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ORIGINAL PAPER

Prolonged QTc indicates the clinical severity and poor prognosis in patients with isolated left ventricular non-compaction

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Abstract Isolated left ventricular non-compaction (LVNC) is a rare cardiomyopathy that leads to severe clinical complications. This study is to investigate whether or not prolonged QTc is a good indicator for evaluating the severity of fibrosis and predicting the prognosis of LVNC, and if native T1 can be used to quantify the fibrosis. 32 LVNC patients and 14 healthy controls with matched age and sex were examined by CMR and ECG to acquire native T1, QTc interval, and ECG abnormalities. 18 LVNC patients had normal QTc and 14 LVNC patients had prolonged QTc. The mean native T1 value of the normal controls, normal QTc and prolonged QTc patients was 1096.0 ± 41.5, 1141.98 ± 45.46, and 1182.67 ± 42.02 ms, respectively. One-way ANVOA showed significant differences in native T1 among three groups ($F = 14.9$, $p < 0.001$). In LVNC patients, the QTc interval significantly correlated with LVEF ($p = 0.003$, $r = 0.51$) and native T1 values ($p = 0.015$, $R = -0.47$). This suggests that prolonged QTc is associated with more severe compacted myocardial fibrosis, more cardiac dysfunction, and a poorer prognosis in LVNC patients. Follow-up data showed significant differences in adverse events between patients with normal QTc and patients with prolonged QTc ($p = 0.036$). Prolonged QTc interval leads to more severe compacted myocardial fibrosis, poorer cardiac dysfunction, and poorer prognosis in LVNC patients.

Keywords LVNC · Corrected QT · Cardiac magnetic resonance imaging · Fibrosis

Introduction

Isolated left ventricular non-compaction (LVNC) is a rare cardiomyopathy caused by the arrest of normal embryogenesis of myocardium during the embryonic period [1, 2]. The pathology of LVNC is characterized by prominent trabeculations and deep intertrabecular recesses within the left ventricular wall [3, 4]. Clinical complications of LVNC patients include heart failure, arrhythmias, and sudden cardiac death [4, 5]. Currently there is no clinical marker for evaluating the severity of fibrosis of compacted myocardium and predicting prognosis of LVNC patients.

Recently, the native T1 mapping of cardiac magnetic resonance imaging (CMR) has been used, without any contrast agent, for quantitative measurement of myocardial tissue fibrosis and evaluation of the prognosis [6, 7]. Bull et al. [6] reported that native T1 values were correlated with histological percentage of fibrosis by biopsy. Claridge et al. [7] reported that in non-ischemic patients, native T1 was the sole predictor of the primary endpoint. Corrected QT interval between the start of the Q wave and the end of the T wave (QTc) in the heart's electrical cycle is significantly associated with heart failure, arrhythmias, and sudden cardiac death [8–11]. Studies have shown that patients with

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LVNC have prolonged QTc [12–14]; for example, Towbin et al. reported that some patients with LVNC had QTc interval prolongation [12], and Steffel et al. [15] found that 52% of the patients with LVNC had QTc interval prolongation. However, the correlation between QTc and native T1 value in LVNC patients has not been demonstrated. In this study, we hypothesized that prolonged QTc is a good indicator for evaluating the severity of fibrosis and predicting the prognosis of LVNC, and that native T1 can be used to quantify the fibrosis.

Methods

Study population

We recruited 32 patients with LVNC between December 2008 and June 2014 in the Department of Cardiology of Peking Union Medical College Hospital. LVNC was diagnosed according to the Jenni echocardiography criteria [3] and Petersen CMR criteria [16] by two senior cardiologists. Patients were excluded from the study if they were pregnant, had contraindications to CMR, or had a history of other cardiomyopathies. The CMR scanning was performed for all recruited LVNC patients. One patient was excluded from the study as he was unable to hold his breath during the CMR scan. As a control, we enrolled 14 healthy volunteers with matching age and gender, and without history of cardiac diseases or known cardiac risk factors (diabetes mellitus, hypertension, and smoking). The study was approved by the local Institutional Review Board and written informed consent was obtained from every subject.

QTc interval measurement

The 12-lead resting electrocardiograms (ECG) were recorded at a paper speed of 25 mm/s on a Marquette Resting ECG recorder. The intervals between the start of the Q wave and the end of the T wave in the heart's electrical cycle were automatically analyzed (GE Medical Systems, Information Technologies, Freiburg, Germany). The determined heart rate was corrected using the Bazett formula [17]. The patients were divided into a prolonged QTc group (QTc interval >440 ms) and a normal QTc group (QTc interval ≤440 ms) [18, 19].

