The Study Of Prolonged Qtc Interval As A Predictor Of Outcome In Patients Admitted With Medical Emergencies

by

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Dissertation submitted to

In partial fulfillment for the degree of

DOCTOR OF MEDICINE
IN
GENERAL MEDICINE

Under the Guidance of

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DEPARTMENT OF MEDICINE

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2019

LIST OF ABBREVIATIONS USED

SCD	:	SUDDEN CARDIAC DEATH
SCA	:	SUDDEN CARDIAC ARREST
ED	:	EMERGENCY DEPARTMENT
QTc	:	CORRECTED QT INTERVAL
TdP	:	TORSEDES DE POINTES
LQTS	:	LONG QT SYNDROME
ESRD	:	END STAGE RENAL DISEASE
RAS	:	RENIN ANGIOTENSIN SYSTEM
DM	:	DIABETES MILLIETUS
CYP	:	CYTOCHROME P ENZYME
ACE	:	ANGIOTENSIN CONVERTASE ENZYME
HF	:	HEART FAILURE
PE	:	PULMONARY EDEMA
CS	:	CARDIOGENIC SHOCK
STEMI	:	ST ELEVATION MYOCARDIAL INFARCTION

ACS	:	ACUTE CORONARY SYNDROME
VPC	:	VENTRICULAR PREMATURE COMPLEXES
VT	:	VENTRICULAR TACHYCARDIA
MI	:	MYOCARDIAL INFARCTION

ABSTRACT

AIM: To study the QTc interval in patients admitted as medical emergencies and to predict in-hospital outcomes of the patients

MATERIAL and METHODS: Prospective observational study carried out in 312 patients admitted in our hospital with Acute medical emergency. Clinical, echocardiographic and laboratory profile and in-hospital outcome of patients with medical emergencies were assessed as a part of work up. QTc interval was calculated by using Bazzets formula with in 24hrs of admission by using standerd 12 lead ECG . Patients with QTc ≥0.44 sec in male and QTc ≥0.46 sec in females were taken as the cutoff value for prolonged QTc interval and values were compared with outcome and duration of stay in hospital . The patients during hospital stay and were observed for out come like duration of stay ,development of major complications or worsening of symptoms ,and death were assessed in relation to the QTc interval .

RESULTS: Prolonged QTc interval ≥ 0.44sec in male and ≥ 0.46sec in female was observed in 113 patients (36.2%). In the study 137(43.9%) patients had cardiovascular emergencies in which 55(48.7%) patients had prolonged QTc,112(35.9%) had presented with neurological emergencies among them 34(30.1%) patients had prolonged QTc,66(21.2%) patients had respiratory emergencies showing QTc prolongation in 27 (23.9%) patients,28(9%)patients had presented with gastrointestinal emergencies have 9(8%) patients with prolonged QTc,35(11.2%) patients had renal emergencies had 9 (7%) patients with long QTc,12(3.4%) patients had endocrine emergenicies like DKA and HHS had 5(4.4%) patients with long QTc .outcome of the patients showing duration of stay was prolonged and deaths were relatively high in patients with long QTc.

CONCLUSION: prolonged QTc interval was found to be an important predictor of in-hospital outcome of the patient .patients with prolonged QTc were showing bad outcome when compared with the patients with normal QTc interval in terms of duration of stay ,improvement and death .

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INTRODUCTION

Electrocardiogram is a invaluable and easily available bedside non-invasive tool in assessing acutely ill patients. Of all the ECG measurements QT interval is one of the important predictors of outcome in critically ill patients[4]. The QT interval represents the onset of electrical depolarization of the ventricles to the end of repolarization of the heart. This interval is measured from the beginning of the QRS complex to the end of the T wave. It is influenced by both physiological and pathological factors including emotional stress, gender, obesity, food consumption, and electrolyte disturbances, as well as diseases of the heart muscle and coronary artery disease. Various drugs can also cause prolonged QT interval which are commonly used in critically ill patients.[1]

QT interval varies inversely with heart rate and is therefore corrected by formulas that take this variation into account; the corrected interval is designated "QTc". The cause of prolongation may be multi factorial but is generally congenital (e.g., long QT syndrome) or acquired (e.g., induced by medications).QTc can be calculated by Bazett's formula QT/RR. QTc prolongation is defined as QTc interval of more than 450 ms for men and that of 460 ms for women.

Patients admitted as medical emergencies has variety of age group and primary disease. These patients have high morbidity and mortality. The acutely ill patients are at increased risk of developing prolonged QTc and Torsedes de pointes due to risk factors, such as renal or hepatic dysfunction, electrolyte abnormalities, brady arrhythmias and increased exposure to drugs causing prolonged QTc interval.

Medical emergencies amount to major heathcare burden world wide. High-quality emergency care has the potential to address and prevent a substantial portion of morbidity and mortality. Its vital role in health systems is being acknowledged, as evidenced by rising number of emergency departments handling growing load of patient volumes over the last few decades. Few high-income countrieshave well-established emergency care systems, but data about the burden of emergency conditions, or how frequently patients seek emergency care is unavailable. It is often difficult to collect this data due to unpredictable and time-sensitive nature of medical emergencies, especially in low- and middle- income countries (LMICs). Systematic analysis of available data is difficult because emergency care is frequently delivered across a variety of settings such as clinics and outpatient departments in absence of formal EDs, even in some high income countries. This lack of basic information about emergency care delivery and the burden of emergency conditions has stalled attempts to understand and improve emergency care, particularly in LMICs(1)

Out of all emergencies Cardiovascular emergencies amounts around 12%, as the second most common cause of all ED visits, each year. This contributes around 8 million patients with symptoms and signs of chest pain and angina equivalents(2). Emergency physicians are required to arrestprioritize e patients and treat according to the severity of the condition ,this kind of accurate assessment and immediate approach to treat provide better outcomes in emergency department. Sudden cardiac arrest (SCA) in the ED is increasingly encountered among younger age groups. Most of the SCA are preceded by a event of arrhythmias which might associated with prolonged QT interval.Despite advances in resuscitation medicine, survival rates of both in-hospital and out-of-hospital

SCA remains poor. Improving prehospital care, and control of risk factors will decrease the incidence, and improve the outcome of SCA(3).

Critically ill patients had first cardiac monitoring around 65 years ago for, but now it has become a routine monitor for causality patients. (4).Current strategies Cardiac monitoring include 12-lead ECGand bedside detectors, which helps physicians for identifying irregular rhythm of heart , lack of blood flow or oxygen to the heart muscle ,STT changes , and QT-interval variations .If initial arrest rhythm that is shockable and primary underlying disease of cardiac origin, the survival rates are better compared to noncardiac emergency. Most Indian studies on SCA are hospital-based, which lack the causes and outcomes factors. Though a study at busy ED of Indian tertiary care hospital had largest cohort of SCAs, and describes the profile of cardiac arrestpatients and the associated factors of outcome(3).

AIMS AND OBJECTIVES

To study the QTc interval in patients admitted as medical emergencies and to predict in-hospital outcomes of the patients

REVIEW OF LITERATURE

Common medical Medical emergencies

1.Cardiovascular emergencies

Acute coronary syndromes

Cardiogenic shock

Syncope

Acute heart failure

Valvular emergencies

Pulmomonary embolism

Hypertension related emergencies

Aortic dissection

Myocarditis

Cardiomyopathies in failure

Pericardial diseases

2.Pulmonary emergencies

Respiratory failure /distress

Acute severe asthama

Acute exacerebation of chronic obstructive pulmonary disease

Spontaneous and iatrogenic pneumothorax

Acute bronchitis

Pneumonia

Hemoptysis

Novel respiratory infections

3.Neurological emergencies

Stoke syndromes and spontaneous subarchnoid hemorrhage

Altered mentation and coma

Seizures and status epilepticus

Central nervous system and spinal infections

Acute vertigo and ataxia

Acute peripheral neurologic lesions

Severe Headache

4.Endocrine emergencies

Diabetic emergencies

Alcoholic ketoacidosis

Adrenal insufficiency

Thyroid emergencies

5.hematooncology

Transfusion related reactions

Acquired bleeding disorders

Anemia with failure

Emergency complications of malignancy

6.Renal emergencies

Acute kidney injury

Rhabdomyolysis

Emergencies in dialysis and renal failure

Acute on CKD

7.GI emergencies

Gastro intestinal bleeding

Acute pancreatitis

Acute hepatitis

Acute liver failure

Hepatic encephalopathy

8.Toxicology

Consumption of any poison

Drug overdose

Snake bite

Unkown bite/sting

9.Others

Electric shock

Hypothermia /hyperthermia

Exposure to toxic gases

Alcohol withdrawl

Sepsis /septic shock

Electrolyte disturbance

Metabolic disorders

Electrocardiography

In contrast to many other techniques in cardiology, the ECG is simple, small, mobile, universally available and cheap, and therefore particularly attractive.(5)

2.1 HISTORY

Willem Einthoven introduced the string galvanometer, and was honored the Nobel Prize for medicine or study of normal function of living organisms and their parts(1924). The 12-lead ECG has become primary investigation of choice for every patient with cardiac complaints. We can detect major portion of cardiac problems by simple ECG like most of the fatal arrhythmias and acute coronary syndrome(5).

The standard for ECG analysis changed since 25 years . Interpretation is mainly based on visual assessment. There are certain clinical needs which are not achieved in the various field of cardiology. There are new devices which helps in ECG interpretation such as clear images , analysis of structural features, frequency content and vectorcardiography(5).

Research assessing repolarization variability can be assessed based on single beat monitoring by standard 12-lead ECG.QTc is one of the simplest marker for assessing repolarizationheterogeneity .prolonged QTc is a risk factor for sudden cardiac deaths even in general population along with long QT syndrome patients. The patients who recovered from sudden cardiac death ,their ECG shows early repolarization changes which may precipitate further cardiac events.(5)

Even present day 24-h monitoring with Halter monitors can not detect arrhythmias which encounters rarely in special situations . There are new generation patch ECG monitors which attach directly to the skin ,no wires and electrodes.the main advantage of this monitor is you can use this with out immobilizing the patient. These monitors provide long term un interrupted and long term monitoring ,and these provide good adhesion to skin and water resistant(6).

1.2 NORMAL ECG

The 12-lead ECG is the standard which is used for assessing recognition and analyzing for the patient with any discomfort in the chest, the anginal equivalents, till date.It is a fastest, method of assessment of patient cardiac status and providing valuable data on electrical activity of heart by detecting changes in membrane potential throughout the cardiac cycle. standard 12 leadECG is most commonly used diagnostic tool in emergency department ,because it is easy to use ,non invasive, easily available ,accessible and cheap .it provides significant information and clues for the diagnosis of cardiac arrhythmias acute myocardial infarction and provides other information.according to European society of cardiology and American college of cardiology and the American heart association any patient enters to emergency department ECG should be taken in with in 10 minutes of arrival.This recommendations are strictly followed because delay in recording of ECG has association with worst outcome.early recognition of ST changes will help the better outcome in a case of acute MI and life saving reperfusion therapy(2).

