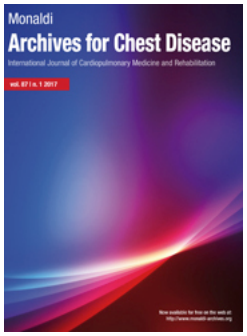

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QT interval prolongation in Takotsubo syndrome: a frightening feature with no major prognostic impact

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Abstract

Despite the frequent and often severe repolarization abnormalities seen in Takotsubo syndrome (TTS), the underlying mechanism of life-threatening arrhythmias is incompletely understood, and the risk remains uncertain. TTS is considered a potential cause of acquired long QT syndrome; however, there is no robust evidence that QT prolongation has a major prognostic impact on these patients' outcomes.

Our aim was to assess the prevalence and clinical implications of acquired long QT during TTS events and compare in-hospital and long-term outcomes between patients with and without corrected QT interval (QTc) prolongation.

This is a retrospective cohort study that included 113 patients admitted to our tertiary care hospital with a diagnosis of TTS. The cohort was divided into two groups: a long QTc group (QTc≥460 milliseconds in any electrocardiogram at admission or during hospitalization) and a normal QTc group. Baseline characteristics, occurrences during hospitalization, and outcome data were obtained from the revision of medical registries and hospital visits.

Of the 113 patients, 107 (94.7%) were female. The mean age was 67.6±11.7 years. QTc prolongation was found in 38%. Demographic characteristics, relevant chronic medication, prevalence of cardiovascular risk factors, and other comorbidities were similar between the groups, except for history of atrial fibrillation, which was more common in the long QTc group. Syncope was more prevalent in the long QTc group. In-hospital complications were not statistically different between patients with long and normal QTc (48.8% *versus* 44.2%, p=0.637), including ventricular arrhythmias and complete atrioventricular block (both 4.7% *versus* 1.4%, p=0.556). In-hospital mortality was 0.9%, corresponding to one patient in the long QTc group. The mean follow-up time was 4.8±3.8 years.

5-year all-cause mortality and the occurrence of the composite endpoint of major adverse cardiac and cerebrovascular events did not differ between the groups (p=0.511 and p=0.538, respectively).

Our study found no association between prolonged QTc interval during TTS events and adverse prognosis, since in-hospital and long-term outcomes were similar between the groups. Our findings suggest that, although QT prolongation is usually a frightening feature on ECG, this repolarization abnormality during the acute phase has no major prognostic implications in the TTS population.

Key words: Takotsubo cardiomyopathy, QT interval, long QT, ventricular arrhythmias, prognosis.

Introduction

Takotsubo Syndrome (TTS) was first described in Japan in 1990 [1] and is characterized by reversible non-ischemic regional motility abnormalities, typically apical ballooning, and transient acute systolic dysfunction, traditionally preceded by exposure to intense emotional or physical stress. Previously believed to be a self-limiting and benign condition, TTS has been increasingly recognized as a much more heterogeneous entity, with potential life-threating complications [2-6].

TTS, though considered primarily a disease of the myocardium, has been associated with ventricular repolarization abnormalities, including acquired long QT interval, and arrhythmic manifestations that affect short- and long-term prognosis [6-14]. Even though the pathophysiology of TTS is complex and not fully understood, several mechanisms have been proposed including catecholamines excess and sympathetic activation as well as microvascular dysfunction, vasospasm, oestrogen deficiency, metabolic impairment, and acute and chronic inflammation [14-18]. This multifactorial etiopathogenesis may contribute to the development of repolarization abnormalities and a wide variety of arrhythmic events, including life-threatening ventricular arrhythmias and atrioventricular block.

Prolongation of the QT interval, often associated with T-wave inversion, is a common finding on the electrocardiogram (ECG) of these patients [3,9,10,12,19]

and is even part of the *Intertak Diagnostic Score* that predicts the likelihood of TTS before additional diagnostic exams being performed [8,20]. QT interval prolongation can be present at diagnosis or, more typically, evolve over the first few hours or days, and, in some cases, it can even be the only detectable change on the ECG, usually with subsequent gradual resolution over days to weeks. However, the association between QT prolongation and clinical outcomes and prognosis in patients with TTS remains not fully understood, with several studies reporting distinct, and sometimes conflicting, results [9,19,21-26].