CMR imaging protocol

All CMR imaging was performed on a 3.0 T MR system (Achieva TX, Philips Healthcare, Best, Netherlands) using a 32-channel phased array (InVivo, Gainesville, Florida, USA). ECG-gated balanced steady-state free precession (bSSFP) cine images were acquired from the long and short axis (SAX) images covering the entire left ventricular wall (LV). Typical scan parameters included TR/TE at 2.7/1.3 ms with 30 heart phases, imaging voxel size at $1.8\times1.5\times8.0$ mm^3, 8 mm slice thickness, and 2 mm in-between gap. The native T1 data were acquired using modified look-locker inversion recovery (MOLLI) imaging protocol [20] at 8 inversion times over an 11-heartbeat breath-hold at end-expiration with 2 inversions using a 5(3)3 scheme [21]. Native T1 values were measured on three SAX slices with 20 mm in-between gap, covering 50 mm of the mid-ventricle cavity. Typical imaging parameters for MOLLI were: bSSFP single shot read out with flip angle of 35°, typical field of view of 300×150 mm^2, slice thickness of 10 mm, voxel size at $1.5\times1.5\times10.0$ mm^3, TR/TE at 2.5/1.1 ms, 0.85 partial echo factor, and parallel imaging factor of 2.5.

CMR image analysis

The images for the compacted wall of the left ventricular (LV) were manually segmented on both SAX SSFP cine images and T1 maps. Papillary muscles were carefully excluded from the LV to avoid ambiguities. The ventricular volumes, left ventricular ejection fraction (LVEF), and LV compacted myocardium mass were quantified using SAX cine stack. The native T1 was averaged over three slices per case before the statistical analysis. All images were processed using MATLAB (MathWorks, Natick, Massachusetts, USA). The maximum ratio of non-compacted and compacted myocardium thicknesses (NC:C ratio) from long axis views (LAX) in the end of diastole was measured. Corresponding wall thickness of compacted myocardium was recorded. The myocardium was divided into 17 segments using the standard AHA model [22].

Follow-up data acquisition

Clinical assessment included a detailed medical history with standardized questionnaires. Medical records were reviewed. Adverse events were defined as sudden death, deteriorating heart failure requiring hospital admission, cardiogenic shock, syncope, and severe arrhythmia (sick sinus syndrome).

Statistical analysis

Data for continuous variables were presented as mean ± SD. Statistical analysis was performed using SPSS Version 20.0 (SPSS, Chicago, IL, USA). Comparison between groups was performed using one-way ANOVA with a post-hoc Student–Newman–Keuls method. The Chi square test or Fisher's exact test was performed to compare discrete data when appropriate. The correlation between continuous

variables was assessed with the Spearman test. Statistical significance was defined as $p < 0.05$.

Result

Baseline clinical data and imaging data

The LVNC patients were divided into two groups based on QTc interval: normal QTc group (QTc ≤ 440 ms, n = 18), and prolonged QTc group (QTc > 440 ms, n = 14). The typical LVNC imaging was shown in the Fig. 1. The healthy volunteers showed normal electrocardiogram. Table 1 shows the baseline characteristics of patients and healthy controls. There were no significant differences in age, or body mass index among patients with normal QTc, patients with prolonged QTc, and the healthy controls. Family history of LVNC was found in seven patients in the normal QTc group and two patients in the prolonged QTc group.

Comparison of electrocardiogram data

All patients in the prolonged QTc group showed abnormalities in the resting electrocardiogram; three patients had left bundle branch block, five had ventricular premature beat, six had higher left ventricular voltage, seven had intraventricular conduction delay, and nine had T wave changes. In contrast, ECG abnormalities in the normal QTc were only seen in one patient with left bundle branch block, one with ventricular premature beat, seven with higher left ventricular voltage, four with T wave changes, and four with intraventricular conduction delay (Table 2).