The 12-lead ECG has 10 electrode. They document the impulses of cardiac muscle where the six chest leads are placed over the anterior chest wall over the heart ,the limb leads are kept on the distal part of limbs .which is the preferred and standard method for taking

resting 12-lead ECG acquisition, and another method is like placing the leads over the junction where the limbs attach to the trunk (Mason-Liker).this is used basically when patient require continuous ECG monitoring like in hospital patients who is critically ill and in case of exercise testing (Figure1)(9). This kind of arrangement of electrodes will records the electrical activity of the heart from all possible directions and mapping of electrical axis. Positive and negative deflection over the ECG are based on the impulse travelling through electrodes.if impulse going towards electrode it shows positive deflection ,if impulse goes away from the electrodes it gives negative deflection. Morphology of wave form will change by using different limb lead positioning which leads to misinterpretation of ECG analysis by computer and you star treating patient like for myocardial infarction. So staff need regular training sessions and guidance for the proper positioning of the electrode for reliability and detailed cardiac surveillance (2).

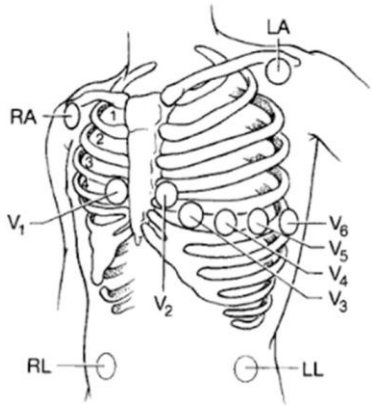


Figure. 1: Mason-Liker positioning of electrodes for continuous ECG monitoring . LA-left arm,LL-left leg,R- right arm, RL- right leg. (2)

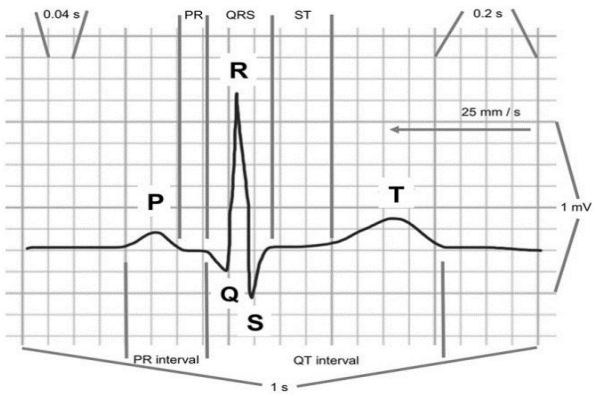
Normal ECG has 1-mm grid .it moves with the speed of 25mm/sec.composed with small and large boxes .each small is equal to 0.04sec,five small boxes forms one large box that

is isequal to 0.2 sec.so five large boxes will be covered in 1sec,vertically each two big boxes covers 10mv . A signal frequency of one large square is equal to a rate of 300/min.(1)(10) .

The normal ECG has p wave,QRScomplex followed by t wave with a rate of 60 to 100beats per minute. (Fig. 2A) .it is called as normal sinus rhythm,if heart rate is more than 100/min it is sinus tachycardia,if it is less than 60/min sinus bradycardia(10).

The P wave is reflects the atrial contraction . on ECG p wave show low amplitude due to less muscle mass of atrium . normal p wave is inverted in lead aVR. The PR interval is a time interval between atrial and ventricular depolarization. Measured as distance between beginning of p wave and beginning of QRS complex which is around 0.12 to 0.2 sec normally. The ST segment is ventricles are depolarization and T wave is repolarization.(10).

The QRS complex reflects depolarization of ventricles. The normal QRS complex is less than 100ms. QT interval is a distance between beginning of QRS complex to the end of T wave.in general normal corrected QT should be less than 440ms.(Figure. 2)(10).



1.3 The QT interval

The QT interval is an electrocardiographic representation of ventricular repolarization and depolarization. It is measured from the start of the QRS complex until the T wave termination. It lengthens with bradycardia and shortens with tachycardia –it is recommended to calculate corrected QT.lengthening of QTc is triggering event for arrhythmias like Torsade de pointes,ventricular fibrillations ,early after depolarization and may present with sudden cardiac death(11).

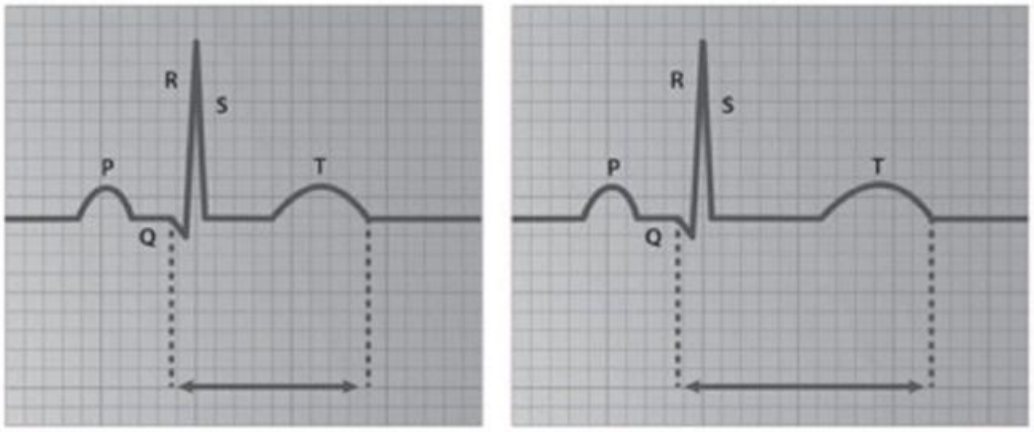


Figure 3: The QT interval. Normal electrocardiogram(Left). Prolonged QT interval(Right).

QT Interval: The QT interval includes the QRS complex, ST segment, and T wave corresponding to phases 0 to 3 of the action potential. It is measured from the beginning of the QRS complex to the end of the T wave. In assessing the duration of the QT interval, multiple leads should be selected and the QT interval is the longest QT that can be measured in the whole 12-lead ECG recording. To determine end of the T wave tangent should be drawn from the steepest downslope which intersect with baseline should be taken as end of T wave.(11)

In presence of notching of T wave end of the entire complex to be taken . The end of the T wave completes the normal cardiac cycle, which includes the P wave, the QRS complex, and the T wave. The T wave, however, may often be followed by a small positive deflection called the U wave. The U wave is not always present, but it may be the last complex in the ECG to be recorded.The size of the normal U wave is small, measuring approximately one-tenth of the size of the T wave.(11)

U waves are best recorded in the anterior precordial leads V2 and V3 because these chest leads are closest to the ventricular myocardium.

U waves are usually visible when the heart rate is slow (65 bpm) and rarely visible with faster heart rates (95 bpm). U waves are not included in T wave for QT calculation .it is difficult to differentiate T from U wave some times and looks like bifid T wave which is characteristic of a congenital LQTS(12).

Corrected QT interval (QTC)

the QT interval is affected by heart rate. It becomes longer when the heart rate is slower and shorter when the heart rate is faster. The QT interval therefore should always be corrected for heart rate.ThecorrectedQT interval is the QTc . For the correct analysis if QT interval and compare measurements at different heart rate and time points there should be adequate rate correction which has to be reliable for the risk stratification(12)

QTc interval has never proved as the predictor for the TdP.Before commencement of a proarrhythmiaagent if a patient has incorrect QT value of 0.46 sec and same value after 8 hrs then at these 2 points the QTc will be varied if the heart rate is changed. For example

: the QTC measurements before the drug is 0.44 and after the drug is 0.52, if predrug heart rate is 70 and post drug rate is 100.

A normal QTC in women is 0.46 seconds and in men is 0.44 seconds. There will be higher risk of torsade's de pointes in both the sex if the QTC is 0.50 second. There are certain exception which is necessary to point out such as there will be marked lengthening of QT interval due to intake of amiodarone with it doesn't have any risk for proarrhythmia (12).

Correction for heart rate

Bazett's formula

The simplest and most commonly used formula for correcting the QT interval for heart rate is the Bazett formula shown here. named after physiologist Henry Cuthbert Bazett (1885-1950), The normal QTc should not exceed 0.42 seconds inmen and 0.44 seconds in women. The QTc is prolonged when it measures 0.44 seconds in men and0.46 seconds in women and children. An easy rule to remember in calculating the QTc when the heart rate is 70 bpm is that the QTc is normal (0.46 seconds) if the QT interval is equal to or less than half the R-R interval

$$QTcB = \frac{QT}{\sqrt{RR}}$$

where QTcB is the QT interval corrected for heart rate, and RR is the interval from the onset of one QRS complex to the onset of

the next QRS complex, *measured in seconds*, often derived from the heart rate (HR) as 60/HR. Here **QT** is measured in milliseconds, hence the result comes in seconds per square root of milliseconds. This QT correction formula is g not considered accurate, because it over-corrects at high heart rates and under-corrects at low heart rates(13).

Fridericia's formula

This is is an alternate for Bazzets formula proposed by Fridericia using the cube-root of RR.

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Sagie's formula

This formula has used for around 5,000 subjucts in Farmingham heart study ,considered as better method (11).

$$QTlc = 1000(QT/1000 + 0.154(1 - RR))$$

3.4 differentiation of regularly used QTc formulae

In the pharmaceutical and clinically the corrected QT interval (QTC) has wide application. Bazetts formula is the commonly used and other formula such as fridericia,hodges , framingham is also used .A study was done at four US hospitals by

comparing the 10,303 normal ECG by the four formula on the same computer program .The distribution of QTC on Bazetts was significantly wider where the other formula are similar. The correlation of QTc heart rate by the global group were calculated as Fridericia 0.24, Hodges 0.11 ,Bazett 0.33 and Framinghas 0.26 with the uncorrected QT-HR being 0.82. Correlation with HR in Hodges QTC is less compared to others .Based on the patient HR and gender there will be selection of QT correction formula .one individual formula can outperform the other because there are subgroup correlation of gender, HR (14).

