Prevalence and prognostic significance of prolonged QTc interval in emergency medical patients: A prospective observational study

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ABSTRACT

Introduction: QTc interval is affected by many factors and prolongation of same may have prognostic significance. A significant number of patients admitted in medical emergency are acutely ill, have multiple comorbidities and are on medications, all of these factors might affect QTc interval and prognosis.

Materials and Methods: Single-center, prospective, observational study was carried out on 279 patients of different illnesses recruited from emergency medical services attached to the Department of Internal Medicine at Postgraduate Institute of Medical Education and Research, Chandigarh, India, a tertiary care hospital.

Results: Out of 279 patients, 95 were found to have prolonged QTc interval with the prevalence of 34.1%. Fifteen patients (5.4%) had markedly prolonged QTc interval (QTc > 500 ms). Of various medical conditions, we found statistically significantly higher number of patients of chronic kidney disease \((P = 0.047)\), chronic liver disease \((P < 0.001)\), hemorrhagic cerebrovascular accident \((P = 0.026)\), and heart failure \((P = 0.009)\) with prolonged QTc interval. Among laboratory abnormalities, patients with low hemoglobin \((P = 0.032)\), with deranged renal functions \((P = 0.033)\), and with hypokalemia \((P = 0.026)\) had a greater share of patients with prolonged QTc interval. There was no difference in duration of hospital stay and frequency of hospital mortality between two groups, although, on subgroup analysis, patients with markedly prolonged QTc interval had significantly higher hospital mortality \((P = 0.029)\). The frequency of ventricular tachycardia was also significantly higher in patients with prolonged QTc interval \((P = 0.008)\).

Conclusion: High prevalence of prolonged QTc interval was found in Indian emergency medical patients. There was no difference in hospital mortality though on subgroup analysis, patients with markedly prolonged QTc interval had significantly more episodes of in-hospital ventricular tachycardia and hospital mortality.

Key Words: Electrocardiography, emergency medical services, QTc interval, ventricular tachycardia

INTRODUCTION

QTc interval on electrocardiography (ECG), is calculated from the beginning of Q wave to end of T wave. It measures the duration of both cardiac depolarization and repolarization. Prolonged QTc interval may result from either a genetic or acquired conditions.\(^1\)\(^-\)\(^5\) Many factors affect myocardial repolarization either by blocking ion...
channels of myocardium and producing structural changes in myocardium or both resulting in QTc prolongation. Studies primarily focusing on a particular condition have found many demographic variables, comorbidities and biochemical abnormalities to be associated with prolonged QTc interval. However, use of specific drugs is also one of the important causes of acquired QTc prolongation. Various cardiac and noncardiac medications can cause QTc prolongation, and these are commonly prescribed. This ECG abnormality has been associated with greater risk of cardiac arrhythmia, known as torsades de pointes (TdP), a potentially life-threatening event and overall increased hospital mortality. Various studies have been carried out in the past to find out the frequency and clinical/biochemical variables associated with a prolonged QTc interval essentially in populations of patients with selected disease conditions. However, there is scarce literature about the prevalence and determinants of QTc interval prolongation in patients admitted to emergency medical services. The prevalence of QTc prolongation is likely to be higher in patients admitted in this area because acutely ill patients often have one or more of aforementioned risk factors and receive multiple drug treatments. QTc prolongation also has prognostic significance, and it is frequently overlooked parameter in ECG. This study was planned to find out the prevalence, and prognostic significance of QTc prolongation in patients admitted to emergency medical services of a tertiary care center. Apart from prevalence and prognostic significance, factors causing QTc prolongation was also explored as by avoiding or correcting these factors, life-threatening arrhythmia might be prevented.