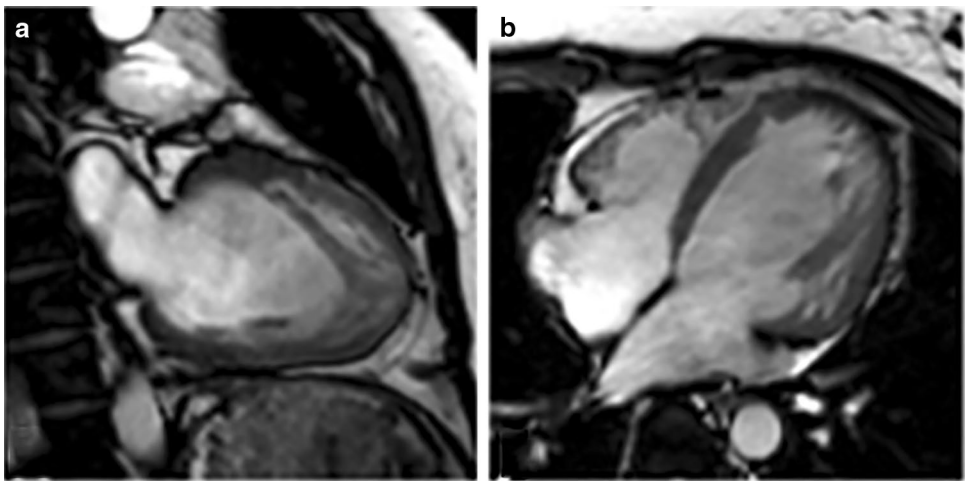

Fig. 1 Representative LVNC morphological features. **a** Diastolic horizontal long-axis (2-chamber view). **b** The diastolic horizontal long-axis (4-chamber view) images. **a** and **b** both show the prominent non-compactions, which link together and looking like a net

Table 1 Clinical characteristics of the study population of patients with LVNC

Characteristics	Mean ± SD or N (%)			p-value	Main effect p
	Normal control (n = 14)	Normal QTc group (n = 18)	Prolonged QTc group (n = 14)		
Age, year	45.42 ± 14.62	36.50 ± 15.68	49.92 ± 10.77*	4.55	0.016
Gender, male	9/14 (64)	11/18 (61)	6/13 (46)	4.30	0.611
Body mass index	23.83 ± 2.30	22.57 ± 3.11	22.80 ± 3.28	0.29	0.749
Family history	0	7/18 (39)†	2/13 (15)	4.31	0.020
NYHA functional class	1	1.60 ± 0.71	2.63 ± 0.72*, ‡	10.34	<0.001
Smoker	0	1	2	2.25	0.442
Hypertension	0	1	2	2.25	0.442
Diabetes	0	0	1	2.47	0.449

BSA body surface area, *LVNC* left ventricular non-compaction, *NYHA* New York Heart Association, *STE* systemic thromboembolism

*$p < 0.05$ for Normal QTc group versus Prolonged QTc group

†$p < 0.05$ for Normal QTc group versus normal control

‡$p < 0.05$ for Prolonged QTc group versus normal control

Table 2 The ECG between LVNC patients with normal QTc and prolonged QTc

Abnormalities	Normal QTc group (n = 18)	Prolonged QTc group (n = 14)	p
Left bundle branch block	1	3	0.295
Ventricular premature beat	1	5	0.064
Higher left ventricular voltage	7	6	0.96
Intraventricular conduction delay	4	7	0.142
T wave changes	4	9	0.029

Fisher's exact test was used for comparison between two groups

Comparison of CMR data

The CMR imaging data are presented in Table 2. The mean T1 values in the healthy controls and LVNC patients (patients with prolonged QTc and patients with normal QTc) were 1096.0 ± 41.5 and 1159.1 ± 47.4 ms, respectively. The mean T1 values in patients with normal QTc and patients with prolonged QTc were 1141.98 ± 45.46 and 1182.67 ± 42.02 ms, respectively (Fig. 2). One-way ANOVA showed significant differences in native T1 among three groups ($F = 14.9$, $p < 0.001$) while Post Hoc Student–Newman–Keuls analysis showed significant differences in native T1 values between any two groups. No significant differences were observed in the thickness of compacted myocardium and the NC: C ratio between normal QTc and prolonged QTc group.

The mean Left Venticular ejection fraction (LVEF) of the healthy controls,normal QTc patients, and prolonged QTc patients were 60.3 ± 6.2, 49.35 ± 10.39 and 31.84 ± 15.87%. One-way ANOVA showed significant differences in LVEF among three groups ($F = 23.36$, $p < 0.001$). In addition, significant differences were found between any two groups by Post Hoc Student–Newman–Keuls analysis.