The purpose of this study was to evaluate the prevalence and clinical implications of acquired long QT interval in the population admitted with TTS in our tertiary care hospital. Furthermore, we aimed to explore differences in demographic and clinical characteristics between patients with TTS with and without QT prolongation and compare in-hospital complications and long-term follow-up between the two groups.

Materials and Methods

Study Design

This is a single-centre retrospective cohort study. Data collected are observational and retrospective. Diagnosis of TTS was based on the modified Mayo Clinic Diagnostic Criteria [6]. Patients in whom information on ECG and QT interval was available during hospitalization were selected. The study protocol was approved by the Ethics Committee of Centro Hospitalar Universitário de São João / Faculdade de Medicina da Universidade do Porto.

Study population and data collection

One hundred and thirteen adult patients admitted in a tertiary care hospital in the north of Portugal between June 2005 and November 2022 with a final diagnosis of TTS were enrolled in the present analysis (Figure 1).

At least one standard 12-lead ECG was recorded for every patient at admission and, depending on clinical course, repeated at least once during hospitalization. Corrected QT intervals (QTc), adjusted for rate using the Bazett formula, were analysed in all 12-lead ECG of the 113 patients (at admission and during

hospitalization). The cohort was divided into two groups, a long QTc group and a normal QTc group, according to the QT evolution on ECG during hospitalization. A QTc ≥ 460 milliseconds (ms) in any ECG since admission until discharge was the criteria to include the patient in the long QTc group.

The baseline characteristics of these patients (including demographics, comorbidities, chronic medication, symptoms, precipitating triggers, electrocardiographic and echocardiographic features, and laboratory values) and the occurrences during hospitalization were collected, analysed and compared between the groups (Figure 1). Data was collected from medical registries.

A composite endpoint of MACCE (major adverse cardiac and cerebrovascular events), including recurrence, acute coronary syndrome, heart failure, arrhythmias, stroke and death, was defined. Differences in long-term mortality and MACCE were assessed between the groups (Figure 1). Outcome data were obtained from careful revision of hospital visits and medical records during follow-up time.

Statistical analyses

Descriptive statistics are reported as absolute frequencies (n) with percentages for categorical variables and as mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables. Categorical variables were analysed using the Pearson Chi-Square or Fisher exact test, when adequate. Student t test or Mann–Whitney U test were executed for continuous variables, depending on the adequacy of a parametric or non-parametric test. Long-term mortality and MACCE was assessed using Kaplan-Meier survival analysis and Tarone-Ware test was applied for group comparison.

Statistical analysis was performed with the use of IBM SPSS Statistics software, version 26 (SPSS). A 2-sided $p < 0.05$ was defined as statistical significance.

Results

Clinical characteristics

A total of 113 patients with a definitive diagnosis of TTS were identified during the study period. Main demographical characteristics, comorbidities, chronic medication, presenting symptoms, precipitating triggers, electrocardiographic and

echocardiographic features, and laboratory results for the entire population and both groups are summarized in Table 1.

The mean age of our population was 67.6±11.7 years. One hundred and seven patients (94.7%) were female. Most of the patients (89.4%) presented at least one cardiovascular risk factor, including arterial hypertension, diabetes mellitus, dyslipidaemia, smoking history and overweight. Psychiatric disorders were the most common comorbidity (50.4%), followed by neurological disorders (19.5%). Structural heart disease was found in 16.8%. Forty patients (35.4%) were taking at least one drug known to potential prolong the QT interval at the time of the episode, including antiarrhythmic (amiodarone, flecainide or propafenone), antidepressant (selective serotonin reuptake inhibitors, tricyclics, and mirtazapine), antipsychotic (olanzapine, risperidone, quetiapine, amisulpride) and antiseizure agents (mostly levetiracetam). Thirty-seven (32.7%) patients had a thiazide or loop diuretic as chronic medication; 21 (18.6%) patients were chronically treated with beta-blockers. A precipitating factor was found in 76.1%. The most frequent symptom at admission was chest pain (69%). Left ventricular (LV) systolic dysfunction was present in 85%; 85.8% presented the typical variant of apical akinesis. The initial ECG commonly showed T-wave inversion (79.6%) or ST-segment elevation (32.7%). Median QTc of the entire population was 447 ms (IQR 58); the median duration of QRS in the index ECG was 99 ms (IQR 16). The measurements were performed in the ECG that displayed the longest QT for each patient (on average, on the second day after diagnosis).