**MATERIALS AND METHODS**

This was a single-center, prospective, observational study carried out on patients with different illnesses recruited from emergency medical services attached to the Department of Internal Medicine at Postgraduate Institute of Medical Education and Research, Chandigarh, a tertiary care hospital. Three hundred patients were screened, and finally, 279 patients fulfilling all inclusion and exclusion criteria were included in the study. All the patients were informed about the study objectives, and informed consent was obtained. The study included patients with the age of 18 years or more admitted to emergency medical services and ECG done within the first 24 hours. The patients who did not give consent for the study, age younger than 18 years, and tachyarrhythmias like atrial fibrillation, bigeminy, QRS complex wider than >120 ms, or baseline ECG with unidentifiable T waves were excluded. After admission to the emergency medical services, detailed history of each patient including demographic data, clinical history and physical examination findings, past history of QTc interval prolongation, torsade de pointes (TdP), or sudden cardiac arrest, underlying and/or concomitant diseases, detailed drug history, main diagnostic categories leading to emergency medical services admission were recorded in a predesigned instrument. Each patient was evaluated with chest X-ray, 12-lead ECG, arterial blood gas, hemogram, random blood sugar, serum electrolytes (potassium, sodium, calcium, magnesium, phosphate), renal function test (blood urea/creatinine), and liver function test. Prescription of medications associated with QTc interval prolongation during emergency services admission, during hospitalization, or during hospital discharge was recorded. We obtained medications list with the potential to cause QTc interval prolongation from the Arizona Center for Education and Research on Therapeutics (AZCERT), Tucson, Arizona (www.qtdrugs.org). We included all risk group lists (1–3) in this study. Any occurrence of TdP and immediate cause of death in case of hospital mortality was recorded. Institute ethics committee approved the study.

We had defined hyponatremia as serum sodium <135 mEq/L, hypernatremia as serum sodium >145 mEq/L, hypokalemia a serum potassium level of <3.5 mEq/L, hyperkalemia as serum potassium >5 mEq/L, hypomagnesemia as serum magnesium level <1.6 mg/dl, hypermagnesemia as serum magnesium >2.5 mg/dl, hypocalcaemia as calcium level <8.6 mg/dl, hypercalcemia as serum calcium >10.5 mg/dl, hypophosphatemia as serum phosphate <2.7 mg/dl, hyperphosphatemia as serum phosphate >4.5 mg/dl, hypoalbuminemia as serum albumin <3.5 g/dl, and elevated serum creatinine as a creatinine level of >1.4 mg/dl.

Patients were categorized as anemic as per the WHO criteria. We had defined sinus tachycardia as heart rate >100/min, bradycardia as heart rate <60/min and left ventricular hypertrophy (LVH) according to Sokolow-Lyon criteria. List of drugs causing QTc interval prolongation was obtained from the Web site http://www.qtdrugs.org (AZCERT, Tucson, AZ, USA).

**Measurements of the QT interval**

Investigator manually measured the RR and QT intervals from the 12-lead ECG done within 24 hours of emergency services admission. We selected lead V2 for QT measurement as it provides the closest approximation of the longest QT interval. Bazett’s formula (QTc = QT/√RR) was applied for correction of QT intervals for heart rate. Even though there are many formulas for QT interval correction, we specifically had chosen this formula as most of the studies have used this formula. Importantly, studies have shown an increased risk of torsade de pointes and sudden death in patients with prolonged QTc intervals based on this formula. Prolonged QTc was defined as a QTc of ≥ 450 ms in men and ≥460 ms in women based on recommendations.
from the American Heart Association and the American College of Cardiology Foundation. Markedly prolonged QTc interval in either sex was considered a QTc interval of above 500 ms as this had been associated with significantly higher risk for torsade de pointes.\textsuperscript{[15,16]}

**Statistical analysis**

Data was maintained on Microsoft excel sheet, and descriptive statistics was used. The measurable data were subjected to one sample Kolmogrov–Smirnov test for normality of the data. The measurement of central tendency and dispersion of data was calculated by using mean or median and standard deviation or interquartile range (IQR) depending on the normality of data. Normally distributed data were presented by means and standard deviation whereas skewed data were presented by median and IQR. Qualitative variables were presented as number and percentage. Prevalence of prolonged QTc among patients with different illnesses was calculated. Differences in various parameters between study subjects with or without QTc interval prolongation was done using Student’ s t-test for continuous variables with normal distribution and for nonnormally distributed, Mann–Whitney U-test was used. Categorical variables were compared using Chi-square test (or Fisher’s exact tests). The values of $P < 0.05$ were considered statistically significant.

