes; hs-cTnT: high-sensitivity cardiac troponin T; TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein- cholesterol; LDL-C: low density lipoprotein- cholesterol; HbA1c: glycosylated hemoglobin A1c; Hcy: homocysteine; FT3: triiodothyronine; K: potassium; Ca: calcium; Mg: magnesium; WBC: white blood cell; PLT: platelet count; Hb: hemoglobin; ALT: alanine transaminase; ALB: albumin; TBA: total bile acids; TBil: total bilirubin; eGFR: estimate glomerular filtration rate.

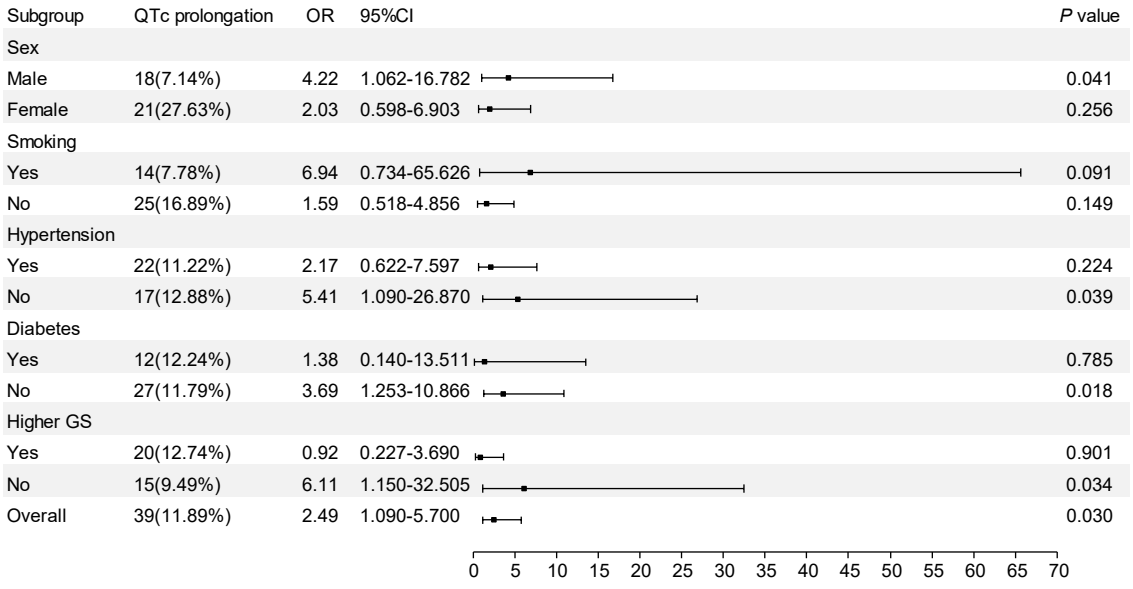

Fig. 2. Forest plot of subgroup analysis in the relationship of TBA and QTc prolongation.

Table 4. Correlation of TBA with serum lipids and inflammatory markers.

Variables	Correlation Coefficient	*P*-value
TC	−0.126	0.022
TG	−0.048	0.389
HDL-C	−0.062	0.268
LDL-C	−0.127	0.023
ApoA	−0.031	0.584
ApoB	−0.124	0.026
ApoE	−0.039	0.486
Lp(a)	−0.037	0.511
WBC	−0.137	0.013
neutrophil	−0.161	0.004
lymphocyte	0	0.995
monocyte	−0.049	0.374
NLR	−0.120	0.030
CRP	−0.047	0.474

TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein- cholesterol; LDL-C: low density lipoprotein- cholesterol; ApoA: Apolipoprotein A; ApoB: Apolipoprotein B; ApoE: Apolipoprotein E; Lp(a): Lipoprotein (a); WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein.

TBA levels were typically elevated. Elevated TBA concentration and altered bile acids composition may lead to cardiac toxicity[21]. Nevertheless, 94.5% (310/328) of participants exhibited serum TBA concentration within the normal range in our study. Li et al.[23] recently reported that lower fasting serum total bile acids levels were highly and independently associated with the presence and severity of coronary artery disease (CAD). Consequently, we hypothesize that the elevated prevalence of QTc prolongation in the low TBA group in this study is associated with the greater severity of CAD. It is probable that the absence of a statistically significant difference in Gensini scores between the low TBA group and the high TBA group is attributable to the limited sample size of the present study. Furthermore, serum TBA is a group of mixtures, and different kinds of BAs may have divergent effects on cardiomyocytes. Indeed, even the same BAs may have different effects on the heart through different mechanisms. For instance, Gao et al.[18] revealed that Deoxycholic acid (DCA) elicited negative chronotropic and positive inotropic effects on the rat heart, while Wang et al.[24] ascertained that DCA levels were significantly reduced in patients with acute myocardial infarction and further corroborated that DCA improves cardiac function and reduces ischemic injury on the 7th day after myocardial infarction. The Taurocholic acid (TCA) has been demonstrated to induce synchronous loss of beat, bradycardia and asystole by affecting calcium signals in myocardial cells[2], whereas Ursodeoxycholic acid (UDCA) exerts a protective effect on ventricular conduction velocity reduction triggered by TCA[25]. Therefore, it can be concluded that the concentration of TBA is not the only factor to be considered; the composition of the substance is also of significance. Further studies are required to examine the serum bile acid profile of those patients.