Of the total 113 patients, QTc prolongation was found in 43 patients (38% of our cohort) (Figure 1 and Table 1). Main demographic characteristics were similar between the two groups, as no age (66.7±12.9 years versus [vs] 68.1±10.9 years, p=0.532) nor sex (93.0% vs 95.7% women, p=0.672) differences were observed between patients with TTS with and without QTc prolongation.

Prevalence of cardiovascular risk factors and other comorbidities was comparable between the 2 groups; the exception was history of atrial fibrillation (AF), which was more common in the long QTc group (11.6% vs 1.4%, p=0.029). There were no statistically significant differences between the groups regarding relevant chronic medication, such as beta-blockers (p=0.615), antiarrhythmic drugs

(p=0.634), diuretic therapy (p=0.704), psychotropic agents, including antidepressants (p=0.349), antipsychotic (p=1.000), and antiseizure drugs (p=0.153). Fourteen (32.6%) patients in the long QTc group and 26 (37.1%) patients in the normal QTc group were medicated, at the time of the diagnosis, with at least one drug known to potential prolong the QT interval (including antiarrhythmic, antidepressant, antipsychotic and antiseizure agents) (p=0.621).

Syncope was more prevalent in the long QTc group, and typical chest pain and dyspnoea were more frequent in the normal QTc group (p=0.004).

No differences were observed regarding precipitating triggers (p=0.560), brain natriuretic peptides (BNP) and troponin I peak levels (p=0.740 and p=0.645, respectively), magnesium and potassium mean levels at admission (p=0.795 and p=0.814, respectively), presence of LV systolic dysfunction (p=0.338) and ballooning pattern (p=0.961).

Regarding electrocardiographic findings, T-wave inversion was almost ubiquitous among patients with prolongation of QT interval (90.7%), while only 72.9% of the patients in the normal QTc group presented this ECG feature (p=0.022). These ECG changes were dynamic and transient as only 2 patients presented the acquired long QT and 11 patients the T-wave inversion (4 in the former long QTc group) in the first follow-up visit after discharge. The QRS duration was similar among the groups; 16.3% of the patients in the long QTc group and 10.0% of the patients in the normal QTc group presented a QRS equal to or wider than 120 ms in the index ECG (p=0.325).

In-hospital complications

The median duration of hospitalization was similar between the groups (p=0.418), 6 days (IQR 6) for the entire cohort. More than one third of the cases were admitted in Killip class ≥II; there were no differences regarding signs and symptoms of heart failure at presentation between the groups (p=0.458) (Table 1).

Although most patients with TTS recovered, the overall risk of in-hospital complications was 46% and included acute pulmonary oedema (11.5%), cardiogenic shock (9.7%), LV thrombus (5.3%), pericardial effusion (12.4%), acute kidney failure (7.1%), supraventricular (10.6%) and ventricular tachyarrhythmias

(2.7%), bradyarrhythmias (2.7%) and death (0.9%). Some patients suffered more than one complication during hospitalization. All in-hospital complications were comparable between TTS patients with and without long QTc (48.8% vs 44.2%, p=0.637), including cardiogenic shock (16.2% vs 5.7%, p=0.100) and arrhythmic complications like life-threatening ventricular arrhythmias (4.7% vs 1.4%, p=0.556), atrial fibrillation (4.7% vs 8.6%, p=0.708) and complete atrioventricular block (4.7% vs 1.4%, p=0.556) (Figure 2). There was only one death during hospitalization (one patient in the long QTc group), the cause was LV rupture.

Long-term prognosis

Long-term follow-up was possible in 106 patients. Mean follow-up time of this cohort was 4.8±3.8 years. During follow-up, 9 (22.0%) patients in the long QTc group and 20 (30.8%) patients in the normal QTc group experienced an adverse cardiac or cerebrovascular event; the composite rate of MACCE at 5 years showed similar outcomes between the group with long QTc during TTS event and the group with normal QTc (p=0.538, Figure 3B). 5-year survival analysis showed no differences in all-cause mortality between the 2 groups (p=0.511, Figure 3A); during this time span, 2 (4.9%) patients of the long QTc group died versus 6 (9.2%) patients of the normal QTc group.