**RESULTS**

This prospective observational study included 279 patients with various illnesses admitted in emergency medical services of a tertiary care hospital over a period of 8 months. There were 175 (62.7\%) males. The mean age of study cohort was 48.82 ± 17.24 years with a minimum age of 18 years and maximum age of 89 years. Various comorbidities were documented in the study cohort, most common were diabetes mellitus and hypertension in 70 (25.1\%) patients each. Other comorbidities noted were coronary artery diseases (CAD) in 65 (23.3\%) patients, chronic liver disease (CLD) in 32 (11.5\%), chronic kidney diseases (CKD) in 25 (9\%), cerebrovascular accidents (CVA) in 18 (6.5\%), chronic obstructive pulmonary disease (COPD) in 17 (6.1\%), and heart failure in 11 (3.9\%) patients. Out of a total 279 study participants, 155 (55.6\%) were found to have hypoalbuminemia. Ninety-four (33.7\%) patients had deranged renal function, 93 (33.30\%) had hypophosphatemia and 71 (25.44\%) patients had hypermagnesemia at presentation. Mean hemoglobin in CKD, and CLD patients at presentation were 8.81 ± 2.04 and 9.11 ± 2.02 g/dL, respectively. Further details of comorbidities and biochemical abnormalities documented in study cohort are elaborated in Tables 1 and 2.

Out of 279 patients, ten patients were taking one or more QTc prolonging drugs (Three each were on ondansetron, trimethoprim – sulfamethoxazole and norfloxacin, respectively, two were on amiodarone, and one was taking amitriptyline) at presentation. Out of these 10 patients, three were taking two QTc prolonging drugs concomitantly, and all of them had prolonged QTc at admission. Remaining seven patients were taking one QTc prolonging drug and three of them had prolonged QTc interval. Six patients were found to have a family history of sudden cardiac death, out of these two were found to have normal QTc interval while 4 had prolonged QTc interval.

The median duration of hospital stay was 6 (IQR: 3–9) days. Out of 279 patients, 200 (76\%) patients were discharged after recovery, 48 (18.25\%) patients died in hospital, 13 (4.9\%) patients took leave against medical advice, and two (0.76\%) were found absconded. Sixteen (5.7\%) patients developed ventricular tachycardia during the period of hospital stay. Out of them, six had survived the event, of them five had been discharged after recovery, and one patient had taken leave against medical advice.

The study aim was to find out the prevalence of QTc prolongation in these patients and prognostic significance of same if any. A total of 95 patients were found to have QTc prolongation with the prevalence of 34.1\%. Fifteen patients (5.4\%) had markedly prolonged QTc interval (QTc>500 ms). Frequency of QTc prolongation in male patients was higher compared to females ([40% vs. 23.3\%], $P = 0.007$). Male patients had more convergence of risk factors as compared to females. Sixty-three (36\%) male patients had one and 54 (30.9\%) had multiple risk factors for prolonged QTc interval. Mean age of patients with prolonged QTc was higher though it was not statistically significant. The further univariate analysis was carried out to compare the frequency of patients with various medical conditions between the groups of patients with prolonged QTc interval with those of patients with not prolonged QTc interval. We found statistically significantly higher number of patients of CKD ($P = 0.047$), CLD ($P < 0.001$), hemorrhagic CVA ($P = 0.026$), and heart failure ($P = 0.009$) with prolonged QTc interval. There was no significant difference in frequency of prolonged QTc interval in patients with diabetes mellitus, hypertension, CAD, COPD, CAP, ischemic CVA, tuberculosis, HIV, sepsis, pancreatitis, and seizure disorder. Various laboratory parameters were also compared between two groups with or without prolonged QTc interval. Among hematological parameters, mean hemoglobin level was significantly lower in patients with prolonged QTc interval ([10.51 ± 2.82 vs. 11.28 ± 2.81 g/dL], $P = 0.032$). Biochemical abnormalities associated with significantly higher percentage of patients with prolonged QTc interval were deranged renal function, hypokalemia and hypercalcemia while the frequency of patients with hypoalbuminemia and other electrolytes abnormalities
was not significantly different in two groups. Various ECG patterns were studied and compared between two groups, out of which patients with left ventricular hypertrophy (LVH) had a significantly higher number of patients with prolonged QTc interval. Details of univariate analysis of the distribution of various comorbidities, biochemical abnormalities and various ECG patterns in two groups are provided in Tables 1 and 2.

Hospital outcome was assessed in the form of the duration of hospital stay, episodes of in-hospital ventricular tachycardia and hospital mortality. There was no difference in duration of hospital stay and frequency of in-hospital mortality between two groups. Study participants with prolonged QTc interval had significantly higher episodes of ventricular tachycardia ($P = 0.008$). Out of 279, 15 patients (5.4%) had markedly prolonged QTc interval ($\text{QTc} > 500 \text{ ms}$). On subgroup analysis, patients with marked QTc prolongation had significantly lower hemoglobin, higher creatinine level and more episodes of ventricular tachycardia. This subgroup was also found to have significantly longer hospital stay ($P = 0.007$) and higher in-hospital mortality ($P = 0.029$) [Table 3]. Twenty patients (22.1%) who had prolonged QTc interval at presentation, received one or more drugs with propensity to cause QTc prolongation during the hospital stay.

