

Association between a prolonged corrected QT interval and outcomes in patients in a medical Intensive Care Unit

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Abstract

Introduction: Patients admitted into a medical Intensive Care Unit (ICU) have varying illnesses and risk factors. An electrocardiogram (ECG) is a useful tool to assess the cardiac status. The aim of the study was to determine the prevalence of QT prolongation of the ECG in patients admitted to a medical ICU in a tertiary hospital, to assess outcomes in terms of mortality, cardiovascular events, and duration of ICU stay. **Materials and Methods:** Prospective observational study, 6 months duration, assessing the prevalence of prolonged corrected QT interval (QTc) at admission into a medical ICU. A QTc calculated by Bazett's formula, of >440 ms for males and >460 ms for females was considered prolonged. Details of illness, clinical and lab parameters were monitored. **Results:** The total number of patients screened was 182. There was a high prevalence of prolonged QTc (30%) on admission to the ICU. This reduced to 19% on day 3 ($P = 0.011$). In patients with a prolonged QTc the odds ratio of adverse outcome from ICU was 3.17 (confidence interval [CI]: 1.52–6.63) ($P = 0.001$) and of adverse outcome for hospital stay was 2.27 (CI: 1.11–4.66) ($P = 0.014$). In the study, 35% of all patients received drugs with QT prolonging action. Of patients with a prolonged QTc at admission 18 (35%) received a QT prolonging drug. **Conclusions:** We found that prolonged QTc is common (30%) in our medical ICU at admission and a large proportion (35%) received drugs capable of prolonging QT interval. These patients with QTc prolongation have a higher odds ratio for adverse outcomes.

Keywords: Critical care, electrocardiography, intensive care unit, India, predictors, QT prolongation

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Introduction

A medical Intensive Care Unit (ICU) has a wide variety of patients varying in age and primary illness. These patients have a high morbidity and a guarded prognosis.^[1] At admission, a thorough clinical and laboratory assessment needs to be made for a clear picture of the diagnosis, severity of the illness,

appropriate supportive, and specific therapy. This also helps to prognosticate the course and outcome. There are numerous scoring systems that are routinely employed especially the Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology

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Score and Sequential Organ Failure Assessment (SOFA) scores.^[2-4] However, these have many variables and do not utilize the electrocardiogram (ECG) among its parameters. An ECG which is taken for all patients in an ICU is a tool which can provide valuable information. The ECG represents the electrical activity of the heart. The QT interval, related to ventricular function, if prolonged has been shown to have associations with poor ICU outcomes.^[5] It is seen that in acutely ill patients the prevalence of a prolonged corrected QT interval (QTc) is much higher than one might expect.^[6,7] These may be due to an underlying cause which may be correctible.^[8] The aim of the study was to determine the prevalence of prolonged QTc at admission and assess associated outcomes in patients admitted to a tertiary care Indian medical ICU.

Materials and Methods

Setting

This was a prospective observational study of 6 months duration in a multidisciplinary medical ICU of a tertiary care academic hospital. This was a 24 bed ICU manned by 24 h in-house doctors and staff comprising of junior and senior level residents, critical care fellows, and specialist intensivists. The period of recruitment was from January to July 2013.

Study participants

Patients above the age of 18 that were admitted to the medical ICU were included in the study. Patients on temporary or permanent pacemaker, those with WPW pattern on ECG and referrals from other ICUs were excluded. The patients had varied illnesses like sepsis, poisonings, hematological posttransplant patients with opportunistic infections, and patients post-attempted suicide by hanging. The approval of the study was sanctioned by the Institution Review Board. Informed consent was obtained. The patients were recruited at admission and followed-up till discharge.

The outcomes

The primary outcome to be assessed was the prevalence of a prolonged QTc in the ICU at admission. Secondary outcomes were association of prolonged QTc and duration of ICU and hospital stay, favorable or unfavorable outcome from ICU and hospital, and duration of ventilation free days. A favorable event was discharge from the ICU/hospital and unfavorable was death or discharged against medical advice. The other outcomes assessed were associations of prolonged QTc and arrhythmias (Torsades de Pointes, bradycardia, ventricular tachycardia, ventricular ectopic beats,

supraventricular complexes), hypotension, cardiac arrest, acute coronary syndrome, intubation, and death.