Discussion

The association between TTS and repolarization abnormalities, including prolonged QT interval, has been well described in the past [2-4,7,11]. ECG changes in the acute and subacute phase of TTS include ST-segment elevation, the evolution of marked T-wave inversion and prolongation of QT interval – all these features are dynamic throughout hospitalization and tend to resolve with time, suggesting that they reflect a transient myocardial insult [7,19]. Acquired repolarization abnormalities may cause life-threatening arrhythmias, the paradigmatic example being the association between long QT syndrome and *Torsades de Pointes* (TdP), with higher risk of sudden cardiac death.

Even though TTS is characterized by a relatively rapid, and often complete, recovery of LV function after the acute phase, in-hospital mortality of patients with

TTS has been demonstrated to be as high as 5% in previous studies [2,6], commonly because of cardiovascular causes, such as life threatening-arrhythmias. Life threatening-arrhythmias, including ventricular tachycardia, ventricular fibrillation and brady-arrhythmias, seem to be predictors of adverse short- and long-term outcomes [4,5,11,13,26-29], and the management of such arrhythmias represents a constantly evolving area of research [30].

Despite these consistent findings, life-threatening ventricular arrhythmias in TTS patients are not as common as ECG repolarization abnormalities, ranging from less than 4 to 14% in the most recent studies [2,6,11,14,27]. Several explanations for the occurrence of ventricular arrhythmias in TTS must coexist besides QT interval prolongation, typically associated with TdP, and the underlying pathophysiology of arrhythmic events may differ in the acute, subacute and chronic phases. In the acute and subacute phases, it seems reasonable to monitor de QT interval and cardiac rhythm closely.

Even though TTS is considered among the causes of acquired long QT syndrome, the evidence on QT prolongation having prognostic impact during hospitalization or long-term follow-up of these patients is sparse, with studies showing somehow conflicting results [9,19,21-25]. For example, Gopalakrishnan et al. (2015) described prolonged QTc interval as a strong predictor of overall outcome in TTS [29], Martín de Miguel et al. (2021) concluded that prolonged QTc at admission was associated with the composite endpoint of all-cause mortality and nonfatal cardiovascular events [19], and Del Buono et al. (2022) found that a QTc ≥460 ms at admission identified patients at high risk for in-hospital arrhythmic complications [9]. On the contrary, previous data of Hohneck et al. (2018) marked QTc interval at admission as an independent negative predictor of long-term outcome in patients with TTS [22]. This retrospective study found a lower rate of in-hospital mortality and higher long-term survival among patients with TTS and acquired long QTc [22]. On the other hand, Santoro et al (2017) concluded that prolonged QTc interval at admission during a TTS event could be associated with a higher risk of cardiovascular rehospitalization at follow-up but dynamic increase of QTc interval after admission showed a trend towards a better prognosis [25].

In our study, we found a significant prevalence of prolonged QT interval (38%), coincident with international studies [9], but a low percentage of in-hospital ventricular arrhythmias (overall 2.7%: 4.7% in the long QTc group versus 1.4% in the normal QTc group, without reaching statistical significance) and death in the (sub-) acute phase (0.9%, corresponding to one patient in the long QTc group that died of cardiac rupture), suggesting other underlying mechanisms for the development of life-threatening arrythmias besides acquired long QT syndrome in our population. Furthermore, the development of AF (7.1%, 4.7% vs 8.6%, p=0.708), supraventricular arrhythmias (3.5%, 4.7% vs 2.9%, p=0.637) and complete atrioventricular block (2.7%, 4.7% vs 1.4%, p=0.556) during hospitalization was also low and did not differ between the two groups.

Long QT syndrome has slightly different definitions in literature and adjusted cutoff values depend on the measuring method, correction formula, age, and sex. We decided to use a threshold of QTc≥ 460 milliseconds for defining a long QT group since this value represents prolongation of QT interval for both sexes and has been reported in previous papers as a criterion of increased risk in TTS patients [9]. However, the selected threshold of 460 ms may partially explain the low rate of major arrhythmic events during hospitalization.