**DISCUSSION**

This was a single-center prospective observational study undertaken in patients with varied medical illnesses admitted in emergency medical services of a tertiary care hospital. Out of 279 patients recruited, 95 (34.1%) were found to have prolonged QTc interval at presentation. Fifteen patients (5.4%) had markedly prolonged QT interval ($\text{QTc} > 500 \text{ ms}$). CKD, CLD, hemorrhagic CVA, and heart failure were the medical conditions associated

## Table 1: Comparison of demographic profile, comorbidities, biochemical abnormalities, electrocardiography pattern, duration of hospital stay, and hospital mortality in 279 patients according to QTc interval at presentation to emergency medical services

| Variables | Whole cohort ($n = 279$) | Not prolonged QTc ($n = 184$) | Prolonged QTc ($n = 95$) | P |
|-----------|--------------------------|-------------------------------|--------------------------|---|
| Age (years), mean ± SD | 48.82 ± 17.2 | 48.18 ± 17.6 | 50.07 ± 16.6 | 0.385 |
| Male, n (%) | 175 (62.7) | 105 (57.1) | 70 (73.7) | 0.007 |
| Comorbidities, n (%) | | | | |
| Diabetes mellitus | 70 (25.1) | 44 (23.9) | 26 (27.4) | 0.528 |
| Hypertension | 70 (25.1) | 46 (25) | 24 (25.3) | 0.962 |
| Coronary artery disease | 65 (23.2) | 44 (23.9) | 21 (22.1) | 0.735 |
| CLD | 32 (11.4) | 11 (6) | 21 (22.1) | <0.001 |
| CKD | 25 (8.9) | 12 (6.5) | 13 (13.7) | 0.047 |
| Ischemic CVA | 18 (6.5) | 12 (6.5) | 6 (6.3) | 0.947 |
| Pneumonia | 18 (6.5) | 11 (6) | 7 (7.4) | 0.654 |
| Sepsis | 18 (6.5) | 9 (4.9) | 9 (9.5) | 0.140 |
| Hemorrhagic CVA | 17 (6.1) | 7 (3.8) | 10 (10.5) | 0.026 |
| COPD | 17 (6.1) | 9 (4.9) | 8 (8.4) | 0.243 |
| Heart failure | 11 (3.9) | 3 (1.6) | 8 (8.4) | 0.009 |
| Tuberculosis | 7 (2.5) | 7 (3.8) | 0 | 0.054 |
| Pancreatitis | 6 (2.1) | 3 (1.6) | 3 (3.2) | 0.413 |
| Seizure | 6 (2.1) | 5 (2.7) | 1 (1.1) | 0.667 |
| HIV | 3 (1) | 2 (1.1) | 1 (1.1) | 1.000 |
| Laboratory abnormality, n (%) | | | | |
| Hypoalbuminemia | 155 (54.9) | 96 (52.2) | 59 (62.1) | 0.114 |
| Hypocalcemia | 99 (35.3) | 71 (38.6) | 28 (29.5) | 0.132 |
| Hyperglycemia | 20 (7.2) | 12 (6.5) | 8 (8.4) | 0.560 |
| Hypokalemia | 42 (15) | 23 (12.5) | 19 (20) | 0.097 |
| Hypophosphatemia | 38 (13.6) | 19 (10.3) | 19 (20) | 0.026 |
| Hypoproteinemia | 61 (22) | 42 (23.9) | 12 (12.6) | 0.007 |
| Hypocalcemia | 61 (22) | 42 (23.9) | 12 (12.6) | 0.007 |
| Hypophosphatemia | 93 (33.2) | 65 (35.3) | 28 (29.5) | 0.326 |
| Hypertension | 47 (16.9) | 30 (16.3) | 17 (17.9) | 0.737 |
| Hypokalemia | 47 (16.9) | 30 (16.3) | 17 (17.9) | 0.737 |
| Seizure | 71 (25.4) | 45 (24.5) | 26 (27.4) | 0.597 |
| Hypomagnesemia | 16 (5.7) | 9 (4.9) | 7 (7.4) | 0.399 |
| ECG pattern, n (%) | | | | |
| Sinus tachycardia | 104 (37.1) | 75 (40.8) | 29 (30.5) | 0.094 |
| MI | 46 (16.4) | 32 (17.4) | 14 (14.7) | 0.571 |
| LVH | 21 | 4 (2.2) | 17 (17.9) | <0.001 |
| Hypertension | 5 | 3 (1.6) | 2 (2.1) | 1.000 |
| BBB | 5 | 2 (1.1) | 3 (3.2) | 0.341 |
| AV block | 3 | 1 (0.5) | 2 (2.1) | 0.268 |
| QTC interval (ms), mean ± SD | 433.73 ± 43.4 | 409.90 ± 31.7 | 479.87 ± 19.1 | <0.001 |
| Ventricular tachycardia, n (%) | 16 (5.73) | 5 (2.7) | 11 (11.6) | 0.008 |
| Hospital stay (days), median (IQR) | 6.0 (3.0-9.0) | 6.0 (2.0-10.0) | 4.5 (2.8-8.0) | 0.213 |
| Hospital mortality, n (%) | 48 (17.2) | 30 (16.3) | 18.0 (18.9) | 0.747 |