We also looked for the prevalence of QT prolonging medication administered to a patient in the first 3 days in ICU.

Methodology

Patients were admitted into the ICU from either the wards or emergency department. After stabilization, an ECG was taken within 4 h of admission. If an ECG was available within 3 h prior to admission from the Causality, it was included. ECGs were taken by trained personnel. The machine for the ECG used was GE Mac 600 using Marquette 12SL ECG analysis program for QT analysis. A data collection Performa containing details of co-morbidities, medications, diagnosis, and need for ICU admission was filled. The relevant blood investigations during the first 12 h period were documented. The APACHE II and SOFA scores were calculated at admission. The APACHE II score assesses the severity of disease at admission utilizing 12 variables with a score upto 71 and correlates with subsequent hospital mortality. It utilizes among clinical variables arterial PaO₂, pH, and electrolytes. The SOFA score comprises of six variables including respiratory, cardiac, hepatic, coagulation, renal, and neurological. Higher scores are associated with increased rate of mortality.

In ICU, the patient underwent continuous heart rate, blood pressure, respiratory rate oxygen saturation, and temperature monitoring. A repeat ECG and blood parameters were noted on day 3 of admission. The collected ECGs of day one and three were scanned printed and analyzed for the QT, RR, and QTc manually.^[9,10] The ECGs parameters were calculated at a later date after the patients were not in ICU, in order to prevent an observation bias. The primary investigator underwent a training process from a cardiac electrophysiologist for appropriate calculation of the ECG parameters. The QT interval was calculated by Caliper method. The distance was taken from the beginning of the Q wave and the end to the T was the intersection between a line marked by a tangent to the downslope of T and the baseline. The machine-generated, RR and QTc interval were noted. The manually calculated values were compared to the automated values in the ECGs. The formula used for calculation of the corrected QT was Bazett's formula. $QTc = QT/\sqrt{RR}$. A comparison between the investigator and the Cardiologist was also done for the QTc calculation. The medication list on day 1 and day 3 was documented and it was checked for potential QT prolonging drugs. The classification of QT-prolonging drugs and a risk of Torsades de Pointes was obtained from

lists maintained by the Arizona Center for Education and Research on Therapeutics (www.azcert.org). Drugs with a “known risk” (list 1) a “probable risk” for TdP (list 2) or a “conditional risk” (list 3) were used to characterize the medication list. At discharge, the final diagnosis, duration of ICU and hospital stay, and outcome were noted [Figures 1 and 2].^[11,12]

Prolonged QTc for this study was taken as >440 ms for males and >460 ms for females.^[13,14]

Statistical methods

The sample size was calculated based on the primary objective of the study. The primary aim of the study is to find out the prevalence of prolonged QTc. From a previous study, the prevalence of prolonged QTc was found to be 24%.^[6] Assuming precision to be ± 6 for the 95% confidence interval (CI), the sample size for estimating prevalence was calculated as 203.

For the analysis, QT levels were compared between males and females, different age groups, and other variables using independent samples *t*-test. Associations between normal, prolonged QT intervals with other categorical variables are assessed using Chi-square test. To find the agreement between machine and manual QTS intra class correlation (ICC) was calculated.

Results

There were totally 182 patients screened. Of this, 2 refused consent, one had a permanent pacemaker, and 5 had poor ECG tracings at admission, hence, the total number included for analysis was 174 [Figure 3].

There were 17% of the patients with a pre-morbid cardiac illness prior to admission.

The mean SOFA score = 8.1 (standard deviation [SD] = 4.46) and APACHE = 23.3 (SD = 8.2).

The mean duration of stay in the ICU was 7 days (SD = 5.8); and stay in the hospital was 13 days (SD = 10.1). Adverse outcome (which included death and those who were discharged against medical advice) was seen in (61) 35% of patients in the ICU. Favorable outcome (which included those who were transferred to the ward) was seen in 65% of patients from ICU [Table 1].

QT interval data

The machine QTc value of the ECGs was used for outcome associations. There were total of 174 machine

values which were available from day 1. In the remaining 5, it was not reported due to poor ECG tracings.