In our population, a medical history of AF was most prevalent in patients who develop QT interval prolongation, suggesting that this comorbidity may be associated with the development of prolonged QT during TTS, even though this is a small cohort. The question of whether this finding may be related to chronic medication used for AF treatment, such as anti-arrhythmic drugs, which may directly affect QT interval, and beta-blockers, possibly inducing QTc prolongation related to drug-induced bradycardia, should be raised. However, this doesn't seem to be the case in our cohort, since most patients recovered a normal QTc after discharge, independently of history of AF, and the only 2 patients who maintained a long QT in the first follow-up visit after discharge had no history of AF or other arrhythmias and they were not taking beta-blockers or anti-arrhythmic drugs; one of these patients had a history of psychiatric illness in the past but was not taking psychotropic agents or other drugs traditionally known to prolong the QT interval at the time of admission. Both patients displayed a wide QRS ≥120 ms with left

bundle branch block (LBBB) morphology and this is possibly the explanation for the maintenance of QT prolongation. The remaining cardiovascular risk factors and comorbidities, including neurological and psychiatric conditions and drugs traditionally used to treat these pathologies, didn't seem to be related to the prolongation of QT interval and these patients showed similar laboratory and echocardiographic features and heart failure rates when compared to the patients who remained with a normal QTc throughout hospitalization. These findings support the hypothesis that the prolongation of the QT interval during the (sub)acute phase of Takotsubo may, in fact, be related to the episode itself and not to other external factors.

Considering long-term follow-up, 5-year all-cause mortality and the occurrence of the composite endpoint of MACCE, including recurrence, acute coronary syndrome, heart failure, arrhythmias, stroke and death, did not differ between the group with prolonged QT interval during hospitalization and the group with normal QT interval. Furthermore, almost all patients in long QTc group recovered a normal QT interval in a short period of time, with only 2 patients displaying long QTc in the first follow-up visit after discharge.

Our study didn't corroborate a potential association between prolonged QTc interval during TTS events and adverse outcomes, since in-hospital complications and 5-year survival and MACCE rate did not differ between the groups.

There are some important limitations that must be considered. Firstly, this is a study of retrospective nature, with a small number of patients enrolled and restricted to a single centre, that relied on the analysis of electronic medical registries. All cases were, however, carefully reviewed and only cases with a confirmed diagnosis of TTS and ECG complete information were included, limiting potential inaccuracies and inclusion of cases with important missing data. Secondly, QTc interval was adjusted for rate using Bazett formula, the most frequently used method in clinical practice, but significant variation between alternative formulae exists, specially at very high or very slow rates; thirdly, measurement of QTc interval has some interobserver variability. Fourthly, the low rate of arrhythmic events may be partially explained by the QTc threshold value chosen to split the groups. A prolongation of QTc ≥500 ms is universally recognized as high risk for ventricular

arrhythmias; however, given the small sample size, this subgroup would correspond to a low number of patients compared with the overall population, which would make comparisons and generalization of conclusions unfeasible. Bearing this in mind, our results need to be confirmed in larger, multicentre and prospective studies.

Despite the common and often severe repolarization abnormalities seen in TTS, the underlying mechanism of life-threatening arrhythmias remains incompletely understood, and the risk remains uncertain. This prompts further evaluation of the true pathophysiological significance of QT prolongation in the context of TTS and of the additional risk factors that can make this a potential predictor of life-threatening arrhythmic events and worse prognosis in some populations, as described in literature.

Conclusions

QT interval prolongation is usually a frightening feature on ECG because of the increased risk of life-threatening cardiac arrhythmias commonly associated with long QT syndrome. In our study, QT interval prolongation during TTS events had no prognostic implications during hospitalization and follow-up of these patients. More studies are needed to fully clarify if prolonged QT interval during a TTS event is a transitory alteration with no prognostic role or a marker of acute and future complications.