Mechanism of the prolongation of the qt interval

During depolarization or phase 0 of the action potential,the fast sodium channels open briefly allowing sodium ions to enter the cell. The entry of positive ions into the cell causes the polarity of the cell to change abruptly from 90to 10 to 20 mV. Depolarization is immediately followed by repolarization consisting of phases 1 through 3 of the action potential. This corresponds to the J point extending to the end of the T wave in the surface ECG. During phase 2, which corresponds to the plateau phase of the action potential, the polarity of the cell is maintained at approximately 0 mV for a sustained duration. This is due to entry of calcium into the cell because of activation of the slow or "L-type" calcium channels during depolarization. This slow but sustained flow of positive ions into the cell is counterbalanced by the flow of potassium out of the cell because the cell membrane is more permeable to potassium than other ions.This loss of potassium makes the inside of the cell more negative as positive ions are lost. Thus, the entry of calcium into the cell (entry of positive ions) combined with flow of potassium

out of the cell (loss of positive ions) results in an equilibrium that is sustained for a prolonged duration corresponding to the plateau or phase 2 of the action potential. (12)

When the calcium channels are inactivated, the entry of calcium into the cell is suddenly prevented although the outward flow of potassium continues. This inequity in calcium entry and potassium outflow advances the action potential to phase 3. Phase 3 or rapid repolarization is due to continuous efflux of potassium from the cell causing the cell to become more negative until the resting potential of –90 mV is reached.(12)

This marks the end of phase 3 of the action potential, which corresponds to the end of the T wave in the surface ECG. As long as the potential of the ventricular myocyte is prevented from reaching –90 mV, which is the normal resting potential, the cell is not fully repolarized. Thus, any mechanism that will prolong or increase the entry of sodium or calcium into the cell will make the inside of the cell more positive and will delay or prolong the duration of the action potential. Similarly, any mechanism that will inhibit or delay the exit of potassium out of the cell will make the cell less negative. This will also prolong the duration of the action potential. Phases 0 through 3 of the transmembrane action potential correspond to the duration of the action potential of individual myocardial cells. (12)

This is equivalent to the QT interval in the surface ECG. Prolongation of phases 1 through 3 will result in prolongation of the QT interval.

Abnormal QTcintervals

Certain drug used in emergency such as antipsychotics, Antiemetics length the QT interval .other coexisting entities that makes the management difficult such as increase in

the drug dosage ,low potassium level .The lengthening of QTc interval has increased the risk of developing ventricular tachy dysarrthymia especially polymorphic ventricular tachycardia. Other factor such as inherited ,heart beat, metabolic disproportion and pharmacotherapy. ED providers should not only know the drug causing effects but also about the relevant history to lengthening of the QTc interval .(2)

Acute prolongation of the QTc interval is an indirect sign of prolonged ventricular myocardial repolarization, it has been observed in various clinical situation and it may present with blackout ,cardiac arrest due to torsades de pointes ,proceeding the prolongation of QTc interval which looks similar to ventricular fibrillation. It may cease itself or worsen by causing cardiac arrest and death .The characteristic of TdP is the changes in the magnitude And the structure of QRS wave around the isoelectric line which looks like twisting around the baseline . The drug that causing TdP events start with the long – short pattern of RR interval with premature ventricular complex(PVC) followed by a compensator pause and another PVC . The corrected QT in female is < 460ms and in male is <440ms .So the increase in QTc in male and female is a risk factor for TdP. Increase in QTc is definitive and acceptable factor for the adverse cardiac incidents . There should be QTc observation in the emergency department (class 1recommendation) for the people with long QT syndrome and related with ventricular arrhythmias.(2)

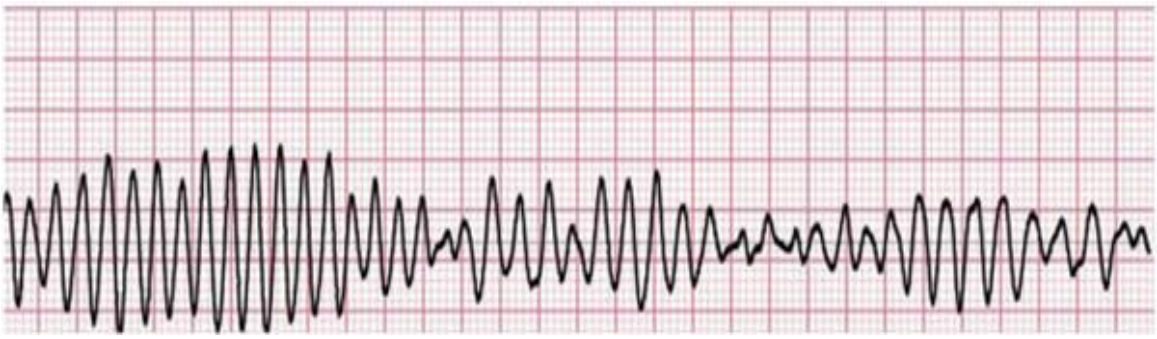


Figure. 4: TdP (Torsade de pointes)(2)

The significance of QTc monitoring in the Emergency department cannot be overlooked because these set patients are very likely to go for developing TdP and other arrhythmias which haave wide distribution of presenting illness and high accuracy. During the risk stratification particular set of people who are more prone for developingTdP should be included .(2).

According to the guidelines once in every 8hrs QTc/QT interval should be measured at the baseline for the patients. The emergency department should monitor QTc/QT if the patient is on the drug known to prolong QTc. It is also necessary for the staff and nurses to know how to analyze and judge about QTc/ QT

QTc monitoring should be required until:

a. The proarrhythmic drug is stoppedand/or reduced the dose and no further QT_c prolongationis noted
b. No further arrhythmias related to QT prolongation ,
c. specific treatment (permanent pacemaker) is accustomed
d. the dyselectrolytemia get corrected. (2)(16)

Indicator for QT interval monitoring:

a. The people on antiarrhythmic agents which are known to cause TdP (sotalol,disopyramide, dofetilide, ,quinidine, procainamide ,ibutilide).
b. Incase of proarrhythmic drug overdose.
c. Presented with recent emergence of bradyarrhythmia(CHB, long sinus pauses).
d. People with severe electrolyte imbalance(low level of potassium and serum magnesium in blood .)

Cardiac Monitoring in the Emergency Department

Cardiac monitoring is used to monitor the broad spectrum of patient condition in ED which was a noninvasive diagnostic tool. For the standard practice ,ECG helps the clinician to decide whether the patient need monitoring .This proposal was given by the expert in electro cardiology and cardiac monitoring .

These practice include all area of hospital in cardiac monitoring which include irregular rhythm of heart , MI and QT interval monitoring. Based on the clinical experience and research the experts opinion was reflected by the guidelines , but the cardiac monitoring in hospital for practices was limited according to the dat. below, which was developed by the American College of Cardiology Emergency Cardiac Care Committee for cardiac monitoring(12).

- Class I: Cardiac monitoring is indicated in most, if not all, patients in this group.

- Class II: Cardiac monitoring may be beneficial to some patients but not considered essential for all patients.
- Class III: Cardiac monitoring is not indicated because a patient's risk of a serious event is so low that monitoring has no therapeutic monitoring benefit"(12).

QTc interval prolongation in emergency

QTc interval on 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(27). 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; various commonly prescribed cardiac and noncardiac medications can cause QTc prolongation(27)(28).

This ECG abnormality has been associated with greater risk of cardiac arrhythmia, known as torsade's 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(27)(28). The patients admitted in the emergencymedical service have scarce literature about the prevalence and determinant of QTc prolongation (29).

Prevalence:

The prevalence of QTc prolongation is likely to be higher in patients admitted in ED because acutely ill patients often have one or more of aforementioned risk factors and receive multiple drug treatments. QTc prolongation also has prognostic significance, though it is frequently overlooked parameter in ECG. The study made in emergency patients in Indiathat they have widespread of QTc prolongation with 34.1% prevalence . Markedly prolonged QTc interval (QTc>500 ms) was found in fifyeen patient (5.4%). 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(29).

"Characteristics of patients at risk for developing torsade de pointes

1. Women
2. Elderly
3. Heart disease
4. Acute neurologic events
5. Bradyarrhythmias with long pauses
6. Electrolyte disturbances (hypomagnesemia, hypokalemia)
7. Malnutrition
8. Polypharmacy
9. Genetics (long QT syndrome, family history of sudden cardiac death, syncope).

Causes of Abnormal Qtc intervals

Genetic causes

The lengthening of QT interval might be due to long QT syndrome and autosomal recessive syndrome of Jervell and Lange Nielson with sensorineural hearing loss . The shortened QT interval might be due to short QT syndrome. Variations in NOSIAP gene is associated with the length of QTc. Single nucleotide polymorphism (SNPs)have been linked to QTc length and to SCD.(17)

Congenital syndromes

Congenital or inherited prolongation of the QT interval affects young individuals especially the first 2 decades of life and is a common cause of sudden death in this age group. Two types of long QT syndrome have been clinically described.The first familial long QT syndrome described by Jervell and Lange-Nielsen is associated with sensorineural deafness. This type of long QT syndrome is inherited as autosomal recessive. The second familial long QT syndrome is the Romano-Ward syndrome and is inherited as autosomal dominant but is not associated with congenital deafness.n With the advent of genetic testing, seven long QT syndromes have been described thus far and are labeled LQT1 to LQT7 according to the sequence in which the abnormal locus of the genetic defect have been discovered. The first three entities—LQT1, LQT2, and LQT3—are the most common Ventricular Arrhythmias and comprise almost 95% of all identified cases of congenital long QT syndromes.(31)

The prolongation of the QT is due to a genetic defect involving the potassium channel in most cases except LQT3 and LQT4, which are due to a defect in sodium transport. The genetic abnormality involves the ion channel in almost all cases except LQT4, which does not affect the ion channel directly, but only its supporting structure.n Patients with long QT syndrome can be confirmed by genetic testing, although a negative genetic test will not exclude the presence of congenital long QT syndrome because up to 40% of patients with congenital long QT have not been linked to any genetic abnormality. Additionally, the use of genetic testing remains very expensive and may not be affordable when screening several family members with history of long QT syndrome or known sudden death in the family. It also takes several weeks before the results are known. Thus, the diagnosis of long QT syndrome is more commonly based on phenotypic ECG abnormalities.n When the ECG is used in the diagnosis of patients with congenital long QT syndrome, marked variability in the duration of the QTc in serial ECGs can occur(31)(32)

Even in normal individuals, the QT interval can vary by as much as 50 to 75 milliseconds over a 24-hour period. Thus, screening of individuals with family history of long QT syndrome and sudden death may not show any initial QT prolongation. Additionally, almost a third of patients who are confirmed carriers have normal or borderline QTc of 0.40 to 0.46 seconds. (31)

The longest QTc, including those measured before age 10 years, provides important prognostic information during adolescence in patients with congenital long qt syndromes.(32)

Thus, a long QTc measuring 0.50 seconds identifies a patient who has increased risk of cardiovascular events and shorter QT intervals of 0.50 seconds decreases the risk of cardiovascular events. In these patients, however, there is no clear cut QT interval that is considered safe because QTc of 0.46 seconds are also at risk for syncope and sudden death.n The following is a summary of the known long QT syndromes(32)

LQT1: Long QT1 is the first mutation to be identified. It is one of the most common, accounting for approximately 50% of known long QT abnormalities. The abnormality involves the short arm of chromosome 11. Homozygous mutation of the gene causes the Jervell and LangeNielsen syndrome. The syndrome is associated with congenital deafness, which is also due to the abnormality in the same potassium channels involved with the production of potassium-rich endolymph in the inner ear.It is a much more common cause of sudden death younger than age 10 years when compared with the other long QT syndromes. Prolongation of the QT is due to delay in phase 3 of the action potential because of delay in the transport of potassium (-subunit of the slow potassium rectifier or IKs). In addition to the prolonged QT, the T wave in the ECG has a slow indistinct onset, but is otherwise normal. Patients with LQT1 are most symptomatic during exertion because the QT interval becomes longer with exercise in contrast to patients with LQT3 who are most symptomatic during rest or sleep. The QT interval can be prolonged by intravenous injection of epinephrine. Thus, in symptomatic individuals,if the initial QT is not prolonged, the long QT can be unmasked with epinephrine

LQT2: Long QT2 is also one of the most common long QT abnormalities with up to 40% of all congenital cases of long QT syndrome. The defect resides in chromosome 7 and the identified gene is called HERG (human ether ago-go related gene) or KCNH2.