The mean QTc on day 1 for the total population was 445.2 (SD = 47.8). Mean QTc for females was 450.2 (SD = 48.7). Mean QTc for males was 440.5 (SD = 46.7) [Table 2].

Number of patients with prolonged QTc on day 1 = 52 (30%).

Among the males, 24 (27%) had prolonged QTc. Among the females, 28 (33%) had prolonged QTc.

Analyzing the QTc in the various age groups the mean QTc was longest in the 40–60 age group, $n = 56$, was 448.25 (SD = 53.4).

On reviewing the medications that patients were on prior to ICU admission, 2 were on HCQ and 1 on phenytoin, which are known to affect the QT interval. Of these only the patient on phenytoin had a prolonged QTc on day 1. The no of patients with QTc >500 = 26 (14.9%).

QTc intervals of the ECGs of day 3 of admission (here QTc of ECGs was available for 109 patients and for the others the machine values were not available).

The mean QTc interval on day 3 = 436.61. The mean for the males = 438.03 and for the females = 436.61.

The percentage of patients with prolonged QTc = 19.3%. The percentage of males with prolonged QTc = 15.7%. The percentage of Females with prolonged QTc = 22.4%.

As seen from Table 3 the patients had a wide range of primary diagnosis admitted into the medical ICU. The most common was infection, followed by cardiac related problems. Often these patients had multiple organ involvements.

Comparison of day 1 and day 3 corrected QT interval

The prevalence of QTc prolongation dropped from 30% on day 1–19% on day 3. There was a reduction in the mean QTc in from 445.2 to 436.6 [Table 2]. The incidence of new prolonged QTc on day 3 was seen in only 9 patients. From the data, it is seen that the mean QTc and the number of patients with prolonged QTc have reduced between day 1 and day 3. This value was found to be statistically significant ($P = 0.011$).

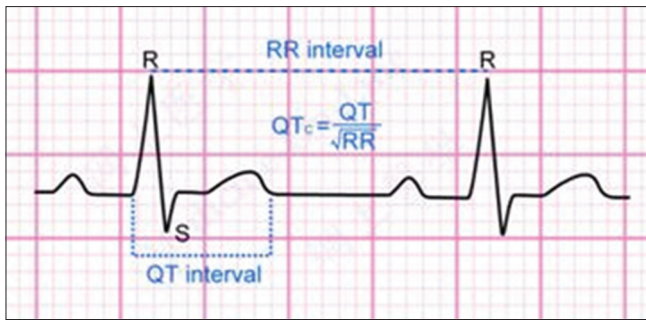


Figure 1: The QT, RR interval, and Bazett's formula

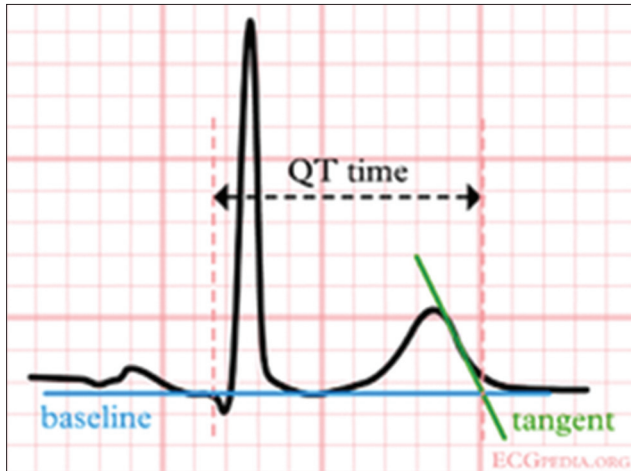


Figure 2: Identifying the end of the T wave^[16,17]



Figure 3: Flowchart of patients

Comparison of machine and manual corrected QT interval

Comparing QTc calculated by investigators. Machine-measure of agreement ICC = 89%. Furthermore, comparing QTc calculated by cardiologist versus investigator. Measure of agreement ICC = 84%.

Analysis of the QT prolonging drugs in the study

In this study, 35% (61) of all patients received drugs with QT prolonging action. Of patients with a prolonged QTc at admission 18 (35%) received a QT prolonging drug. These drugs included azithromycin, ondansetron, levofloxacin, amiodarone, haloperidol, and fluconazole. QTc prolonging drugs given in the ICU [Figure 4].