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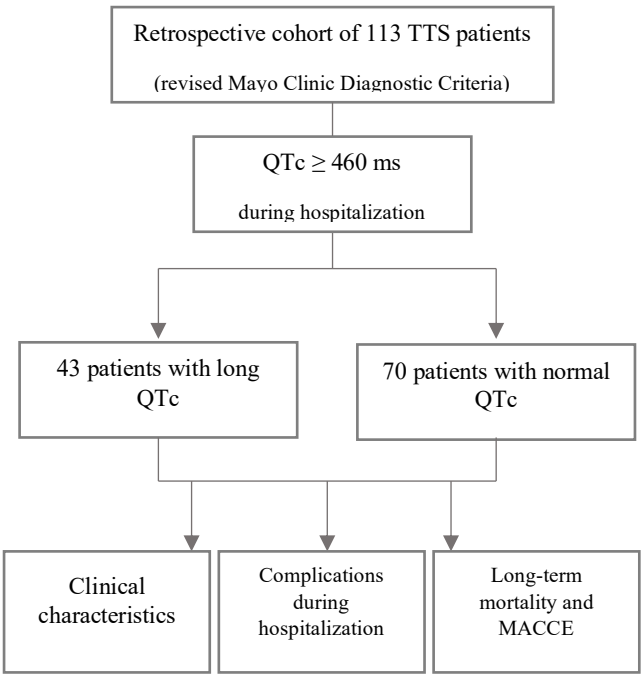
Table 1. Characteristics of Takotsubo syndrome patients with and without prolongation of QTc during hospitalization.

		All (n=113)		Long QTc (n = 43)		Normal QTc (n=70)		p-value
Age - mean±SD		67.6±11.7		66.7±12.9		68.1±10.9		0.532
Gender - n (%)								0.672
	Women	107	(94.7)	40	(93.0)	67	(95.7)	
	Men	6	(5.3)	3	(7.0)	3	(4.3)	
≥ **1 CV risk factors** - n (%)		101	(89.4)	37	(86.0)	64	(91.4)	0.368
Chronic kidney disease - n (%)		6	(5.3)	3	(7.0)	3	(4.3)	0.672
Neurologic disorders - n (%)		22	(19.5)	10	(23.3)	12	(17.1)	0.426
Psychiatric disorders - n (%)		57	(50.4)	26	(60.5)	31	(44.3)	0.095
Atrial fibrillation - n (%)		6	(5.3)	5	(11.6)	1	(1.4)	0.029
Structural heart disease - n (%)		19	(16.8)	6	(14.0)	13	(18.6)	0.524
Chronic Medication	Diuretics - n (%)	37	(32.7)	15	(34.9)	22	(31.4)	0.704
	Antidepressants - n (%)	32	(28.3)	10	(23.3)	22	(31.4)	0.349
	Antipsychotics - n (%)	7	(6.2)	3	(7.0)	4	(5.7)	1.000
	Antiseizure drugs -n(%)	4	(3.5)	3	(7.0)	1	(1.4)	0.153
	Antiarrhythmics- n (%)	4	(3.5)	2	(4.7)	2	(2.9)	0.634
	β-blockers - n (%)	21	(18.6)	9	(20.9)	12	(17.1)	0.615
Presenting symptoms - n (%)								0.004
	Chest Pain	78	(69.0)	25	(58.1)	53	(75.7)	
	Dyspnoea	16	(14.2)	4	(9.3)	12	(17.1)	
	Syncope	5	(4.4)	3	(7.0)	2	(2.9)	
	Other	14	(12.4)	11	(25.6)	3	(4.3)	
Precipitating trigger - n (%)								0.560
	No trigger	27	(23.9)	10	(23.3)	17	(24.3)	
	Emotional stress	58	(51.3)	20	(46.5)	38	(54.3)	
	Physical trigger	28	(24.8)	13	(30.2)	15	(21.4)	

Killip class ≥ II – n (%)	45	(39.8)	19	(44.2)	26	(37.1)	0.458
ECG **QTc** (ms) - median (IQR)	447	(58)	503	(50)	434	(15)	<0.001
QRS duration (ms) – median (IQR)	99	(16)	97	(19)	99	(14)	0.915
QRS ≥ 120 ms – n(%)	14	(12.4)	7	(16.3)	7	(10.0)	0.325
ST elevation – n(%)	37	(32.7)	13	(30.2)	24	(34.3)	0.656
ST depression – n(%)	5	(4.4)	2	(4.7)	3	(4.3)	1.000
T-wave inversion – n(%)	90	(79.6)	39	(90.7)	51	(72.9)	0.022
LV systolic dysfunction - n (%)	96	(85.0)	36	(83.7)	60	(85.7)	0.774
LV severe dysfunction – n (%)	33	(29.2)	12	(27.9)	21	(30.0)	0.812
Balloning pattern – n (%)							0.961
Apical	97	(85.8)	37	(86.0)	60	(85.7)	
Atypical	16	(14.2)	6	(14.0)	10	(14.3)	
BNP levels* (pg/mL) - median (IQR)	324	(709)	480	(712)	273	(727)	0.740
Troponin I peak levels (ng/mL) - median (IQR)	1.70	(2.71)	1.49	(4.21)	1.75	(2.39)	0.645
Potassium mean levels (mEq/L) - mean±SD	3.94±0.49		3.96±0.51		3.94±0.47		0.814
Magnesium mean levels (mEq/L) - mean±SD	1.60±0.24		1.59±0.20		1.61±0.26		0.795
Hospitalization (days) - median (IQR)	6	(6)	6	(7)	6	(4)	0.418