Similar to LQT1, this gene is also involved with the potassium current. Unlike LQT1 that affects the slow potassium currents (called slow K rectifier or IKs), the gene is involved with the fast potassium currents (called rapid K rectifier or IKr), which is the most important in determining the duration of the action potential. Most pharmacologic agents that prolong the QT interval also inhibit the same potassium channel. In LQT2, the shape of the T wave in the ECG is bifid or split. Mutation of the HERG gene causes another abnormality characterized by an unusually short QT interval of 0.30 seconds called congenital short QT syndrome, which is also associated with sudden death.

LQT3: Unlike LQT1 and LQT2, which are involved with potassium transport, LQT3 involves mutation of the gene encoding a sodium channel. The abnormality is located in chromosome 3 and the gene is called SCN5A. LQT3 is less common than the first two long QT syndromes. The abnormality in the sodium channel causes prolongation of phase 2 of the action potential. This is due to delayed closure of the fast sodium channels on completion of rapid depolarization resulting in continuous entry of sodium ions into the cell, thus prolonging the duration of the action potential. The baseline ECG will show asymmetric T waves with a steep downslope. Most patients are symptomatic at rest or sleep, which causes the QT interval to prolong because of bradycardia. Mutation of the gene SCN5A has been implicated as the cause of the Brugada syndrome, where most of the arrhythmic events occur during sleep (see Brugada Syndrome).

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Due to pathological conditions

Prolongation of the QT interval may be due hyperthyroidism and also low level of calcium in the blood causing the ventriculardysrhythmia . Increase in the level of calcium in the blood causin the shortened QT interval (19)(20).

Rheumatoid arthritis

Rheumatoid arthritis is a common inflammatory arthritis, linked with increased death rate from cardiovascular death as per studies (19). A study in 2014 reveals by Panoulas et al reveals that increase in the death rate by 2.17 due to the increase in QTc interval of 50ms (424ms) of the patient with rheumatic arthritis than with a low Qtc interval . It also reveals that the prolongation of QTc interval due to the inflammation which produce arrhythmia shows that there is higher mortality rates. However, the mechanism by which C-reactive protein is associated with the QTc interval is still ambiguous(19)(20).

Diabetes

The findings regarding the QT and QTc intervals durations used to be also a little bit controversial. While Heller has detected in DM 1 patients QT and QTc intervals prolongation, positive correlation between QT interval and HbA1C level has been found. (24).

Diurnal variation

Circadian QTc changes have been reported, with conflicting results. Spontaneous QTc variability is important for pharmaceutical cardiac safety studies. Large QTc variability largely results from methodologic imprecision. Little QTcvariability is present in daytime recordings of healthy subjects. Consequently, QT-related pharmaceutical cardiac safety studies can be made smaller without decreasing their power(26).

Racial susceptibility

Determinants of the QT interval include a complex interplay of electrical current across the myocardial cell membrane involving ion channels of sodium, calcium, and potassium. In the general population, the average heart rate-corrected QT interval is longer in women than in men, race-dependent, and increased with age.(35) Specific factors that have been associated with an individual's baseline QT interval include the following: age (increased by 10 ms each decade), gender (females > males by 10 ms), race (Whites > Blacks by 5-10 ms), and genetic markers on chromosomes 7 and 11. However, Blacks with Congenital Long QT Syndrome (LQTS) have significantly longer QTc than Whites without corresponding differences in cardiac event rates.(36) There is significant racial susceptibility to drug-induced QT prolongation on acute overdoses. QT prolongation occurred in 12.7%. Blacks had two-fold increased odds of drug-induced QT prolongation and Hispanics had 48% decreased odds of drug-induced QT prolongation .(37)

Chronic renal failure

There are increased death rate in the patient of end stage renal disease even after improvements in quality of dialysis . Coronary artery disease and left ventricular hypertrophy are the main cause of death . myocardial remodeling is heterogeneous phenomenon affecting ventricular repolarization leading to the irregularity in QT interval. The increased value of QTc, QTcd and left ventricular mass index in hemodialysis patient.

The warning sig for sudden cardiac death due to ventricular arrhythmia is QT Prolongation. In which death of the patient of end stage renal disease (ESRD) is around 1.4 to 25 %. There are many factor which are distinctive to ESRD and increased in renin angiotensin system due to the chronic hemodialysis, remodel the cardiac ion channel leading to the lengthening of ventricular repolarization which later exhibits as QT prolongation. The genetic factor which causing QT prolongation such as polymorphism of RAS gene. Myocardial infarction and ventricular fibrillation shows QT irregularity due to the insertion and deletion of the D allele of angiotensin in converting enzymes. Other factor such ad angiotensin type 1 receptor -A1166C (AT1R - A1166C) and angiotensinogen- M235T (AGT- M235T) , ACE DD gene type RAS polymorphism ,within RAS gene – gene interactions(53). Medication which are known to TdP that require dose adjustment in patients with renal disease are enlisted as below;

- Ciprofloxacin
- Disopyramide
- Dofetilide

- Eribulin
- Flecainide
- Fluconazole
- Levofloxacin
- Procainamide
- Sotalol
- Vandetanib

Due to adverse drug reactions

Adverse drug reaction may present as prolongation of the QT interval. certain drugs, such as haloperidol,vemurafenib, ziprasidone, methadoneand sertindole,second-generation antihistamines, such as astemizole, and high blood alcohol can lengthen QT interval. Certain drug that work by prolongationof QT interval such as antiarrthymic drug like sotalol and also macrolides antibiotics. There will be QT prolongation by the interaction between the selective serotonin receptor inhibitors and thiazide diuretics. It was recently found that there is increase in cardiovascular death due to the intake of azithromycin (18 concomitant administration of ≥2 QTc interval–prolonging drugs may lead to elevated plasma concentrations of QTc interval–prolonging drugs increase the risk of drug-induced TdP, including pharmacokinetic drug interactions (Table 1)(18). The risk factors for torsades de pointes are as follows:

- QTc interval >500 ms
- Increase in QTc interval >60 ms compared with pretreatment value

- Advanced age
- Female sex
- Acute myocardial infarction
- Heart failure with reduced ejection fraction
- Hypokalemia
- Hypomagnesemia
- Hypocalcemia
- Bradycardia
- Treatment with diuretics
- Concurrent administration of >1 QTc interval–prolonging drugs
- Elevated plasma concentrations of QTc interval–prolonging drugs
    - Inadequate dose adjustment of renally eliminated drug in patients with acute kidney injury or chronic kidney disease
    - Rapid intravenous infusion of QTc interval–prolonging drug
    - Drug interaction(s)
- Possible genetic predisposition

Table 1: Pharmacokinetic drug interactions associated with the highest risk of drug-induced QT_c interval prolongation and torsades de pointes(18)

Precipitant drug	Mechanism	QT_c interval–prolonging drug
Antifungal agents: Itraconazole Ketoconazole Posaconazole Voriconazole	Inhibition of CYP 3A4	Amiodarone Disopyramide Dofetilide Pimozide
Macrolide antibiotics*: Erythromycin Clarithromycin Telithromycin	Inhibition of CYP 3A4	Amiodarone Disopyramide Dofetilide Pimozide
HIV drugs: Atazanavir Darunivir/ritonavir Fosamprenavir Indinavir Nelfinavir Ritonavir Saquinavir Tipranavir	Inhibition of CYP 3A4	Amiodarone Disopyramide Dofetilide Pimozide

Antidepressants: Bupropion Duloxetine Fluoxetine Paroxetine	Inhibition of CYP 2D6	Flecainide Quinidine Thioridazine
Others: Terbinafine	Inhibition of CYP 2D6	Flecainide Quinidine Thioridazine

*Not azithromycin.

CYP, hepatic cytochrome P-450 enzyme; (18)

Relationship to drug-induced QTc prolongation

There are some drugs having significant association of QTc prolongation which triggers torsade de pointes (TdP).TdP is a type of polymorphic ventricular tachycardia with prolonged QTc. there are many reasons for TdP including drugs which prolong QTc. drugs which were identified till now showing marked QTc prolongation only when it is given in higher doses, and prolongation was dependent on the frequency of exposure to the drug. There are some drugs which cause marginal QTcprolongation with less incidence of TdP.TdP is a major and fatal adverse effect of these drugs ,which causes QTcprolongation(31)(32).

These pro-arrhythmic events related to drug over dose is one of the major factor .With some exaggeration, one state that sensitive individuals develop TdP or proarrhythmia if each of the chemical is compound than sodium or glucose. Till date there is no clear

demarcation of pro arrhythmic and and normal drugs . but there are some drugs that cause frequent pro-arrhythmic episodes and TdPlike quinidine ,and some drugs cause TdP only in special situations like fexofenadine. So it is difficult for approving drugs in this scenario. careful assessment is required before doing any risk–benefit considerations specific to drugs(32).

Because of recent advancement and precision of ECG measurements, and influence of autonomic system on the heart muscle repolarization and due to various other mechanisms , drug-related QTc prolongation changes are found with so many safe compounds(32).