Patient outcomes

A favorable outcome was - discharge from ICU and hospital while an adverse was defined as death or discharged against medical advice.

Table 1: Baseline data of admitted patients

Characteristic	Number (%)
Age	45.4 (SD= 17.9)
Females	85 (49)
Males	89 (51)
Admitting reason*	
Respiratory distress	119 (42)
Hemodynamic compromise	86 (31)
Neurology	44 (16)
Poisoning	30 (11)
Scores	
SOFA	8.1 (SD=4.46)
APACHE II	23.3 (SD=8.2)
Mean duration of stay	
ICU	7 days (SD=5.8)
Hospital	13 days (SD=10.1)
Adverse outcome from ICU	61 (35)

*Some patients had more than one reason for admission into ICU. SD: Standard deviation; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation; ICU: Intensive care unit

On comparing those with normal and prolonged QTc and the outcome from ICU and hospital [Table 4] in the normal QT group 25% and 32% had an adverse outcome in the ICU and hospital respectively versus 52% in the prolonged QT group, respectively. The Odds ratio for an adverse event in the patients with a prolonged QTc was 3.17 (CI: 1.52-6.63) (P = 0.001) in ICU and 2.27 (CI: 1.11-4.66) (P=0.014) for the hospital stay. The duration of ICU stay was not different 7.2 days, in the normal QTc group versus 7.3 days in the prolonged QTc group.

Ventilator-free days is a representation of the duration of ventilation in the ICU and assesses therapies in an ICU. It combines the effect of duration of ventilation, morbidity, and mortality. VFD = number of days where the patient breathed without ventilation (28-X). If the patient dies or is ventilated over 28 days, the value is 0. On assessing the ventilator-free days, the normal QT group had a longer period 18.3 versus 11.5 implying a better outcome [Figure 5].

Among the monitored events, there was a trend toward increased number of supraventricular tachycardia, premature ventricular complexes, ventricular tachycardia, and fibrillation in the prolonged QT group, but the numbers were not statistically significant [Table 5].

Discussion

This to our knowledge is the first Indian study to analyze the QTc interval in patients who are acutely ill in a medical ICU. This was a population with varying illnesses and age groups who have chronic as well as acquired risk factors, which are potentially correctible. Here the mean age of the patients was 45 years and this is in contrast to ICUs in the west where more population are

Table 2: Comparison of QT intervals of day 1 and day 3

Characteristic	Day 1 total=174	Day 3 total=109
Prolonged QTc (%)	52/174 (30)	21/109 (19)
Males	24/89 (27)	8/51 (16)
Females	28/85 (33)	13/58 (22)
Mean QTc	445.2 (SD=47.8)	436.61 (SD=45.16)
Males	440.5 (SD=46.7)	438.03 (SD=45.28)
Females	450.2 (SD=48.7)	436.61 (SD=45.4)

SD: Standard deviation; QTc: Corrected QT interval

Table 3: Primary diagnosis and QTc interval

Diagnosis	Total number	Prolonged QT	Mean QT (SD)
Cardiac	33	15	456.8 (65.1)
Neurological	17	5	441.2 (34.5)
Respiratory	30	8	439.8 (45.6)
Infection	52	13	441.5 (41.1)
Poisoning	30	7	432.1 (38.1)
Miscellaneous	12	4	459.8 (62.4)
Total	174	52	455.2 (47.8)

Cardiac: Diagnosis included acute coronary syndromes (NSTEMI and unstable angina) and cardiac failure; Neurological causes included: Hanging (partial and complete), heat-related illnesses and benzodiazepine related altered sensorium and TB meningitis; Respiratory: Pneumonia, pleural effusion, malignancy, COPD, and asthma exacerbations; Infection: Undifferentiated febrile illness, febrile neutropenia, scrub typhus, pyelonephritis, cholangitis, and infections in chronic inflammatory diseases; Poisonings included: Organophosphorus, alprazolam, olanzapine, oleander, and oduvanthalai poisoning; Miscellaneous: Pancreatitis, flare of inflammatory diseases like SLE, DKA. SD: Standard deviation; QTc: Corrected QT interval; NSTEMI: Non-ST segment elevation MI; TB: Tuberculosis; COPD: Chronic obstructive pulmonary disease; SLE: Systemic lupus erythematosus; DKA: Diabetic ketoacidosis

of older age.^[15] There was an equal gender distribution, consisting of 49% females the patients were also quite morbid with a mean APACHE = 23.3 (SD = 8.2). There were a higher proportion of patients with infections and poisonings.