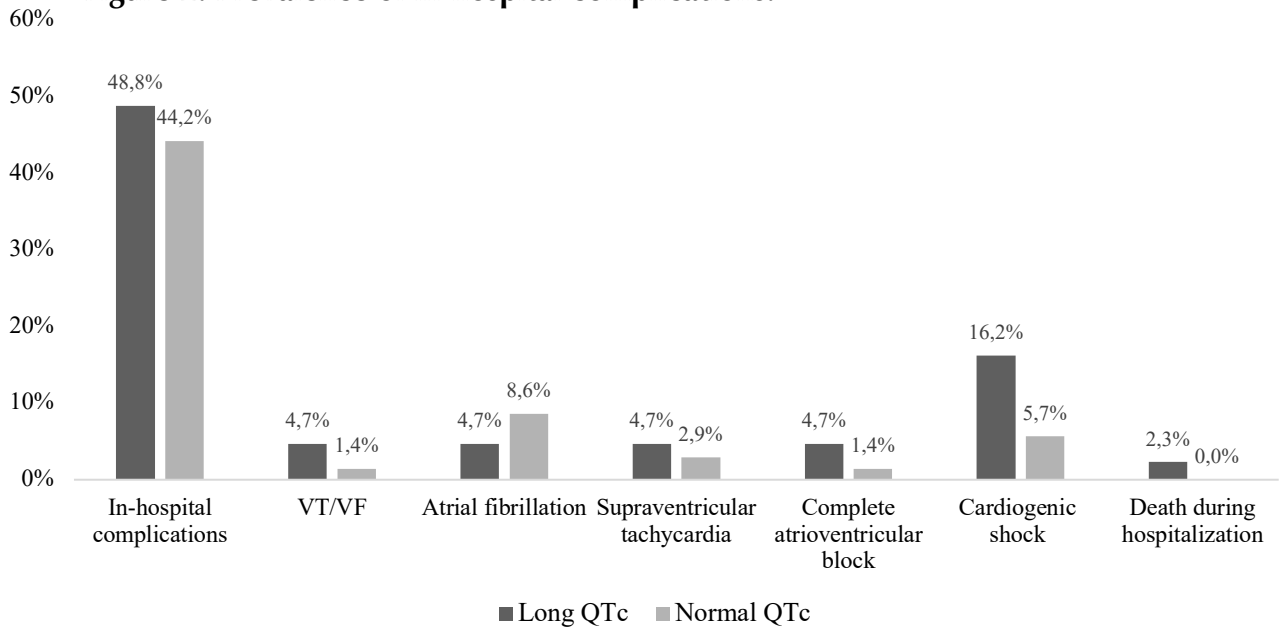
Descriptive statistics are given as counts with percentages for categorical variables and as mean ± SD or median (IQR) for continuous variables. Categorical variables were analysed using the Pearson Chi-Square or Fisher exact test. Student t test or Mann-Whitney U test were executed for continuous variables. * 18 missing values for BNP levels. Abbreviations: BNP = brain natriuretic peptides, CV = cardiovascular, IQR = interquartile range, LV = left ventricle, mEq/L = milliequivalents per liter, ms = milliseconds, ng/mL = nanograms per millilitre, pg/mL = picograms per milliliter, QTc = corrected QT interval, SD = standard deviation, TTS =Takotsubo syndrome.

Figure 1. Study flowchart, summarizing patients' selection and respective analysis.