| AV: Atrioventricular, IQR: Interquartile range, ECG: Electrocardiography, SD: Standard deviation |

CLD: Chronic liver disease, CKD: Chronic kidney disease, CVA: Cerebrovascular accident, COPD: Chronic obstructive pulmonary disease, HIV: Human immunodeficiency virus infection, RFT: Renal function test, MI: Myocardial infarction, LVH: Left ventricular hypertrophy, BBB: Bundle branch block, AV: Atrioventricular, IQR: Interquartile range, ECG: Electrocardiography, SD: Standard deviation |
Table 2: Comparison of baseline laboratory parameters of 279 patients according to QTc interval at presentation to emergency medical services

| Variables                  | Whole cohort (n = 279) | Not prolonged QTc (n = 184) | P       |
|----------------------------|------------------------|-----------------------------|---------|
| Hemoglobin (g/dl)          | 10.9 ± 2.8             | 11.3 ± 2.8                  | 0.024   |
| TLC (/µL)                  | 12,276.6 ± 7457.9      | 12,089.7 ± 7645.4           | 0.563   |
| Platelet (x 10^9/µL)       | 211.6 ± 132.2          | 217.8 ± 133.8               | 0.280   |
| Sodium (mEq/L)             | 136.6 ± 7.3            | 136.1 ± 7.3                 | 0.078   |
| Potassium (mEq/L)          | 4.2 ± 0.8              | 4.2 ± 0.7                   | 0.530   |
| Urea (mg/dl), median (IQR) | 43.0 (27.0-85.0)        | 36.5 (26.0-76.5)            | 0.009   |
| Creatinine (mg/dl), median (IQR) | 1.0 (1.0-2.0)     | 1.0 (0.6-2.0)               | 0.051   |
| SGOT (U/L), median (IQR)   | 41.0 (28.0-86.0)        | 40.5 (27.0-74.5)            | 0.520   |
| SGPT (U/L), median (IQR)   | 29.0 (19.0-56.0)        | 27.0 (19.0-58.0)            | 0.712   |
| ALP (U/L), median (IQR)    | 115.0 (89.0-179.0)      | 114.0 (91.3-178.8)          | 0.729   |
| Total bilirubin (mg/dl), median (IQR) | 1.0 (0.5-4.0)      | 1.0 (0.1-4.0)               | 0.008   |
| Total protein (g/dl)       | 6.5 ± 1.0              | 6.5 ± 1.1                   | 0.902   |
| Serum albumin (g/dl)       | 3.2 ± 0.9              | 3.2 ± 0.9                   | 0.616   |
| RBS (mg/dl)                | 130.7 ± 67.8           | 127.7 ± 63.3                | 0.302   |
| Serum calcium (mg/dl)      | 9.10 ± 0.8             | 8.99 ± 0.7                  | 0.001   |
| Serum phosphorus           | 3.51 ± 1.7             | 3.43 ± 1.6                  | 0.270   |
| Serum magnesium            | 2.27 ± 0.6             | 2.26 ± 0.6                  | 0.865   |