In our study, almost one-third of the population had a prolonged QTc on day 1 of admission. Other studies have also shown similar trends in the prevalence of a prolonged QTc in ICUs [Table 6]. In a study by Pickham *et al* it was 24%, Kozik *et al* 52% and Tisdale 28%.^[6,7,16] From the data, it is seen that the mean QTc and the number of patients with prolonged QTc had reduced between day 1 and day 3 (30–19%). This value was found to be statistically significant ($P = 0.011$).

The high prevalence is possibly due to the acquired risk factors for a QTc prolongation in a newly admitted critically ill patient. The resolution is possibly explained by the fact that after 2 days in ICU the patient is stabilized with less biochemical derangements and control of the underlying acute illness.

It is found that among patients with a prolonged QTc at admission 18 (35%) received a QT prolonging drug. In other studies by Tisdale *et al.*, 34.7% of the population

with a prolonged QTc received a QT prolonging drug.^[7] It was noted that an additional QT prolongation of >60 ms occurred in 57.1% of these patients. The study by Kozik and Wung noted that 59% received a drug with known QT prolonging action.^[16] In this study, the potential QT prolonging drugs used were azithromycin, ondansetron, levofloxacin, amiodarone, haloperidol, and fluconazole.

Assessing the association with QTc and outcomes we found that the patients with a prolonged QTc had three times the odds of an adverse outcome in the ICU than those with a normal QTc at admission. This was also represented in the hospital stay adverse outcome and number of ventilator-free days.

This was similarly noted in a study by Haugaa *et al.* and Pickham *et al.*^[5,6]

Even in patients with organophosphorous poisoning in a medical ICU, conducted by Shadnia *et al* the period of hospitalisation and mortality rate was higher in the prolonged QTc group.^[17]

Although bradycardia can cause a prolongation in QTc, in Table 5 we note that patients in both groups had tachycardia, but we see that the population in the group with QTc prolongation had a slower heart rate. Though this may be statistically significant, it cannot be extrapolated to clinical significance.

We did a univariate analysis to determine any predictors of a prolonged QTc particularly age, sex, admission diagnosis, history of stroke, cardiac illness, and biochemical abnormalities (potassium, calcium, magnesium, and creatinine). We did not find any strong associations.

We also performed a logistic regression for predictors of adverse outcomes in ICU using similar variables along with admission diagnosis and the SOFA and APACHE scores. The significant variables were the QTc and the composite scoring systems.

This study, being observational in nature, does not attribute a causative effect of a prolonged QTc and an adverse outcome but indicates a strong association. It was not powered to determine the potential predictors of a prolonged QTc or adverse outcome.

The QT analysis employs a simple ECG from which the QT interval can be calculated with simple instructions.

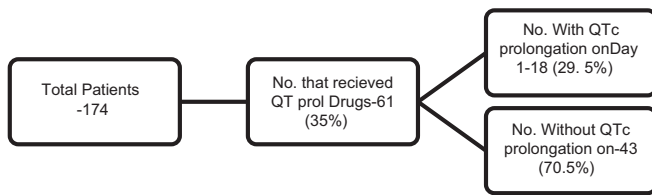


Figure 4: Corrected QT interval prolonging drugs given in the Intensive Care Unit

Table 4: Comparison of outcomes based on QTc

QTc	ICU outcome		Hospital outcome		Total
	Favourable	Adverse	Favourable	Adverse	
Normal	91	31	83	39	122
Prolonged	25	27	25	27	52
Total	116	58	108	66	174

QTc: Corrected QT interval; ICU: Intensive care unit

Table 5: Demographic and clinical variable differences between those with normal and prolonged QTc