Currently there is no accurate data available related to short qt interval and its pro arrhythmic effects ,and no link has been established between QT shortening and arrhythmias . As the QTc prolongation is important to observe similar importance should be given to QTc shortening. There are certain drug that causes the repolarization heterogeneity by abolishing by prolonged APD in the mid –myocardium making the repolarization more synchronous and less susceptible to after polarization and variant pro arrhythmias (32)

Drugs with associated with a high risk of QT prolongation and TdP:

In normal individuals with normal QTc, several pharmacologic agents can prolong the QT interval. These include type IA antiarrhythmic agents(quinidine, disopyramide, and procainamide), type III antiarrhythmic drugs (dofetilide, ibutilide, sotalol, and amiodarone), antipsychotic agents (chlorpromazine,thioridazine, and haloperidol), macrolide antibiotics (erythromycin, clarithromycin), antifungal agents (ketonazole and

itraconazole), electrolyte disturbances notably hypomagnesemia and hypokalemia, and other agents such as pentamidine and methadone. A long list of pharmacologic agents that can prolong the QT interval can be accessed at www.torsades.org. (36)

Although the use of a single pharmacologic agent (quinidine or ibutilide) may cause QT prolongation and torsades de pointes almost immediately, occasionally, a combination of two agents may be needed to prolong the QT interval such as the concurrent use of erythromycin and ketonazole. Erythromycin, a macrolide antibiotic, and ketonazole, an antifungal agent, are both metabolized by the liver through the cytochrome P-450 3A4 (CYP 3A4) metabolic pathway. Either agent can potentially prolong the QT interval although prolongation of the QT interval is more significant when both agents are taken concurrently because they compete for the same metabolic pathway resulting in increased plasma concentration of both agents.(36)

Similarly, an agent that does not prolong the QT interval but depends on the CYP 3A4 metabolic pathway for clearance such as a calcium channel blocker (verapamil) when combined with a drug that prolongs the QT interval such as erythromycin can result in further prolongation of the QT interval since verapamil also depends on the same pathway as that of erythromycin for clearance. The effect on QT prolongation and potential for torsades de pointes may be more delayed, however.(36) The list of drugs Table 3includes the more common drugs that have been associated with QT prolongation but is not all.

Table 3: List of drugs with associated with a high risk of QT prolongation and TdP(36)

Cardiac drugs	• Amiodarone
	• Sotalol
	• Disopyramide
	• Dofetilide
	• Procainamide
	• Quinidine
Antidepressants	• Selective serotonin re-uptake inhibitors: citalopram, escitalopram, fluoxetine
	• Moclobemide
	• Tricyclic antidepressants*
	• Lithium
Antipsychotics	• Amisulpride
	• Chlorpromazine
	• Haloperidol
	• Ziprasidone
	• Thioridazine
Antihistamines	• Loratadine
	• Astemizole
	• Diphenhydramine
Antimicrobials	• Ciprofloxacin, moxifloxacin, sparfloxacin

	• Clarithromycin, erythromycin
	• Fluconazole, voriconazole
	• Pentamidine
Other drugs	• Chloroquine
	• Cisapride
	• Dolesatron
	• Methadone
	• Arsenic

Ondansetron is known to cause QT interval prolongation. In a prospective, observational, single-center cohort study it was found that while QTc prolongation does occur in adult ED patients receiving IV ondansetron, though the clinical impact is questionable(37).

The first line of drug for acute asthma exacerbation during shortness of breath and also for COPD at stable period and acute exacerbation is Albuterol (salbutamol) which is a B2 agonist.

Hemorrhagic Stroke

Cardiovascular complications are extremely common following stroke and represent a major form of morbidity. These complications may be caused by focal cerebral injury or may be a manifestation of preexisting cardiac disease, which is common. International guidelines recommend: all patients with acute stroke need an ECG performed at the moment of admission to document any heart abnormalities(39). The association between heart-rate corrected QT (QTc) interval and cardiovascular morbidity and mortality is well

established. A multitude of ECG changes are observed in either ischemic or hemorrhagic acute strokes. 90% of unselected stroke victims had in particular, repolarization changes, such as prolongation in the QTc interval, adding to management and diagnostic dilemma, of physicians as well as neurologists. Another concern is that these cardiac electrophysiological changes might be responsible for sudden death in stroke sufferers. In a observational study prolongation in the QTc interval was “statistically” associated with acute sub arachnoid hemorrhage only. No gender difference was noted; whether this observation is clinically significant or not, it needs further analytic studies(40)(41)(42).

Acute coronary artery disease

In patients studied for acute chest pain(ACHP), the QTc on the hospital admission electrocardiogram correlates with the underlying myocardial ischemia. AQTc>or=450ms selects a group of people at risk of presenting a moderately or severely abnormal STS, regardless of ST abnormalities and troponin release. The corrected QT interval (QTc) is prolonged in the setting of acute coronary artery disease(44).

ECG is an important emergency technique to diagnose Left main trunk (LMT) infarction. Either ST-segment elevation in lead aVR and marked prolongation of both the QRS width and QTcinterval with a prominent abnormal axis deviation or ST-segment elevation in the broad anterior precordial lead with a normal QRS axis strongly suggests LMT infarction(45).

Electrolyte disturbances

Prolonged QTc (corrected QT) interval and torsade de pointes (TDP) are associated with hypocalcemia, hypomagnesaemia, hypokalemia, possibly alkalosis and may result in syncope and sudden cardiac death.

QTc duration is highly sensitive to hypokalemia, particularly in women. Methadone prolongs QTc remarkably compared to other non-cardiologic medicines. QTc>500 with normal QRS often signifies profound illness and substantial mortality risk, though not necessarily imminent TdP(46). It is strongly recommend that psychiatric patients should be screened for hypokalemia on admission as it is associated with lengthening of QT interval(47).

Hypocalcemia may be associated with reversible cardiac dysfunction including QTc interval prolongation and depressed left ventricular systolic function. The available evidence is very limited and does not provide a rationale for a certain threshold or a recommendation for calcium replacement. Future research is needed in this important and common metabolic disorder(48).

However in a study it was found that admission electrolyte values were not associated with QTc intervals.The association of metabolic derangements and QTc abnormalities may not be as strong as is widely believed(49).

Diabetic ketoacidosis

Due to low carbohydrate diet ketosis occur with many conditions such as DKA and alcoholic ketoacidosis . It is noticed that children who consume ketogenic diet there is a prolongation of QTc but the effect of cardiac in ketosis has not been investigated. There

should be cardiac monitoring for the children with DKA and for the patient with other ketotic condition electrocardiographic screening is done.

Syncope

Electrocardiogram (ECG) is a common diagnostic tool for the patient presenting with the complaints of syncope in ED. In a prospective, observational study at 11 EDs in adults 60 years or older the association between with syncope or near syncope and increasingly prolonged QTc intervals was evaluated. There were 1678 patients (64.3%) that had QTc intervals <451 ms; 544 (20.8%) were 451-470 ms; 302 (11.6%) were 471-500 ms, and 85 (3.3%) had intervals >500 ms. Composite 30-day serious outcomes was associated with increasingly prolonged QTc intervals (13.0%, 15.3%, 18.2%, 22.4%, $p = 0.01$), but this association did not persist in multivariate analysis. Thus older patients presenting with syncope, increased QTc interval was a marker of but was not independently predictive of composite 30-day serious outcomes(51).

Acute ethanol intoxication

Acute alcohol intoxication can prolong repolarization time and QT dispersion along with QT prolongation. And QT interval has positive correlation with duration of alcohol consumption and amount of consumption . P wave, PR, QRS and QTc intervals were prolonged when the subjects had high blood ethanol (at admission) than at discharge(54).

Thyroid disorders

Overt hypothyroidism is associated with many cardiac manifestations, such as prolongation of QRS and QT intervals. QT prolongation and increased QTc have been shown to be directly related to TSH level in overt hypothyroidism(55). Hypothyroidism

is associated with a decreased sympatho-vagal modulation of the heart rate and with an increased inhomogeneity of ventricular recovery times. The assessment of heart rate variability and QT dispersion in patients with overt hypothyroidism may represent a useful tool in monitoring the cardiovascular risks(56). hyperthyroidism can also lead to prolonged QTc.QTc values are lengthened in hyperthyroid subjects compared to normal healthy adults.QTc has proportionately prolonged with free T3,T4 levels in blood, and patients QTc values were improved with hyperthyroidism treatment and QTc prolongation is noticed even in subclinical hyperthyroid with high FT4(57)(58). Use of antithyroid drugs was associated with sudden cardiac death. In children hyperthyroidism is more common who takes antihistamines as a treatment of hyperthyroidism may prolong the QT value. So it is important to measure the QTc value before starting any other drug which prolong the QTc interval and precipitate the cardiac events(59).

Risk score for identifying patients at greatest risk of QT_c interval prolongation

As risk factors are important for the development of QTc interval prolongation/TdP, quantification of risk may be helpful in targeting patients at greatest need of pharmacist intervention/monitoring. A risk score for predicting the development of QTc interval prolongation in patients hospitalized in cardiac care units has been developed and validated (Table 2). Roughly 50% of patients with a risk score ≥7, in the moderate-to-high range, proceeded to develop QTc interval prolongation. This risk score was incorporated into a clinical decision support computer alert; when a patient was admitted to the cardiac care units, a computer alert was generated when the patient was prescribed

a QTc interval–prolonging drug and the calculated risk score indicated that the patient was at moderate or high (but not low) risk of developing QTc interval prolongation

" Table 2: Risk score for identifying patients at greatest risk of QT_c interval prolongation. (18)

Risk factor	Points
Age ≥68 years	1
Female	1
Loop diuretic	1
Serum potassium ≤3.5 mmol/L	2
Presenting QT_c interval ≥450 ms	2
Acute myocardial infarction†	2
Heart failure with reduced ejection fraction	3
1 QT_c interval-prolonging drug‡	3
≥2 QT_c interval-prolonging drugs‡	3
Sepsis†	3
Maximum score	21

*Risk score category: low risk = <7; moderate risk = 7 to 10; high risk = ≥11. †During acute event/disease; QT_c interval generally returns to normal following resolution.

