QTc interval prolongation and life-threatening arrhythmias during hospitalization in patients with COVID-19. Results from a multi-center prospective registry.

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Brief Summary: After 7 days of hospitalization, 14% of patients with Covid-19 developed prolonged QTc interval; age, basal heart rate and dual antiviral therapy were independent predictors of pQTc. Life threatening arrhythmias have an incidence of 3.6% and were associated with outcome.

Abstract

Background: Prolonged QTc interval and life-threatening arrhythmias (LTA) are potential drug induced complications previously reported with antimalarial, antivirals and antibiotics.

Objectives: To evaluate prevalence and predictors of QTc interval prolongation and incidence of LTA during hospitalization for COVID-19 among patients with normal admission QTc.

Methods: 110 consecutive patients were enrolled in a multicenter international registry. 12-lead ECG was performed at admission, after 7 and 14 days; QTc values were analyzed.

Results: Fifteen (14%) patients developed a prolonged-QTc (pQT) after 7 days (mean QTc increase 66±20msec, +16%, p<0.001); these patients were older, had higher basal heart rates, higher rates of paroxysmal atrial fibrillation, lower platelet count. QTc increase was inversely proportional to baseline QTc levels and leukocyte count and directly to basal heart rates(p<0.01).

At multivariate stepwise analysis including age, male gender, paroxysmal atrial fibrillation, basal QTc values, basal heart rate and dual antiviral therapy, age(OR 1.06, 95% C.I. 1.00-1.13, p<0.05), basal heart rate(OR 1.07, 95% C.I. 1.02-1.13, p<0.01) and dual antiviral therapy(OR 12.46, 95% C.I. 2.09-74.20, p<0.1) were independent predictors of QT-prolongation.

Incidence of LTA during hospitalization was 3.6%. One patient experienced cardiac arrest and three non-sustained ventricular tachycardia. LTAs were recorded after a median of 9 days from hospitalization and were associated with 50% of mortality rate.

Conclusions: After 7 days of hospitalization, 14% of patients with Covid-19 developed pQTc; age, basal heart rate and dual antiviral therapy were found as independent predictor of pQTc. Life threatening arrhythmias have an incidence of 3.6% and were associated with poor outcome.

Keywords: Arrhythmia, Covid-19; ECG; QTc prolongation; Risk Prediction.

Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus, presenting mainly as a severe acute respiratory syndrome [i]. Firstly, reported in China in December 2019, it has quickly spread all over the world becoming pandemic in few months. Actually, there is no standard therapy and no clear consensus from scientific societies in the absence of solid clinical data. First observational data suggested that a combined approach with an antimalarial drug (hydroxychloroquine) and an antibiotic, macrolide, may have some effect [ii]. Other suggested approaches consist of antivirals as remdesivir or lopinarivir [iii] or anti-interleukin-6 in case of increased inflammatory response [iv]. However, no therapies have been shown effective to date [v].

Some of the drugs currently used for this disease may have interaction with myocardial cells, especially during the repolarization phase, and may results in QTc interval prolongation and torsade de pointes [vi]. In case of QTc prolongation >500 msec, drugs should be withdrawn or continuous ECG monitoring should be started. The arrhythmic risk in Covid-19 patients seems to be increased in relation with several factors as increased sympathetic activity and direct myocardial injury that may also increase the risk [vii].

Aim of the study was therefore to evaluate potential predictors of QTc-interval prolongation and incidence of life threating arrhythmias in COVID-19 patients admitted with normal QTc-interval that started therapy during hospitalization.

Methods

Study population: We prospectively enrolled 154 consecutive patients with a diagnosis of COVID-19 from February 25 to March 30 2020, admitted into four hospitals: Infectious Diseases Unit and Intensive Care Unit: Hospital-University Polyclinic of Bari, Italy, Department of Infectious disease, Vittorio Emanuele II Hospital, Bisceglie, Italy, Department of Infectious Disease, San Carlo Hospital, Potenza, Italy, First Department of Medicine, Faculty of Medicine, University Medical Centre Mannheim (UMM), Germany. The study was approved by institutional review board of each hospital involved. All patient's information was de-identified.

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Inclusion criteria: The diagnosis of COVID-19 was based on the definition of the world health organization [viii].

Exclusion criteria: Patients already in treatment with antiarrhythmic or prolonging QTc-interval drugs were excluded from the study. Patients already in treatment with ant-COVID-19 drugs before hospitalization. Patients with ECG recorded >12 hours after admission (N=14 pts) and patients with admission QT > 450 msec in men and 470 msec in women (N=30 pts) were excluded from the analysis of one clinical end-point, prolonged QT evaluation.