TLC: Total leucocyte count, IQR: Interquartile range, SGOT: Serum glutamate oxaloacetate transaminase, SGPT: Serum glutamate pyruvate transaminase, ALP: Alkaline phosphatase, RBS: Random blood sugar

Table 3: Comparison of various demographic characteristics, vital parameters, comorbidities, and laboratory abnormalities in patients with or without markedly prolonged QTc interval at presentation to emergency medical services

| Variables                  | Patients with QTc | >500 ms (n = 15) | P     |
|----------------------------|-------------------|------------------|-------|
| Age (years), mean ± SD     | 48.8 ± 17.1       | 48.4 ± 15.4      | 0.947 |
| Vital signs at presentation, mean ± SD |                     |                  |       |
| Systolic blood pressure (mmHg) | 123.7 ± 27.2      | 118.0 ± 36.3     | 0.369 |
| Diastolic blood pressure (mmHg) | 75.6 ± 15.1       | 71.3 ± 20.3      | 0.383 |
| Pulse rate (/min)          | 95.1 ± 19.9       | 97.5 ± 26.9      | 0.533 |
| Comorbidities, n (%)       |                   |                  |       |
| Diabetes mellitus          | 68 (25.8)         | 2 (13.3)         | 0.370 |
| Hypertension               | 67 (25.4)         | 3 (20)           | 0.768 |
| CAD                        | 61 (23.1)         | 4 (26.7)         | 0.756 |
| CVA                        | 17 (6.4)          | 1 (6.6)          | 1.000 |
| CKD                        | 23 (8.7)          | 2 (13.3)         | 0.632 |
| COPD                       | 15 (5.6)          | 2 (13.3)         | 0.232 |
| Liver cirrhosis            | 28 (10.6)         | 4 (26.6)         | 0.078 |
| Lab values at presentation |                   |                  |       |
| Hemoglobin (g/dl)          | 11.2 ± 2.8        | 8.7 ± 2.8        | 0.021 |
| TLC (mm³)                  | 12,268 ± 7298     | 12,400 ± 10,186  | 0.609 |
| Serum creatinine (mg/dl)   | 1.8 ± 1.7        | 2.8 ± 2.7        | 0.042 |
| Outcome, n (%)             |                   |                  |       |
| Ventricular tachycardia     | 9 (3.4)           | 7 (46.7)         | <0.001|
| Hospital stay (days), median (IQR) | 5.0 (3.0-8.8) | 3.0 (2.0-4.0) | 0.007 |
| Hospital mortality         | 41 (15.5)         | 7 (46.7)         | 0.029 |

CAD: Coronary artery disease, CVA: Cerebrovascular accident, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, TLC: Total leucocyte count, IQR: Interquartile range, SD: Standard deviation

with QTc prolongation. Among laboratory abnormality, patients with low hemoglobin, with deranged renal parameters and with hypokalemia had a greater share of patients with prolonged QTc interval. Subgroup of patients with markedly prolonged QTc interval had greater episodes of ventricular tachycardia and also significantly higher in-hospital mortality rate.

QTc interval is calculated from beginning of Q wave to the end of T wave on surface ECG, and thus it measures the duration of both cardiac depolarization and repolarization. Corrected QT interval is calculated by using various formulas, of them Bazette’s formula is most widely accepted. QTc interval is affected by various factors including increasing age, female gender, several medical conditions, electrolyte abnormalities, and many drugs. Pathogenesis of QTc interval prolongation includes alteration of ion channels and intracellular potassium leading to heterogeneous intra-cardiac repolarization and early after-depolarization. Furthermore, structural alteration in cardiomyocytes and conduction pathways may have added role in causing repolarization abnormalities leading to QTc interval prolongation. Prolonged QTc interval, especially duration of repolarization is well known to cause life-threatening cardiac arrhythmias including TdP and ventricular tachycardia.

Various studies regarding the prevalence and prognostic significance of prolonged QTc interval have been
undertaken in selected medical conditions including liver cirrhosis, intracranial hemorrhage, HIV, CAD, but little is known about the prevalence of QTc prolongation in nonselected emergency medical patients having a convergence of many potentially QTc prolonging medical conditions, electrolyte abnormalities, and medications. This study was conducted to find out the prevalence of prolonged QTc interval in emergency medical patients, factors predisposing it and prognostic significance in terms of duration of hospital stay, occurrence of ventricular tachycardia and hospital mortality.