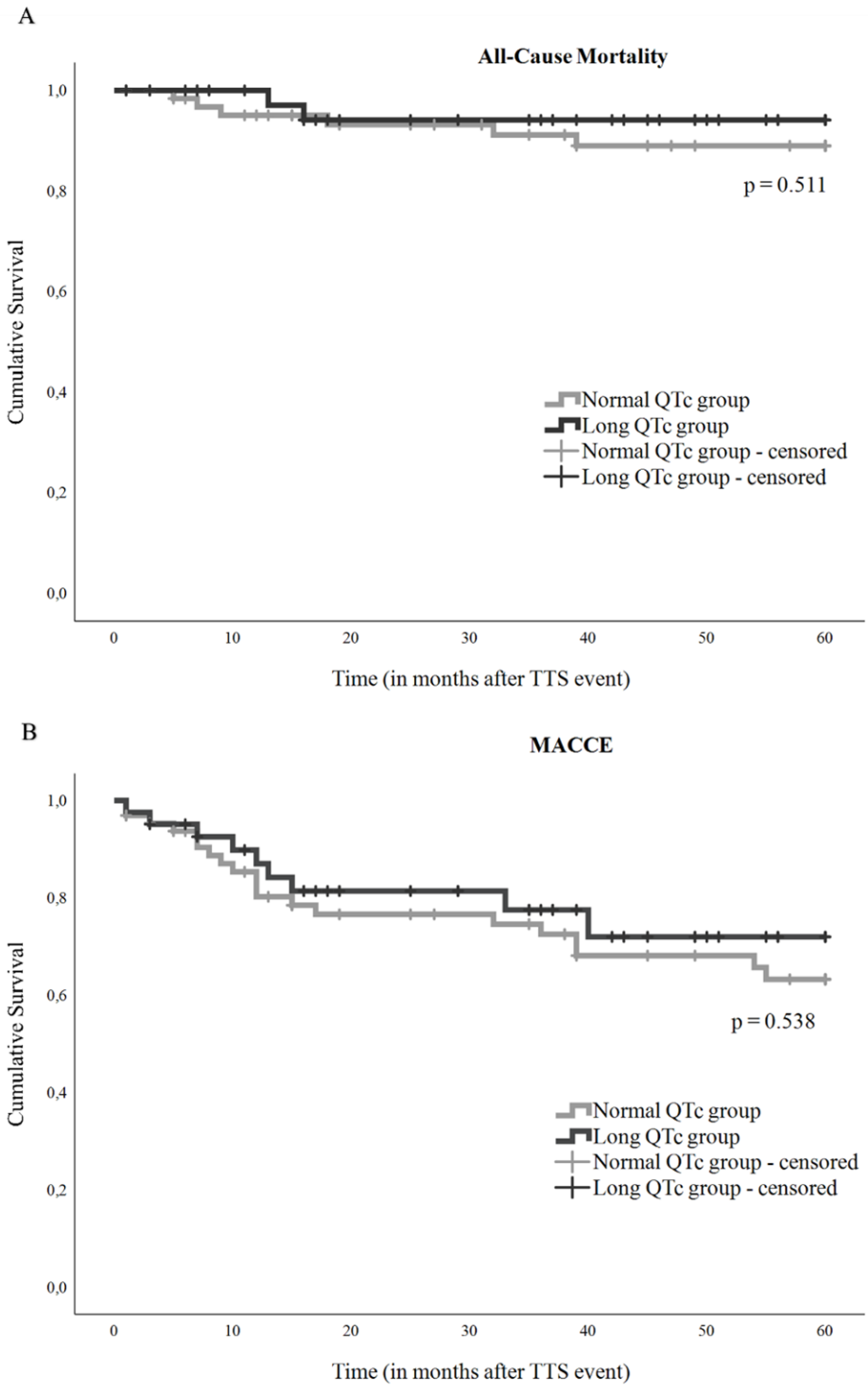
QTc, corrected QT interval; ms, milliseconds; TTS, Takotsubo syndrome; MACCE, major adverse cardiac and cerebrovascular events.

Figure 2. Prevalence of in-hospital complications.



QTc, corrected QT interval; VT/VF, ventricular tachycardia/fibrillation

Figure 3. Kaplan-Meier survival analysis was used to assess long-term mortality (A) and major adverse cardiac and cerebrovascular events (B), a composite endpoint of recurrence, acute coronary syndrome, heart failure, arrhythmias, stroke and death. Tarone-Ware test was applied for group comparison.



MACCE, major adverse cardiac and cerebrovascular events; QTc, corrected QT interval; TTS, Takotsubo syndrome.