Clinical data: All patients underwent clinical examination; age, gender, medical history and previous therapy were recorded.

Blood sample collection: Circulating levels of C-reactive protein (CRP), high sensitivity (HS) Troponin, D-dimer, LDH, ferritin, creatinine, electrolytes (Sodium, Potassium, Calcium, Magnesium), blood count with formula were obtained by venipuncture at the admission. Normal values were <19.8 pg/ml for HS-troponin, <1 mg⁄L for C-reactive protein (CRP), between 313-618 U/L for LDH, between 0.61-1.24 for Creatinine, 150–400 × 10^9/L for the platelet count, 4.3–10.0 × 10^9/L for total White Blood Cells, 2.0–7.0 ×10^9/L for neutrophils and 0.95–4.5 × 10^9/L for lymphocytes.

Treatment approach: treatment was based on operator choice according mainly with Italian guidelines of the infectious disease society [ix].

Electrocardiogram analysis: Standard 12-lead ECGs were serially recorded within 12 hours after admission and then repeated after 7 and 14 days. The QT and RR interval were measured in 3 consecutive beats in sinus rhythm and 5 consecutive beats in atrial fibrillation and then averaged [x]. Framingham formula was used in all cases in order to get the best assessment of QT intervals also in of bundle branch block [xi].

Definition of outcome:

Clinical endpoints were QTc interval prolongation and life-threatening arrhythmias during hospitalization.

QTc prolongation group: patients included presented with normal QTc interval value at admission and developed after 7 days QTc interval values greater than 450 ms for men and 470 ms for women [12]. Patients presenting at admission with QTc interval greater than 450 ms for men and 470 ms for women were excluded from the study.

Life threatening arrhythmias included ventricular tachycardia (VT), ventricular fibrillation, torsade de pointes, asystole or complete atrioventricular block. The presence of rhythm disorders was assessed by ECG independently reviewed by two experienced cardiologists during hospital stay. Non sustained VT was defined as a ventricular rhythm faster than 100 bpm lasting less than 30 seconds.

Statistical analysis

Continuous variables were reported as means ± standard deviation or median with interquartile range (IQR) and compared with Student's t-test for either paired or unpaired groups and the Mann-Whitney (for unpaired data) and the Wilcoxon rank test (for paired data) as required, dichotomic variables as percentage and compared with χ^2 test of Fisher test as required. Repeated measures were analyzed with analysis of variance test (ANOVA). Multiple regression analysis was used to identify predictors for prolonged QTc after 7 days and for correcting bias of principal confounders; odds ratio and 95% confidence intervals (CI) were also calculated. A p value <0.05 was considered as statistically significant.

Results

Patients' characteristics

One hundred and ten consecutive patients were enrolled in the study. All baseline features are reported in **table 1**; 66% were male and the mean age was 58±14 years. Mean QTc interval at admission was 409±26 msec. 5% of patients presented with atrial fibrillation at admission. Admission heart rate was 73±15 bpm. Overall death rate during hospitalization was 9% (10 out 110 patients).

QTc prolongation during hospitalization

Mean QTc interval after 7 days was 429±30 msec and after 14 days 435±26 msec (**Figure 1**). Fifteen (14%) patients developed a prolonged QTc interval after 7 days (mean QTc at admission 414±16 vs 481±21 msec after 7 days, mean QTc interval increase 66±20 msec, +16%, p<0.001, **Figure 2**). These patients were older (66±12 vs 56±14 years, p<0.05), had higher basal heart rates (87±26 vs 71±11 bpm, p<0.001), higher rates of paroxysmal atrial fibrillation (20% vs 2%, p<0.01), lower platelet count (169±41 vs 231±112 *1000/mm^3, p<0.05) (**Table 1-2**).

At 7 days, no relevant differences in electrolyte concentrations were found. When comparing patients with QT-prolongation and those without, no differences were found in terms of hydroxychloroquine (93% vs 91%, p n.s).; the use of other drugs (93% vs 32% lopinavir/ritonavir, p=0.01; 20% vs 76% azithromycin, p<0.001; 60% vs 26% cephalosporin, p=0.01; tocilizumab 0% vs 27%, p<0.05), single (100% vs 74% p=0.03) and dual antiviral therapy (40% vs 9%, p <0.01), however was significantly different (**Table 3**).