The study shows a high prevalence of QTc interval prolongation at the time of presentation to emergency services in patients with varied medical illnesses. This finding is consistent with a retrospective study in nonselected emergency medical patients that reported 35% prevalence rate. In a retrospective review of patients identified through an institution-wide, electronic medical record-based QT alert system, out of 7522 patients with ECG at the emergency department, 93 (1.2%) patients had prolonged QTc interval, triggering electronic QT alert. These patients had more than one QT-prolonging conditions such as electrolyte disturbances in 51%, a QT-prolonging condition in 56%, and QT-prolonging drugs in 77% of them. High prevalence of prolonged QTc interval was also reported in a study conducted in medical ICU patients in India. Prevalence of QTc prolongation in index study though was more than reported prevalence of 22.3% in a cross-sectional study conducted at Swiss teaching hospital in medical inpatients. Higher prevalence of QTc prolongation in the study was possibly due to the recruitment of acutely ill patients with a variety of illnesses presenting in emergency medical services who often had one or more risk factors for QTc prolongation including the prescription of QTc prolonging drugs. Prevalence of markedly prolonged QTc interval noted in our study is consistent with findings reported in these older studies. In this study, significantly higher number of male patients had prolonged QTc interval. This observation is consistent with the findings reported in a study by Pasquier et al. Many of the previous studies, on the contrary, reported a higher number of female patients with prolonged QTc interval. It is postulated that sex hormones modulate cardiac repolarization. Testosterone by increasing IKr causes shortening of QTc interval and decrease the risk of TdP. In this study, the high prevalence of QTc prolongation in male gender can be explained by the convergence of many potential risk factors for QTc prolongation in these acutely sick male patients.

Of various medical comorbidities, patient’s with hemorrhagic CVA, CKD, CLD, and decompensated heart failure were found to have significantly more frequent occurrence of prolonged QTc interval in this index study. Similar observations were reported in previous studies done in patients selectively having these illnesses. Studies by Cichoż-Lach et al. and Day et al. in CLD patients reported a high prevalence of QTc prolongation in these patients, especially in alcohol and chronic hepatitis C related cirrhosis. In cirrhotic cardiomyopathy, abnormality in a pathway involving β adrenergic signaling, hypertrophy of myocardium and defects in various ion channels are responsible for repolarization abnormalities and prolonged QTc interval. In a study by Voiculescu et al., chronic renal failure patients showed a high prevalence of QTc prolongation. It is postulated that structural alteration (LVH and cardiomyopathy) and ion channel defect secondary to dyselectrolytemia cause repolarization abnormalities and diastolic dysfunction in these patients. Nigerian study in CHF patients reported a high prevalence of QTc prolongation and poor prognosis in patients with long QTc interval in these patients. It may be explained by cardiac structural defects and dyselectrolytemias secondary to diuretic therapy responsible for QTc prolongation. A study by Purushotum et al. on ECG abnormalities in CVA patients reported a high prevalence of QTc prolongation in these patients. In a retrospective study among nonselected medical patients, Seftchick et al. reported that QTc prolongation was significantly associated with structural heart disease, stroke, and renal failure. Cross-sectional study in unselected medical inpatients by Pasquier et al. also showed liver cirrhosis as a risk factor for QTc prolongation. In a prospective, observational study in an adult intensive care unit involving 1039 patients who underwent continuous QTc monitoring, QTc prolongation was detected in 24% of patients. Medications with the potential to cause QTc prolongation, female gender, low serum potassium and serum calcium levels, high blood sugar, deranged renal function, history of stroke, and hypothyroidism were found to be predictors of QTc prolongation.

Of various hematological parameters, mean hemoglobin was significantly lower in patients with prolonged QTc interval, and even more, severe anemia was noted in patients with QTc interval >500 ms. A Serbian study in chronic anemia patients, without any comorbidity also showed significantly prolonged QTc interval in these anemic patients. In the index study, prolonged QTc in patients with low hemoglobin can be explained by multiple comorbidities such as CLD, CKD, and infective/inflammatory states which in fact were associated with prolonged QTc interval and concurrently were found to have low hemoglobin as well.