‡Three points for taking 1 QT_c interval–prolonging drug; 3 additional points for taking ≥2 QT_c interval–prolonging drugs (for a total of 6 points)".(18)(30)

Management of QTc prolongation or TdP

Polymorphic ventricular tachycardia may or may not be associated with prolonged QT interval. When the PVT is associated with prolonged QT interval, the VT is called as TdP.TdP should be differentiated from regular PVT because management of TdP and regular PVT are entirely different. First step in the management includes confirm the ECG findings, then the cause for QT prolongation should be identified ,is it acquired or congenital long QT. Any identifiable cause of QT prolongation should be corrected immediately. main treatment includes

Reverse myocardial ischemia

Correction of electrolyte abnormalities

Antiarrhythmic agents

There are many drugs which cause QT prolongation should be stopped immediately. If patient is hemodynamically stable one to 2gm of IV magnesium sulphate with in an hour in a 50 to 100ml dilution of 5%dextrose.this is followed by 10 to 20 gm in the next 24hrs irrespective of patient magnesium levels.class class1A and class3 antiarrhythmics are absolutely contraindicated because these drugs itself cause QT prolongation.lidocaine can be used as it doesn't cause QT prolongation.Assessment of electrolyte abnormality is more important in the management of TdP, hypokalemia and hypomagnesaemia may prolong the QT interval. in hemodynamically unstable patients who is in hypotension or shock with diminished response or not responding ,requires immediate cardioversion with asynchronized shock, because in TdP it is not possible to give synchronized cardioversion (60). Most of the hemodynamically stable TdPwill respond to intravenous

magnesium therapy(61). If patient is not responding to magnesium assess for rhythm and rate if Tdp is not associated with bradycardia can go for a defibrillation. If patient has TdP with bradycardia start intravenous isoproterenol 2-10mcg/min continuous infusion which usually serves as a bridge before a temporary pacemaker can be inserted. It is usually effective as a temporary treatment in patient with acquired long QT syndrome with significant bradycardia,AVblock,or there are pause dependent TdPs. TdP which is associated with sotalolis managed with hemodialysis or peritoneal dialysis if they are not responding to the conventional therapy. (62).

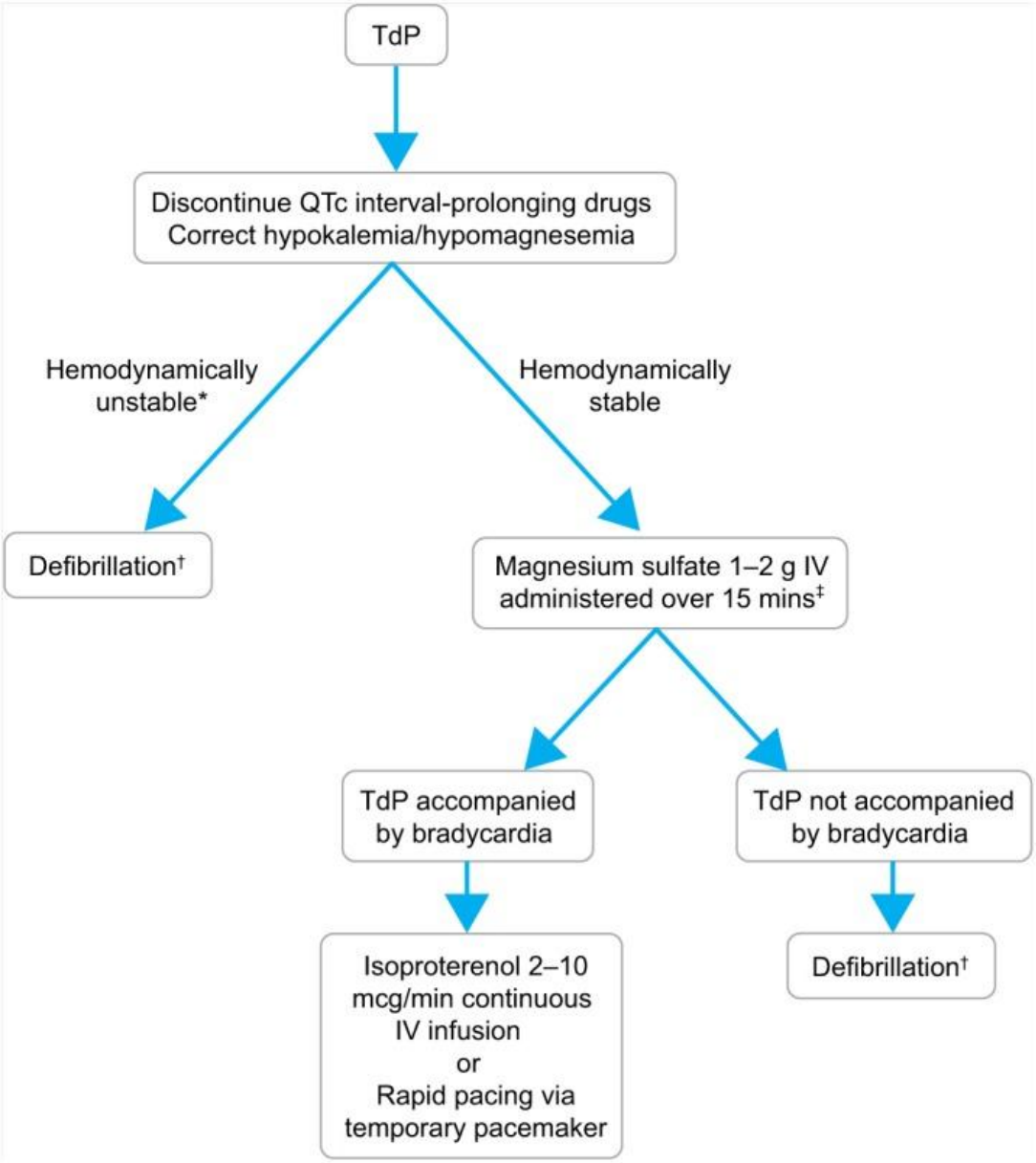


Figure : approach to TdP management(18)

Methods to reduce the risk of drug-induced torsades de pointes are as follows:

Where possible, stop the medications which lengthens the QT value in patients who has baseline QTc value >0.45 s.

- with hold or stop the QTc lengthening medications if QTc value reach>500 ms.
- stop or discontinue the medications which lengthens the QTc value more than 60ms from the baseline value.
- Treat hypokalemia cautiously .
- Maintain serum magnesium concentration within normal range.
- Maintain serum calcium concentration within normal range.
- Where possible, avoid the use of QTc interval–prolonging drugs in patients with heart failure and a left ventricular ejection fraction <20%.
- watch for drug interactions.
- drug dosing should be titrated according to the patient kidney status.
- Drugs which cause QTc prolongation should not be given fast.
- Where possible, avoid concomitant administration of >1 QTc interval–prolonging drug.
- if patient had previous history of drug-induced torsades de pointes or those who had survived earlier from sudden cardiac death should not receive QTc lengthening drugs again.
- in patients who are known congenital long QT syndrome should try to avoid using QTc lengthening drugs.

is a simplified review of the ionic changes that occur in the ventricular myocyte that can result in prolongation of the QT interval. 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. It is seen that in acutely ill patients the prevalence of a prolonged corrected QT interval (QTc) is much higher than one might expect. These may be due to an underlying cause which may be correctible. In a clinical study the prevalence of prolonged QTc at admission and associated outcomes were assessed in patients admitted to a tertiary care Indian medical ICU. 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(63).

MATERIALS AND METHODS

1. SOURCE OF DATA

Patients admitted with 'acute medical emergencies ' at B.L.D.E.U'S Shri B.M .Patil Medical College Hospital and Research centre, Vijayapur between December 2017 to August 2019.

2. METHOD OF COLLECTION OF DATA:

A. STUDY POPULATION

This study was done in Shri B M Patil Medical College Hospital and Research centre, Vijayapur, from December 2017 to August 2019, individuals with acute medical emergencies were studied.

B. INCLUSION CRITERIA:

Patients with Acute medical emergencies

C. EXCLUSION CRITERIA

1. All cardiac arrhythmias

2.Patients age less than 18 yrs

3. METHODOLOGY

To determine the clinical out come of the patient in relation to the prolonged QTc interval in patients who has admitted to the _____with acute medical emergency , a standardized assessment will be performed.

Clinical history and examination, electrocardiogram at admission, cardiac enzymes-Troponin I, CPK MB,Echocardiograhy,CT/MRI brain ,ABG analysis and other relavent laboratory investigations were done. QT interval was calculated for all the patients who admitted with medical emergency with in the 24hr of admission .QT

interval was corrected with heart rate by using Bazzets formula, which is most commly used for the QTc calculation. A 12 lead ECG will be done using BPL CARDIART 6108-T ECG machine and ECG will be analysed.The QT interval was calculated from V3 lead .if lead led V3 was not clear V2 followed by lead 2 was preferred.the formula to calculate QTc is mentioned below.

Bazzets formula = $\frac{QT}{\sqrt{RR}}$

4. SAMPLE SIZE:

With the prevalance of medical emergencies , 1- 10%, at 95% confidence level and at 5% margin of error, the sample size was 146.

$$n = \frac{Z\alpha^2 \times P \times (100-P)}{(MOE)^2}$$

$Z\alpha$ = Z value at α level=95%

P = Prevalance rate=5%

MOE = Margin of error =5%

6. STATISTICAL ANALYSIS:

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables.

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript "c" are the degrees of freedom. "O" is observed value and E is expected value.

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft office 2007

7. DATA REPRESENTATION BY:

Graphical presentation

Percentage Distribution

Investigations required in this study are standardized procedures.

INVESTIGATIONS

1. Blood

   -Complete blood count

   -Blood glucose

   -Renal function test

   -Serum electrolytes

   -Troponin I

   -CPK MB

2. Urine Examination
3. Electrocardiogram.

4. Chest X ray

5. 2D Echocardiography and colourdoppler study.

6. CT/MRI brain

7. ABG analysis

8. USG abdomen & Relavent investigations

RESULTS

The study of prolonged QTc interval s a predictor of outcome in patients admitted with medical emergencies was done in patients admitted to Shri B M Patil Medical College and Research Centre from December 2017 to August 2019. Total of patients were admitted with acute medical emergencies. 312 patients were included out of 327 patients. Other patients were excluded due to arrhythmias, age less than 18years and patients with mechanical heart valves.