The increase in QTc values was inversely proportional to baseline QTc levels and leucocyte count, both in absolute and in relative terms (r -0.52, r -0.57, p<0.001; r -0.20, r -0.19, p<0.05, respectively), directly to basal heart rates (r 0.33, r 0.28, p<0.01, **Figure 3**).

At multivariate forward stepwise logistic regression analysis including age, male gender, presence of paroxysmal atrial fibrillation, basal QTc values, basal heart rate, and dual antiviral therapy, age (OR 1.06, 95% C.I. 1.00-1.13, p<0.05), basal heart rate (OR 1.07, 95% C.I. 1.02-1.13, p<0.01) and dual antiviral therapy (OR 12.46, 95% C.I. 2.09-74.20, p<0.1) were independent predictors of QT-prolongation (odds ratio 1.05, 95% CI 1.00-1.09, p=0.03) with a model accuracy (ROC area under the curve) of 0.85 (95% C.I. 0.76-0.91).

Life threatening arrhythmias

One patient experienced cardiac arrest due to asystole and was resuscitated with advanced circulatory support and three patients had non sustained ventricular tachycardia managed with intravenous beta-blocker (metoprolol) (**Table 4**). Patients experienced life threatening arrhythmias after a median of 9 days (6-21 days) from hospitalization. Life threatening arrhythmias were associated with poor outcome, two out of four patients died 24±12 hours after the index event.

Interestingly, one patient showed transient “Brugada type I” ECG pattern during fever that disappeared after paracetamol infusion; the patient was continuously ECG monitored, did not experience arrythmia during hospitalization. He had no history of syncope and was treated during hospitalization with hydroxychloroquine and azithromycin.

Drug therapy during hospitalization

In the overall population 93% of patients received therapy with hydroxychloroquine, 95% antibiotic therapy (71% macrolide (azithromycin), 30% cephalosporin, 10% betalattamics), 77% antivirals (40% lopinavir/ritonavir, 27% darunarvir/cobicistat, 13% oseltamivir, 6% tenofovir). Among patients receiving dual antiviral therapy (13%), 66% received lopinavir/ritonavir and oseltamivir, 18% lopinavir/ritonavir and darunarvir cobicistat and 16% oseltamivir and darunarvir cobicistat.

Discussion

We report one of the first multi-center registry on COVID-19 patients aiming to evaluate electrocardiographic changes during hospitalization and life-threatening arrhythmias. We found that:

1) After 7 days of hospitalization 14 % of patients developed prolongation of QTc interval, dual antiviral therapy, age and basal heart rate were an independent predictor of pQT.
2) Life threatening arrhythmias have an incidence of 3.6% and may present after a median of 9 days of hospitalization with cardiac arrest and non-sustained VT.
3) Life threatening arrhythmias were featured by poor outcome with 50% of mortality.

QTc prolongation is quite common among patients treated with antimalarial, antivirals and antibiotics. Therefore, aim of the study was to evaluate changes of QT interval during hospitalization and potential correlation with life threatening arrythmias among patients with COVID-19 and normal admission QTc interval.

Although no adequately sized randomized trials have been published on treatment of COVID-19, a combination of hydroxychloroquine and azithromycin is commonly used to treat this infection. Moreover, some centers started also a combination of antiviral drugs such as lopinavir/ritonavir or remdesevir. These

drugs, especially in combination, may increase the risk of QT interval prolongation and subsequently ventricular arrhythmias [xii]. Hydroxychloroquine blocks the KCNH2-encoded hERG/Kv11.1 potassium channel and can potentially prolong QTc interval. Some case report showed life threatening arrhythmia due to chronic use of hydroxychloroquine [xiii] [xiv]. However, in a registry of 28 patients with systemic lupus erythematosus receiving chronic treatment (7 months) with chloroquine, no conduction disturbances were reported [xv]. Antiviral drugs as lopinavir/ritonavir may also induce QT prolongation [xvi]. Arrhythmogenic effect of azithromycin has been reported in single cases [xvii], but conflicting data have been published on this risk [xviii] [xix].

Borba et al. evaluated in a randomized trial on COVID-19 patients the effect of high-dosage hydroxychloroquine (ie, 600 mg CQ twice daily for 10 days) vs low-dosage CQ (ie, 450 mg twice daily on day 1 and once daily for 4 days). High dose group had higher prevalence of QTc interval greater than 500 milliseconds (18.9 vs 11%) [xx]. Chorin et al. found a mean baseline QTc-prolongation from 435 to 463 ms after 3.6 days of therapy in COVID-19 patients treated with hydroxychloroquine (400 mg twice daily on the first day, followed by 200 mg twice daily) and azithromycin (500 mg daily). QTc was severely prolonged to >500 ms in nine (11%) patients. There was no torsade de pointes events recorded for any patients, including those with a severely prolonged QTc [xxi].