After adjusting for body surface area, one-way ANOVA showed significant differences in LV mass, LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV) among the three groups ($F = 10.8$, $p < 0.001$; $F = 17.5$, $p < 0.001$; $F = 13.2$, $p < 0.001$; respectively). The post-hoc with Student–Newman–Keuls analysis showed significant differences in LV mass, LVESV, and LVEDV among three groups, but no significant differences were observed between all patients and healthy controls (Table 3). There was no difference in non-compaction segments between normal QTc and prolonged QTc group ($p = 0.79$). The distribution of non-compaction segments of the two groups are shown in the Fig. 3.

The relationship between QTc, native T 1 values, and LVEF

In LVNC patients, the native T1 relaxation times positively correlated with QTc interval ($r = 0.51$, $p = 0.003$) (Fig. 4a). The QTc interval was significantly increased and negatively correlated with LVEF ($r = -0.47$, $p = 0.015$) (Fig. 4b) in LVNC patients. In addition, the Multiple Regression Line Analysis have shown that that QTc interval is significantly correlated with LVEF ($p = 0.006$) and native T1 values ($p = 0.025$).

Follow-up

The mean follow-up duration was 30.4 ± 3.4 months. Ten adverse events were found in five patients (Fig. 5). A significant difference ($p = 0.028$) was observed in QTc interval between the patients with (466.3 ± 40.4 ms) and without adverse events (427.3 ± 31.3 ms). Follow-up data showed significant differences in adverse events between

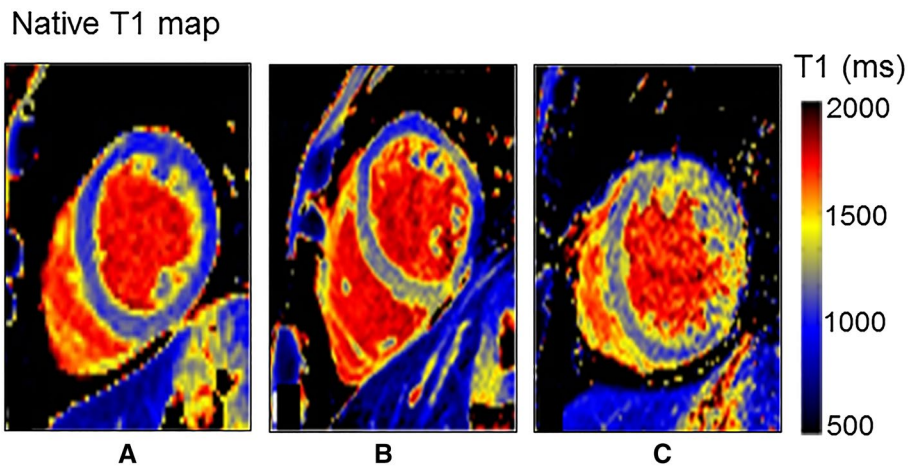

Fig. 2 Cardiac magnetic resonance images of native T1 maps. **a** A normal control. **b** A normal QTc LVNC patient. **c** A prolonged QTc LVNC patient

Table 3 Characteristics of cardiovascular magnetic resonance imaging of the study population

CMR parameters	Normal controls (n = 14)	QTc < 440 ms group (n = 17)	QTc ≥ 440 ms group (n = 14)	F-value	Main effect p-value
NC/C ratio	–	3.81 ± 0.74	3.45 ± 1.25	42.60	<0.001
C thickness (mm)	7.67 ± 2.33	4.33 ± 1.59†	5.17 ± 1.87‡	12.29	<0.001
NC segments per patient	0	7.17 ± 2.2.36†	7.54 ± 2.21‡	4.62	<0.001
LV mass of compaction/ body surface area (g/m^2)	47.6 0 ± 5.54	42.08 ± 16.97	60.94 ± 23.61*,‡	4.88	0.010
LV end-diastolic volume/ body surface area (ml/m^2)	66.88 ± 10.88	86.52 ± 21.50	128.38 ± 61.11*,‡	10.29	<0.001
LV end-systolic volume/ body surface area (ml/m^2)	25.83 ± 6.77	46.37 ± 22.08	95.85 ± 63.0*,‡	12.98	<0.001
LV ejection fraction (%)	60.3 ± 6.2	49.35 ± 10.39†	31.84 ± 15.87*,‡	23.36	<0.001
Native T1 value (ms)	1096.01 ± 41.54	1141.98 ± 45.46†	1182.67 ± 42.02*,‡	14.90	<0.001