Predictors (n)	QT normal-n (%) or mean±SD (n)	QT prolonged-n (%) or mean±SD (n)	P
	Total=122	Total=52	
Age (174)	44.6 (122)	46.8 (52)	0.429
Male (89)	65 (73)	24 (27)	0.390
Female (85)	57 (67)	28 (33)	0.389
Reason for admission			
Respiratory	80	39	0.221
Hemodynamic	59	27	0.667
Neurological	33	11	0.413
Poisoning	23	7	0.389
Clinical history (%)			
Diabetes (58)	44 (76)	14 (24)	0.028
Hypertension (57)	39 (68)	18 (32)	0.544
IHD (18)	12 (67)	6 (33)	0.172
Old CVA (11)	9 (81)	2 (19)	0.516
Renal failure (18)	7 (39)	11 (61)	1.000
Lab parameters			
Sodium (169)	134.7±15.6 (118)	134.9±8.9 (51)	0.918
Potassium (171)	4.0±1 (119)	3.8±1 (52)	0.152
Calcium (147)	4.3±1.2 (103)	4.1±1.0 (42)	0.377
Magnesium (52)	2.4±1.6 (42)	2.4±1.1 (10)	0.971
Creatinine (171)	2.1±1.9 (121)	2.6±3.2 (50)	0.376
Glucose (158)	142.4±113	149.4±45	0.555
ACS (13)	8	5	0.483
Arrhythmias (33)	22	11	0.631
HR on ECG (n=150)	119±31 (106)	109±26 (44)	0.050
QTc	419.1 (SD=19.9)	506.6 (SD=36.4)	0.000

Arrhythmias: Supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, premature ventricular contraction, atrial fibrillation, heart blocks, sudden cardiac arrest, and Torsades de pointes. SD: Standard deviation; ACS: Acute coronary syndrome; IHD: Ischemic heart disease; QTc: Corrected QT interval; HR: Heart rate; ECG: Electrocardiography; CVA: Cerebrovascular accident

Table 6: Prevalence of prolonged QTc in different studies

Study	Our study	Pickham et al. ^[6]	Kozik ^[14]	Tisdale et al. ^[7]
QTc prevalence (%)	30	24	52	28

QTc: Corrected QT interval

The correlation with the machine and the calculated value implies that this can also be used in a standardized machine. Considering that QTc is an index of severity

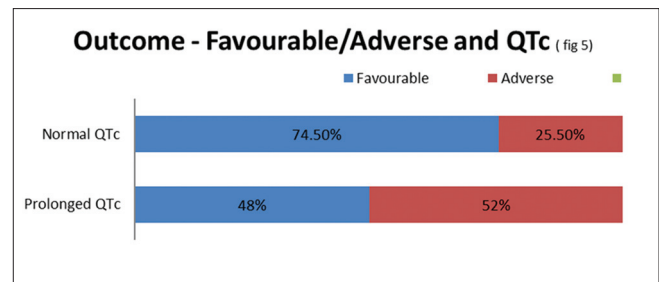


Figure 5: Outcome - Favorable/adverse and corrected QT interval

of the underlying illness and a predictor of adverse ICU outcomes, it can be incorporated into predictive diagnostic scores.

Limitations

This was limited to a single center experience and the patient profile compared to western data consisted of more morbid patients. QT variations can be transient and continuous ECG monitoring was not possible, hence we could have missed out other prolonged QT intervals or arrhythmias. A longer follow-up period in the ICU could have revealed a clearer trend to the QT intervals in relation to the variables analyzed. We did not have a baseline ECG or an ECG at discharge which would demonstrate premorbid values.

Conclusions

This study demonstrates the high prevalence (30%) of a prolonged QTc in patients at admission in a Medical ICU. It was noted that 35% of these patients received a drug that could further prolong the interval. Acutely ill patients with prolonged QT intervals had nearly a three times odds ratio for an adverse event in the ICU, twice for the hospital stay. A simple ECG and a calculated QT interval can be used to plan management and caution us on probable electrolyte abnormalities and drug therapies. It can even be incorporated as a tool for prognostication of patients in a medical ICU.

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Conflict of interest

There are no conflict of interest.

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