AGE DISTRIBUTION

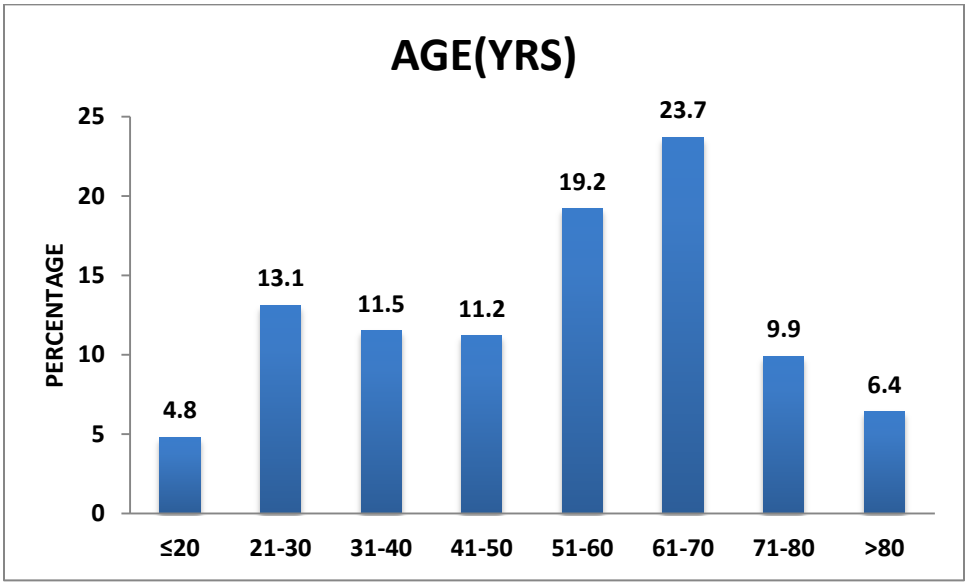
Patients are grouped with an age frequency of 10 years. Out of 312 patients included in the study, patients aged between 21 to 30 yrs were 41, patients aged between 31-40 yrs were 36(11.5%), patients between the age 41-50 yrs were 35(11.2%), patients between the age 51-60 were 60(19.2%), patients between the age 61-70yrs were 74(23.7%), patients between the age 71-80 yrs were 31(9.9%), patients aged more than 80 yrs were 20(6.4%) The most common age group was 61-70 years (74patients). Table 1, Figure 2.

TABLE 1: DISTRIBUTION OF CASES ACCORDING TO AGE

AGE(YRS)	N	%
≤20	15	4.8
21-30	41	13.1
31-40	36	11.5
41-50	35	11.2
51-60	60	19.2
61-70	74	23.7
71-80	31	9.9
>80	20	6.4
Total	312	100

	Min	Max	Mean	SD
AGE(YRS)	18	99	53.5	19.2

FIGURE 1: DISTRIBUTION OF CASES ACCORDING TO AGE



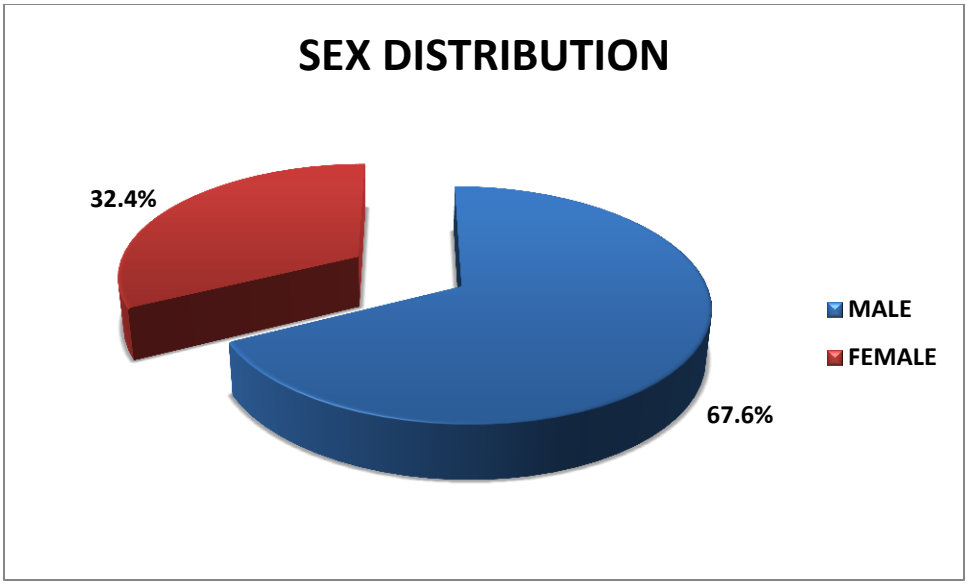
SEX DISTRIBUTION

Out of 312 patients in the study, 211 patients(67.6%) were male and 101patients(32.4%) were female. In this study male patients were more than females. Table 2, Figure 2.

TABLE 2: DISTRIBUTION OF CASES ACCORDING TO SEX

SEX	N	%
MALE	211	67.6
FEMALE	101	32.4
Total	312	100

FIGURE 2: DISTRIBUTION OF CASES ACCORDING TO SEX



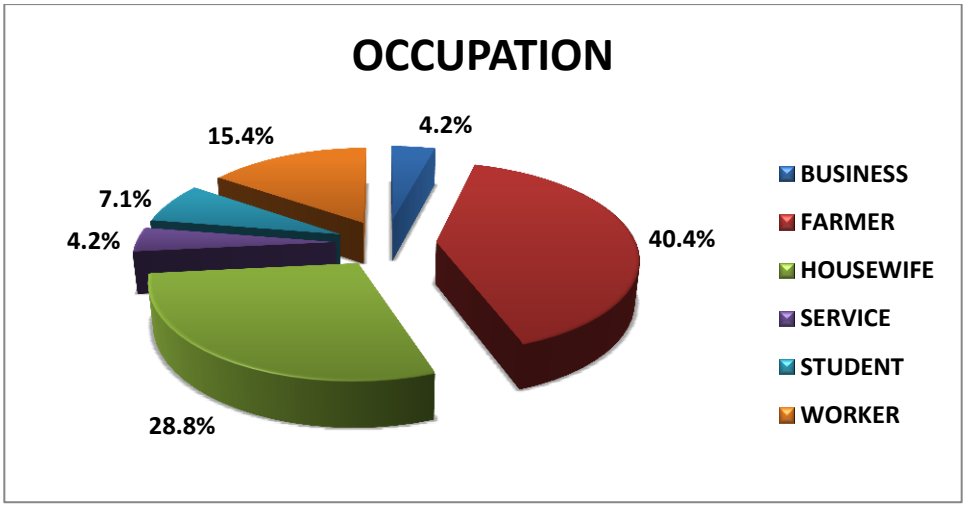
DISTRIBUTION ACCORDING TO OCCUPATION:

Out of 312 patients in the study, 126 patients(40.4%) were farmers, 90 patients(28.8%) were housewife, 48patients(15.4%) were labourers, 13 patients(4.2%) were business, 13 patients(4.2%) were service and 22 patients(7.1%) were unemployed. The most common occupation associated with ACS in this study was Farming followed by home makers, labourer, business, service. Table 4, Figure 4.

TABLE 3: DISTRIBUTION OF CASES ACCORDING TO OCCUPATION

OCCUPATION	N	%
BUSINESS	13	4.2
FARMER	126	40.4
HOUSEWIFE	90	28.8
SERVICE	13	4.2
STUDENT	22	7.1
WORKER	48	15.4
Total	312	100

FIGURE 3: DISTRIBUTION OF CASES ACCORDING TO OCCUPATION



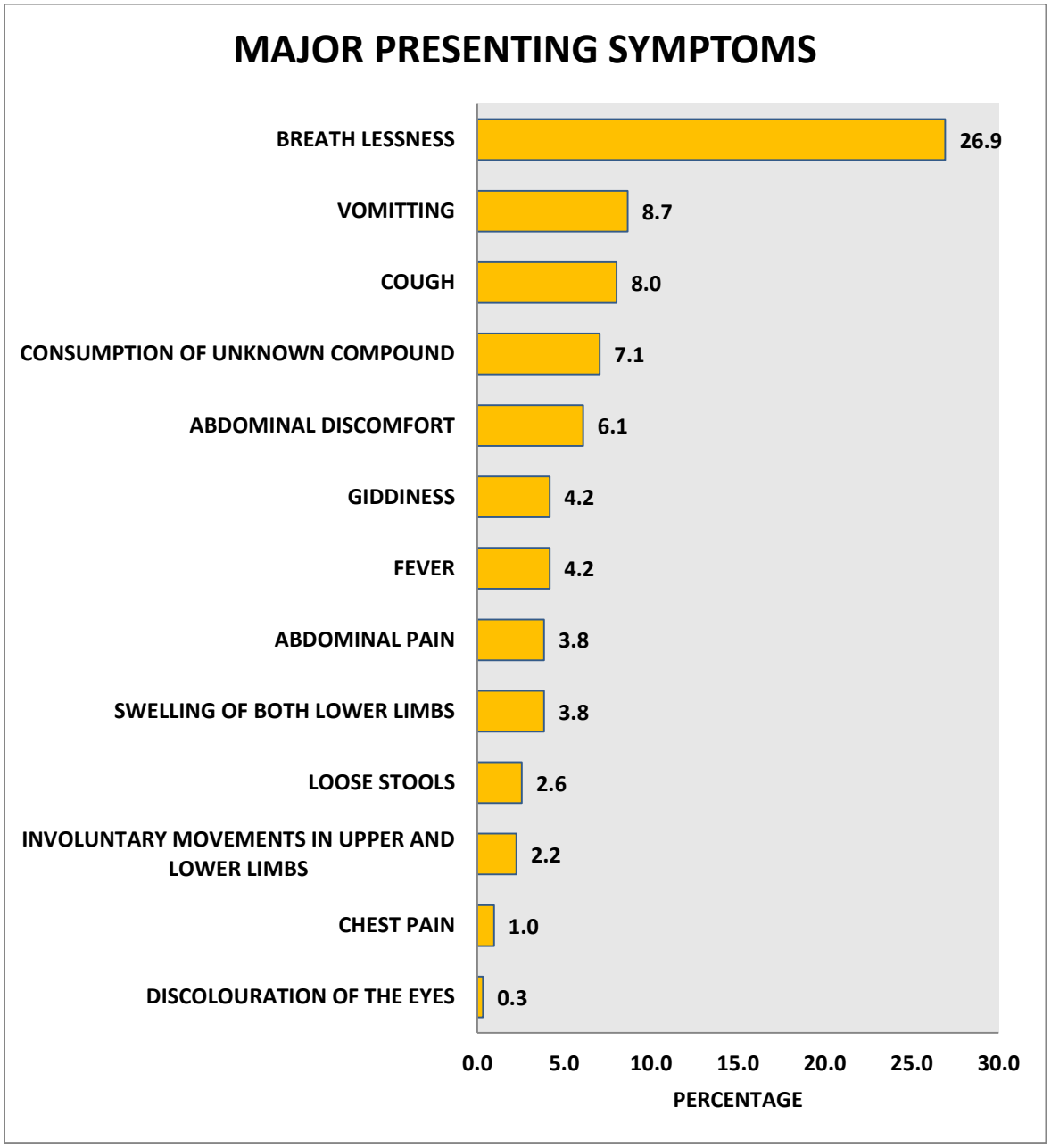
DISTRIBUTION ACCORDING TO SYMPTOMS:

Out of 312 patients in this study, 84 patients(26.9%) had breathlessness and chest pain, 27 patients(8.7%) had headache and vomiting, 25 patients(8%) had cough with expectoration, 22patients(7.1%) had presented with consumption of unknown compound,31 patients(9.9%) had abdominal pain ,and 15 patients(4.2%) had fever, giddiness presented in 13(4.1%)patients, swelling of lower limbs in 12 patients(3.8),abdominal distension in 12 patients(3.8),convulsions were seen in 7 patients(2.2).in the study most common presenting symptoms are chest pain ,breathlessness ,vomiting followed by headache . Table 5, Figure 6.