In addition to TBA, we observed that female and LDL levels were also independent risk factors associated with QTc prolongation in NSTEMI patients. Obviously, there are significant differences in QTc interval between males and females, with females having a longer QTc interval than males most of the time, and the sex difference is greatest in the post pubertal population, with differences in QTc interval between males and females gradually decreasing with age[26]. One study have found that ovarian resection in animal experiments can shorten the QT period, while estrogen replacement can extend the QT interval[27]. Similarly, previous studies reported a positive significant correlation was found between LDL-C and QT interval[28]. Besides, we observed that FT3 was an independent protective factor associated with QTc prolongation. Consistently, primary hyperparathyroidism patients had shorter QTc intervals compared to other thyroid disease controls[29]. After geriatric patients with hypothyroidism accepting thyroid hormone replacement therapy, their FT3 was significantly higher than those before treatment, and QTc interval were significantly lower than before[30].

Subgroup analysis shown that lower TBA values were associated with prolonged QTc interval in the subgroups of male patients, without hypertension patients, without diabetes patients, smoking patients, without higher GS patients, while no significant relationship was found in other subgroups. This may be because female[26], hypertension[31], diabetes[32] and severer myocardial ischemia resulting from coronary stenosis[33] themselves were the risk factors for prolongation of QTc interval, and which cover up the role of TBA. And the sample size was too small to find a correlation between TBA groups and QTc prolongation in the subgroup analysis of smoking.

The primary finding of our research indicated a significant association between fasting serum TBA levels and QTc prolongation in patients with NSTEMI, meanwhile, we observed that serum TBA concentration was negatively correlated with serum lipids and inflammatory markers. Hence it is reasonable to speculate that BAs influenced myocardial electrical activity by regulating lipid metabolism and inflammation. In sterol homeostasis, the principal pathway for cholesterol excretion is through the hepatic conversion of cholesterol to BAs and their subsequent excretion in the stool[34], and this pathway is regulated by negative feedback[35]. In addition, LDL-C levels can be reduced through enhanced fecal BAs excretion and compensatory upregulation of BA synthesis in the liver[36]. It is universally acknowledged that chronic inflammation is a major cause of myocardial infarction and other coronary artery events[37]. Previous studies have shown that higher white blood cell counts are associated with higher risk of future heart-related adverse events in the general population[38] and patients with coronary artery disease[39]. Several clinical studies have reported that NLR serves as an independent predictor of major adverse cardiovascular events in patients with coronary heart disease[40,41]. An increasing amount of research indicated that BAs play a wide range of roles in innate and adaptive immunity[42–44].

Conclusions

Our findings first revealed that lower serum TBA levels was an independent risk factor associated with QTc prolongation in NSTEMI patients, and serum BAs may affect cardiac electrical activity by influencing lipid metabolism and inflammation.

Therefore, assessing TBA levels in NSTEMI patients can help identify high-risk groups with QTc prolongation and an increased risk of arrhythmias. In clinical practice, metabolic and electrophysiological monitoring should be strengthened in these patients.

Limitations

Nonetheless, our study has certain limitations. First, this is single-center research. The present results require validation through extensive, multi-center prospective studies. Second, we just analyzed the serum TBA concentration, and the BAs profile in NSTEMI patients is unclear. At last, there is only a single data in this study, and we didn't observe that relationship dynamically. Additional prospective studies are required to corroborate our findings.

Abbreviations

BAs, Bile Acids; CAD, coronary artery disease; CAG, Coronary Angiography; CKD, chronic kidney disease; DCA, Deoxycholic acid; GS, Gensini scores; LDL-C, low density lipoprotein- cholesterol; NSTEMI, Non-ST Elevation Myocardial Infarction; QTc, corrected QT; TBA, total bile acids; TC, total cholesterol; TCA, Taurocholic acid.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by The First Affiliated Hospital of Xi'an Jiaotong University's Human Research Committee (XJTU1AF2023LSK-019). The patients/participants provided their written informed consent to participate in this study.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

MJF, JL, ZJG, YRZ, and YLH designed the study. YLH and MJF analyzed and interpreted the data. MJF, JL, and ZJG drafted the manuscript. YRZ and YH revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

Availability of data and materials

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

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