Of biochemical parameters, deranged renal function test was associated with significantly prolonged QTc interval. This finding is in consonance with results of a retrospective study done in emergency medical patients and another prospective, observational study undertaken in an adult intensive care unit involving 1,039 patients. A study carried out in medical ICU in India though
did not reveal a significant association with deranged renal functions.\textsuperscript{[19]} Of various electrolyte abnormalities, hypokalemia was more frequent in prolonged QTc cohort. A study by Pasquier et al. and QTIP study also reported hypokalemia as a risk factor for prolonged QTc.\textsuperscript{[20,21]} Hypokalemia causes QTc prolongation by paradoxically decreasing IKr by enhanced activation or exaggerated competitive block by sodium. Among other electrolyte abnormalities, hypercalcemia was found to be significantly associated with QTc prolongation, and hypocalcemia had inverse association with QTc interval. This paradoxical result might be due to a small number of patients with hypercalcemia. In hypocalcemic group, we did not have ionized calcium reports, which could have given us true serum calcium values and most likely had led to this unexpected result. Previous studies including a study by Seftchick et al. in emergency medical patients showed prolongation of QTc interval with hypocalcemia.\textsuperscript{[27]} Other studies including study in medical inpatients and study in elderly pneumonia patients did not reveal any association of hypo or hypercalcemia with QTc interval.\textsuperscript{[20,24]} Of various electrocardiographic abnormalities, LVH was significantly associated with prolonged QTc interval as shown by the previous study which reported LVH as a risk factor for QTc prolongation.\textsuperscript{[25]} LVH causes altered conduction and ventricular repolarization and QTc prolongation.

The study showed that as many as 21% of patients with prolonged QTc interval were receiving one or more QT prolonging drugs during their hospital stay. Previous studies in nonselective emergency medical patients also showed that frequency of prescription of QTc prolonging drugs was significantly higher in these patients.\textsuperscript{[4,5,19,20]} Study by Tisdale et al. in cardiac care unit revealed 26% of patients who already had prolonged QTc, received one or more QTc prolonging drugs and 18% of them had cardiac events.\textsuperscript{[26]} QTIP study also showed a high prevalence of prolonged QTc interval and a significant proportion of patients receiving one or more QTc prolonging drugs.\textsuperscript{[21]} This is an important modifiable risk factor as studies have revealed that pharmacological intervention by withholding or prescribing alternative medications led to normalization of QTc interval and potentially ameliorated the risk of life-threatening cardiac arrhythmias.\textsuperscript{[16-26]}

In this study, prognostic significance in terms of duration of hospital stay and hospital mortality was not different in the two study groups, although patients with markedly prolonged QTc interval had significantly higher hospital mortality. The previous studies showed mixed results in terms of outcome in these patients. The Oregon sudden unexpected death study and Rotterdam study suggested increased mortality in patients with prolonged QTc interval and showed linear relationship between degree of QTc prolongation and all-cause mortality, while retrospective study by Seftchick et al. and cross-sectional study at Swiss teaching hospital did not show poor outcome in terms of increased mortality in the patients with prolonged QTc interval.\textsuperscript{[6,17,20,27]} In Indian study, prognosis was worse in patient of prolonged QTc interval with Odds ratio of 3 for adverse outcome from Intensive Care Unit.\textsuperscript{[19]} In a retrospective review of 7522 patients with ECG done at emergency services, an electronic QT alert was activated in 93 (1.2%). All-cause mortality was significantly higher (39%) for QT alert patients than patient’s without an electronic alert (27%).\textsuperscript{[18]} In this study, rate of ventricular arrhythmias was higher in patients with prolonged QTc interval group patients and patients with markedly prolonged QTc interval had significantly higher hospital mortality rate.

The study had several limitations. First, it was a single center study undertaken in patients presenting in emergency medical services, and hence, the findings of this study cannot be extrapolated to patients from different clinical set up. The study also had relatively small study population. Second, consecutive patients could not be recruited. Third, only one time assessment of ECG at presentation was done for QTc calculation. Also continuous ECG monitoring was not done so episodes of QTc prolongation during hospital course could have been missed.

CONCLUSION

The prevalence of prolonged QTc interval is high in Indian emergency medical patients. There was no difference in hospital mortality though on subgroup analysis, patients with markedly prolonged QTc interval had significantly more episodes of in-hospital ventricular tachycardia and hospital mortality. A variety of factors including certain comorbidities, biochemical abnormalities and drugs were associated with QTc prolongation. Based on findings of index study, it would be prudent to closely monitor QTc interval, especially in patients with certain comorbidities and biochemical abnormalities, avoid medications associated with QTc prolongation.

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Conflicts of interest
There are no conflicts of interest.

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