In the present study we found that a combination of antivirals may predict prolonged QTc interval, however due to the heterogenous antivirals combination, no conclusion can be provided. Fifteen patients received two antiviral drugs, among these 10 patients were treated with Lopinavir/ritonavir (200/50 mg daily) and Oseltamivir (75 mg daily).

Ritonavir and Oseltamivir are both associated with QT prolongation in previous studies [xxii] [xxiii], therefore their combination could increase risk this risk.

In the present study also age and basal heart rate were found to be predictor associated with pQT. These findings may reflect patient's comorbidities and higher fragility of this subset of patients. Indeed, there was a trend not statistically significant of higher rate of intensive care stay for patients that developed prolonged QT interval after 7 days (13 vs 4%).

Life threatening arrhythmias in patients with viral infection have been previously described in the context of myocardial inflammation. Several mechanisms are involved in this process: increased oxidative stress and

inflammation can increase the release of inflammatory cytokines such as tumor necrosis factor-a and interleukin-6, leading to Ca2+/calmodulin Protein Kinase II (CaMKII) activation [xxiv]. Viruses can also alter the function or expression of ion channels or induce structural remodeling of the myocardium. Coxsackie virus can increase the ICa, leading to action potential duration (APD) prolongation [xxv].

In the present study most of the arrhythmias were cardiac arrest and non-sustained ventricular tachycardia. Arrhythmias occurred mainly during the second week of hospitalization and two patients died after 24±12 h from the index event due to multiorgan failure. Management was conservative and betablockers were administered. As shown also in previous studies[24], no patients experienced ventricular fibrillation following torsade de pointes.

Moreover, three out of four patients that experienced lifer threatening arrhythmias were in intensive care unit; therefore, arrhythmias seem to be related more with a severe progression of the disease. During intensive care unit stay, sedatives - hypnotics, benzodiazepines or alpha-2 adrenergic agonist were also administered to obtain light sedation, that was useful to tolerate mechanical ventilation. However, especially the use of dexmedetomidine, an alpha-2 adrenergic agonist, was associated with bradycardia that could increase the risk of QTc prolongation [xxvi].

This study shows that young patients without significant comorbidities may be candidate for domiciliary treatment with a relative low risk of arrhythmic complication. However, baseline ECG with exclusion of inherited long QT syndrome and conduction disturbances (as bundle branch block) should be warranted to all patients before treatment.

Limitations

Some limitations have to be considered for the present investigation. The study evaluated a relatively low number of patients. Continuous ECG monitoring was performed only in case of intensive care unit hospitalization. The population enrolled consisted of symptomatic patients that required hospitalization.

Conclusions

During hospitalization, 7 days after admission, 14% of patients developed QTc prolongation; Dual antiviral therapy, age and basal heart rate were the only independent predictors of QT prolongation at 7 days. Life threatening arrhythmias have an incidence of 3.6% and were associated with poor outcome.

Conflict of interest

None to disclose.

Figure Legends

Figure 1 QTc intervals over time in general population (mean ± 95% confidence interval, p<0.001 for all repeated measures).

Figure 2 QTc intervals over time among patients that developed or not prolonged (above cut-off levels) QTc interval at the seventh day of hospitalization (mean ± 95% confidence interval, p<0.001 for all repeated measures).

Figure 3. Correlations between QTc increase, baseline QTc levels and basal heart rate (p values <0.01 respectively).