Significant difference of ANOVA with post-hoc Student–Newman–Keuls analysis

C compaction, *NC* non-compaction, *LV* left ventricular

*Normal QTc group versus. Prolonged QTc group

†Normal QTc group versus normal control

‡Prolonged QTc group versus normal control

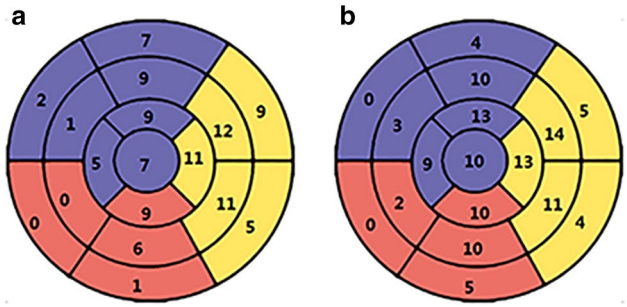

Fig. 3 Distribution of non-compaction (NC) segments. **a** Normal QTc LVNC patient. **b** Prolonged QTc LVNC patient. The heart was divided into 17 segments according to AHA standard segments. The number in each segment shows the total NC segments. For example, at the apical, **a** and **b** pictures have seven and ten subjects with NC segments, respectively

patients with normal QTc and patients with prolonged QTc (p = 0.036).

The ROC analysis showed that the QTc interval yielded an area under the ROC curve of 0.87 ± 0.07. At a cutoff value of 443.5 ms, QTc interval has an 80% diagnostic sensitivity and 77% diagnostic specificity for identifying LVNC patients with adverse events (Fig. 6).

Discussion

This study investigated the relationships among the QTc interval and the native T1 values of CMR, cardiac function, and the prognosis of LVNC patients. We found that the mean native T1 value was highest in patients with prolonged QTc, followed by patients with normal QT, and then normal controls. Furthermore, the QTc interval positively correlated with the native T1 values. These suggest that patients with prolonged QTc interval suffer more serious fibrosis. The QTc interval was significantly negatively correlated with LVEF, suggesting that the QTc interval may reflect the cardiac systolic function. In addition, follow-up results showed that the patients with prolonged QTc had a poor prognosis.

Previous studies have observed the QTc interval prolongation in LVNC patients [12, 15, 17]. Our previous study revealed that native T1 is an independent indicator of myocardial late gadolinium enhancement [23] and can detect early myocardial fibrosis. One major finding in this study is that prolonged QTc interval positively correlates with increased native T1 values in LVNC patients. In a histological study, the QTc interval prolongation correlates with the progression of myocardial fibrosis in Alström syndrome patients [24]. Inoue et al. reported that clinically unrecognized myocardial fibrosis was significantly associated with a longer QT interval [25]. It may suggest that the QTc prolongation is associated with cardiac conduction system abnormality caused by myocardial fibrosis. Therefore, the combined evaluation of the CMR and QTc interval might result in a more accurate understanding of the severity of myocardial fibrosis in LVNC patients.

In this study, we found that the QTc interval negatively correlates with LVEF, which is consistent with findings in a previous study in heart failure models [26]. Previous studies have also demonstrated that low LVEF is related to fibrosis [27, 28], which leads to the cardiac conduction system abnormality. Thus, the QTc interval prolongation

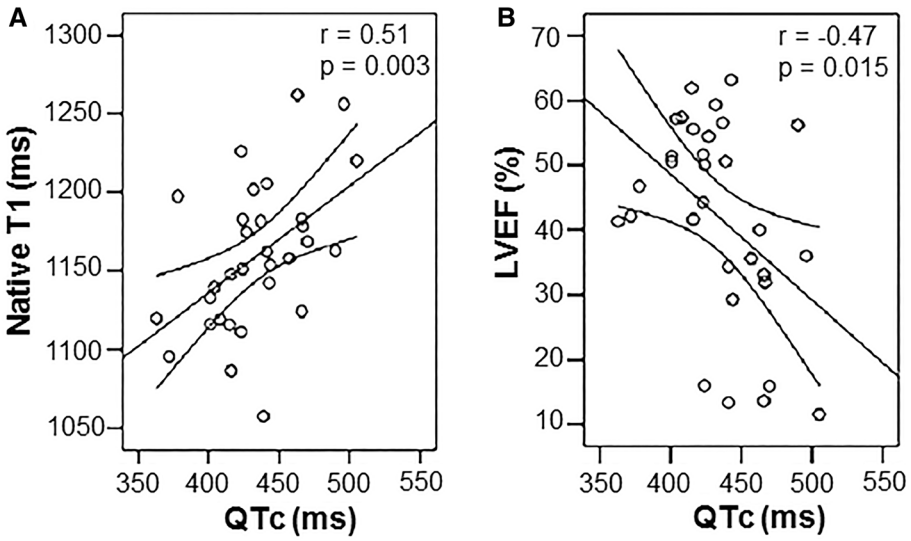

Fig. 4 Correlations among T1, LVEF, and QTc. **a** Positive correlation between native T1 and QTc ($p=0.003$, $r=0.51$). **b** Negative correlation between native QTc and EF ($p=0.015$, $r=-0.47$)