Tables

	General population	Prolonged QTc	no	p value
n. patients	110	15	95	
Age, y	58 ± 15	66 ± 12	56 ± 14	**0.01**
Male sex	80%	80%	64%	0.23
CLINICAL BASELINE PROFILE				
Hypertension	39%	20%	43%	0.09
Diabetes	13%	0%	18%	0.80
Obesity (BMI > 30)	15%	13%	16%	0.91
Renal insufficiency (ClCr < 30 ml/min)	8%	0%	10%	0.21
History of lung disease	16%	20%	17%	0.78
History of heart disease	21%	13%	26%	0.44
History of cancer	8%	13%	7%	0.43
Clinical features at admission				
Fever	75%	80%	74%	0.88
Hypo/anosmia	6%	6%	6%	0.86
Diarrhea	6%	0%	6%	0.38
Myalgia/artralgia	18%	6%	19%	0.44
Laboratory data				
Admission LDH levels	328 ± 286†	240 ± 89†	380 ± 403†	**<0.001**
Admission D-dimer levels ng/mL	753 ± 976†	592 ± 407†	773 ± 2493†	0.06
CRP peak during hospitalization mg/dl	75 ± 132†	70 ± 94†	78 ± 146†	0.78
Admission creatinine levels (mg/dl) (0.2-8.5)	0.9 ± 0.3†	1 ± 0.3†	0.9 ± 0.3†	**<0.05**
Admission Leucocytes count ($x10^9$/L)	6325 ± 4150†	4600 ± 2550†	6534 ± 4385†	**0.02**
Admission Lymphocyte ($x10^9$/L)	866 ± 527†	840 ± 570†	876 ± 516†	0.75
Admission Platelets count ($x10^9$/L)	187 ± 101†	161 ± 48†	197 ± 101†	**0.02**
COMPLICATIONS				
ICU stay	6%	13%	4%	0.15
Death	9%	0%	11%	0.19

Table 1. Baseline clinical features and during hospitalization in patients with prolonged Qt interval at 7 days after admission (data are provided as mean ± S.D., median and IQR†, and counts as percentages).

ECG FEATURES	General population	Prolonged QTc	No	p value
n. patients	110	15	95	
ADMISSION				
Negative T waves	9%	0%	12%	0.16
ST elevation	0%	0%	0%	0.99
ST depression	1%	0%	1%	0.69
Mean QTc interval (msec)	409 ± 26	415 ± 15	408 ± 27	0.36
7 days				
Negative T waves	9%	0%	10%	0.35
ST elevation	0%	0%	0%	0.99
ST depression	0%	0%	0%	0.99
Mean QTc interval (msec)	429 ± 30	481 ± 21	421 ± 22	**0.01**
14 days				
Negative T waves	5%	0%	6%	0.42
ST elevation	0%	0%	0%	0.99
ST depression	1%	0%	2%	0.69
Mean QTc interval (msec)	**435 ± 26**	**464 ± 28**	**430 ± 23**	**0.01**

Table 2. Electrocardiographic features during hospitalization in patients with prolonged QTc intervals 7 days after admission (data are provided as mean ± S.D. and counts as percentages).

THERAPY DURING HOSPITAL STAY	General population	Prolonged Qt group	Non prolonged QT group	p value
Use of cloroquine or similar	93% (100)	93% (14)	91% (86)	0.98
Use of corticoids	31% (34)	0%	35% (34)	**0.01**
Use of antiviral drugs	77% (85)	100% (15)	74% (70)	**0.03**
- **Lopinavir/ritonavir**	40% (44)	93% (14)	32% (30)	**0.01**
- **Darunavir/cobicistat**	27% (30)	13% (2)	29% (28)	0.23
- **Oseltamivir**	13% (14)	26% (4)	11% (10)	0.09
- **Tenofovir**	6% (7)	7% (1)	6% (6)	0.99
Use of Tocilizumab	24% (26)	0%	27% (26)	**0.01**
Use of antibiotics	95% (98)	87% (13)	90% (85)	0.76
- **macrolid (azitromicin)**	71% (75)	20% (3)	76% (72)	**0.01**
- **beta-lactames**	10% (13)	13% (2)	12% (11)	0.88
- **cephalosporin**	30% (34)	60% (9)	26% (25)	**0.01**
Anticoagulation	30% (29)	13% (2)	28% (27)	**0.01**
Antiplatelets	7,% (12)	7% (1)	12% (11)	0.80
ACE-I	4% (3)	0%	3% (3)	0.25
ARB	9% (8)	13% (2)	6% (6)	0.29

Table 3: Drug therapy during hospitalization among patients with prolonged Qt interval during the 7th day of hospitalization and not. Data are reported as percentage and number of patients.

	Patient 1	Patient 2	Patient 3	Patient 4
Age, y	79	74	59	53
Sex (M=male; F=female)	F	F	F	M
CLINICAL BASELINE PROFILE				
Hypertension	Y	N	Y	N
Diabetes	N	Y	N	N
Obesity (BMI > 30)	N	Y	Y	N
Renal insufficiency (ClCr < 30 ml/min)	N	N	N	N
History of lung disease	N	N	N	N
History of heart disease	N	N	N	N
History of cerebrovascular disease	N	Y	N	N
History of cancer	N	N	N	N
ECG features				
Admission QTc interval (msec)	425	380	410	449
7 days QTc interval (msec)	409	470	410	460
14 days QTc interval (msec)	470	580	451	407
Use of vasoactive drugs	Y	Y	Y	N
Hydroxycloquine administration	Y	N	Y	Y
Antiviral therapy:				
- **Lopinavir/ritonavir**	N	Y	N	N
- **Darunavir/cobicistat**	Y	Y	N	N
Antibiotic therapy:				
- **Azythromicin**	Y	Y	Y	Y
ARRHYTHMIAS DURING HOSPITAL STAY				
- **cardiac arrest**				
- **VT**	Y	N	N	N
- **NSVT**	N	N	N	N
- **Days from admission**	N	Y	Y	Y
	21 days	6 days	12 days	6 days
Death	Y	Y	N	N

Table 4: Clinical features, in-hospital therapy and adverse events in patients with life threatening arrhythmias during hospitalization.

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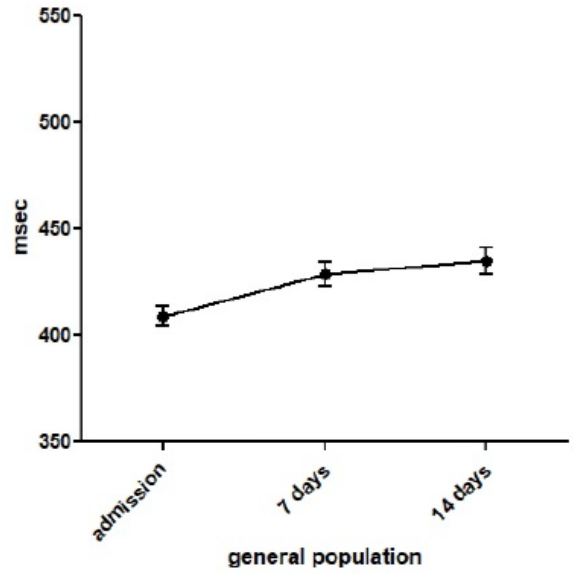
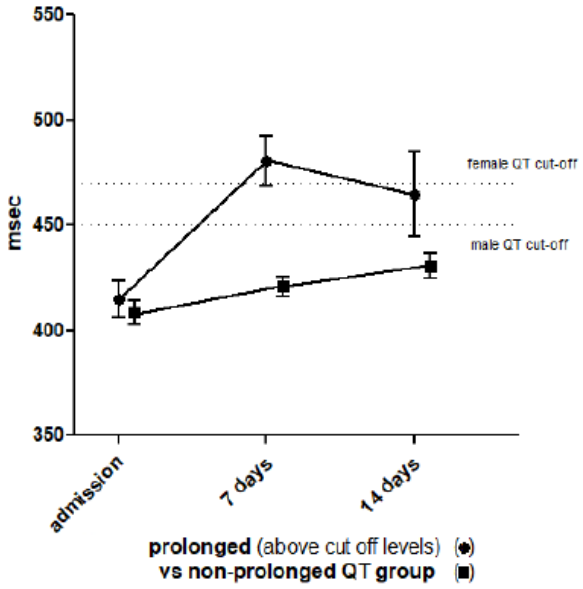

550
500
450
400
350
msec
admission
7 days
14 days
general population

Figure 1

Figure 2


550
500
450
400
350
msec
female QT cut-off
male QT cut-off
admission
7 days
14 days
prolonged (above cut off levels)
vs non-prolonged QT group

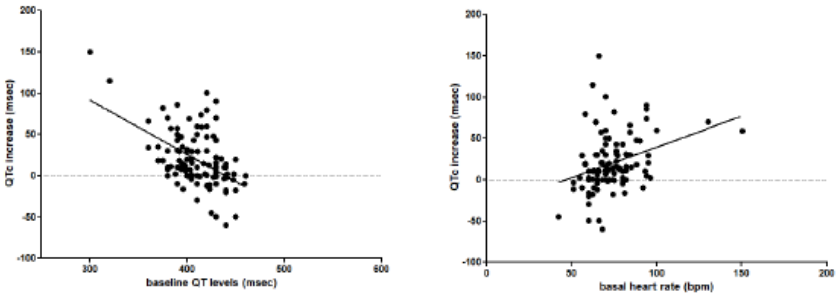

QTc increase (msec)
200
150
100
50
0
-50
-100
300
400
500
600
baseline QT levels (msec)
QTc increase (msec)
200
150
100
50
0
-50
-100
0
50
100
150
200
basal heart rate (bpm)

Figure 3