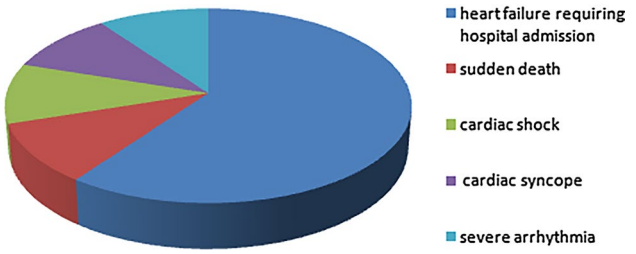

Fig. 5 A pie chart of adverse events. More than a half of adverse events was heart failure

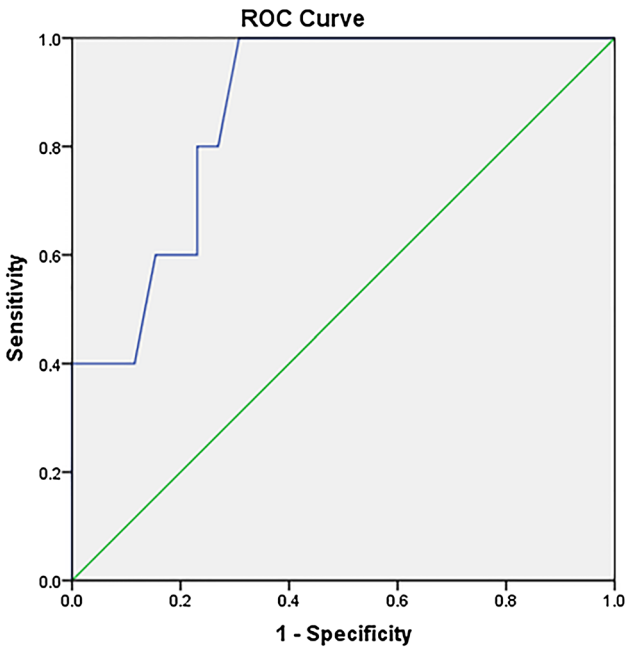

Fig. 6 The ROC showed that the QTc interval yielded an area of 0.87 ± 0.07 ($p<0.01$) under the ROC curve. At a cutoff value of 443.5 ms, QTc interval has an 80% diagnostic sensitivity and 77% diagnostic specificity for identifying LVNC patients with adverse events

may correlate with cardiac systolic dysfunction. We also observed that more adverse events occurred in patients with prolonged QTc interval than patients with normal QTc interval. This may indicate that patients with prolonged QTc are more susceptible to adverse events than the patients with normal QTc. Our previous study demonstrated that the adverse events are associated with the decrease in cardiac function [23]. The follow-up results in this study are consistent with the study by Pickham et al., which demonstrated that prolongation of QTc interval correlates with the severity of cardiac disease and poor prognosis [29]. Other studies have also found that the QTc interval is significantly correlated with ventricular arrhythmias and sudden death, which are the main clinical characteristics of LVNC [15, 30].

This study has several limitations. First, this study was conducted in a single center. Second, this study used a relatively small sample size due to LVNC being a rare disease. Thirdly, the diagnosis was based on CMR cine pictures, and not all patients with coronary artery disease can be ruled out by invasive coronary angiography. Fourthly, the clinical follow-up time was reduced from what could be optimal. Finally, we only analyzed the T1 value of the compacted wall dense layer of myocardium. A report showed fibrosis occurred in the non-compact myocardium in the inner wall based on the autopsy of a patient's heart [31]. Prior study already showed that non-compacted and compacted myocardium exhibited different signal intensity on T2-weighted image [32]. Thus, the future study should compare the T2 value between non-compact and compacted myocardium.

In conclusion, prolonged QTc interval may suggest more severe compacted myocardial fibrosis, more cardiac dysfunction, and poorer prognosis in LVNC patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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