TABLE 4: DISTRIBUTION OF CASES ACCORDING TO SYMPTOMS

MAJOR PRESENTING SYMPTOMS	**N**	**%**
BREATH LESSNESS/CHEST PAIN	84	26.9
VOMITTING AND HEADACHE	27	8.7
COUGH	25	8.0
CONSUMPTION OF UNKNOWN COMPOUND	22	7.1
ABDOMINAL DISCOMFORT	19	6.1
FEVER	13	4.2
GIDDINESS	13	4.2
SWELLING OF BOTH LOWER LIMBS	12	3.8
ABDOMINAL DISTENSION	12	3.8
LOOSE STOOLS	8	2.6
INVOLUNTARY MOVEMENTS IN UPPER AND LOWER LIMBS AND WEAKNESS OF LIMBS	7	2.2
CHEST PAIN	15	1.0
DISCOLOURATION OF THE EYES	1	0.3

FIGURE 4: DISTRIBUTION OF CASES ACCORDING TO SYMPTOMS



DISTRIBUTION OF CASES ACCORDING TO COMORBIDITIES

Out of 312 patients 109 patients(34.9%) had diabeties and 113patients (36.2%)had presented with hypertension as comorbidities

TABLE 5 : DISTRIBUTION OF CASES ACCORDING TO COMORBIDITIES

COMORBIDITIES	N	%
DIABETES	109	34.9
HYPERTENSION	113	36.2
FAMILY HISTORY	5	1.6

FIGURE 5 :DISTRIBUTION OF CASES ACCORDING TO COMORBIDITIES

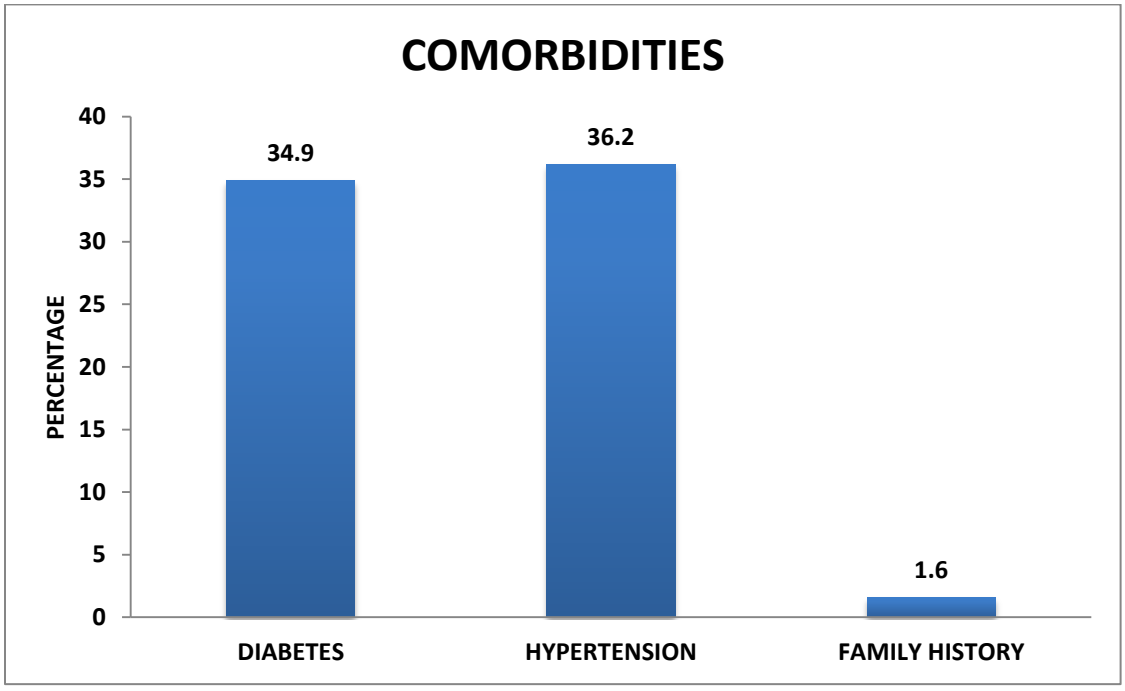


TABLE 6 : DISTRIBUTION OF CASES ACCORDING TO HABITS

HABITS	N	%
SMOKING	81	26
ALCOHOL	66	21.2
TOBACCO CHEWING	8	2.6

FIGURE 6 : DISTRIBUTION OF CASES ACCORDING TO HABITS

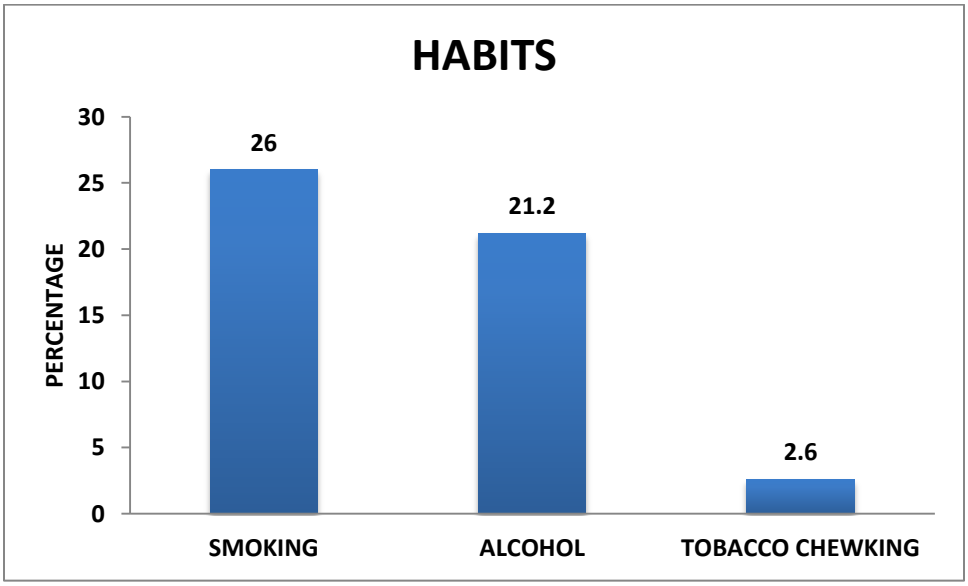


TABLE 7 : DESCRIPTIVE STATISTICS OF PHYSIOLOGICAL PARAMETERS

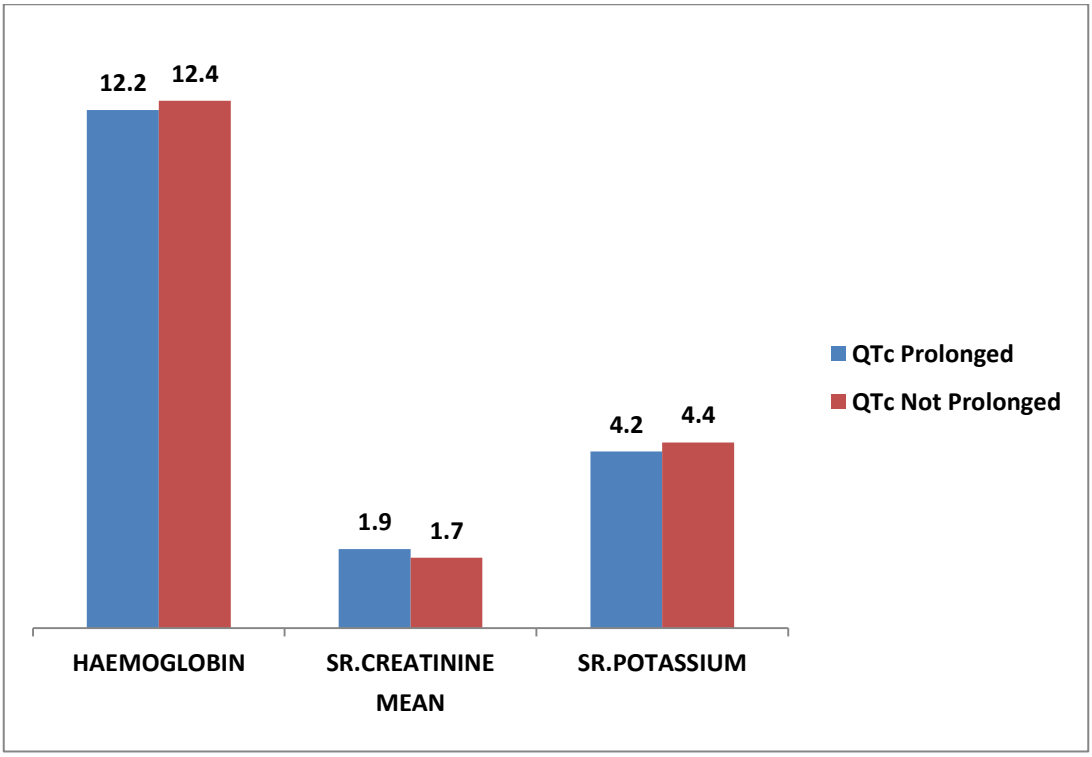
PARAMETERS	Min	Max	Mean	SD
PR	38	160	88.0	16.2
SBP	60	270	126.0	31.4
DBP	40	150	77.8	14.2
RR	12	141	18.3	9.9
TEMPERATURE	36.4	98.4	37.8	4.7

DESCRIPTIVE STATISTICS OF PATHOLOGICAL PARAMETERS

	Min	Max	Mean	SD
HAEMOGLOBIN	4.2	18	12.6	6.6
TOTAL WBC COUNT	1080	57640	13877.3	7938.9
ESR	1	134	32.8	31.8
RBS	36	525	144.7	103.7
SR.CREATININE	0.5	12	1.7	2.2
SR.SODIUM	103	154	133.8	20.9
SR.POTASSIUM	1.3	6.4	4.4	3.6
CPK-MB	3.0	300	46.6	64.5
TROPONIN-I	0.012	40000	2864.2	8977.5

Parameters	QTc				p value
	Prolonged		Not Prolonged		
	Mean	SD	Mean	SD	
HAEMOGLOBIN	12.2	3.6	12.4	2.7	0.535
SR.CREATININE	1.9	2.3	1.7	2.2	0.441
SR.POTASSIUM	4.2	0.9	4.4	1.4	0.132

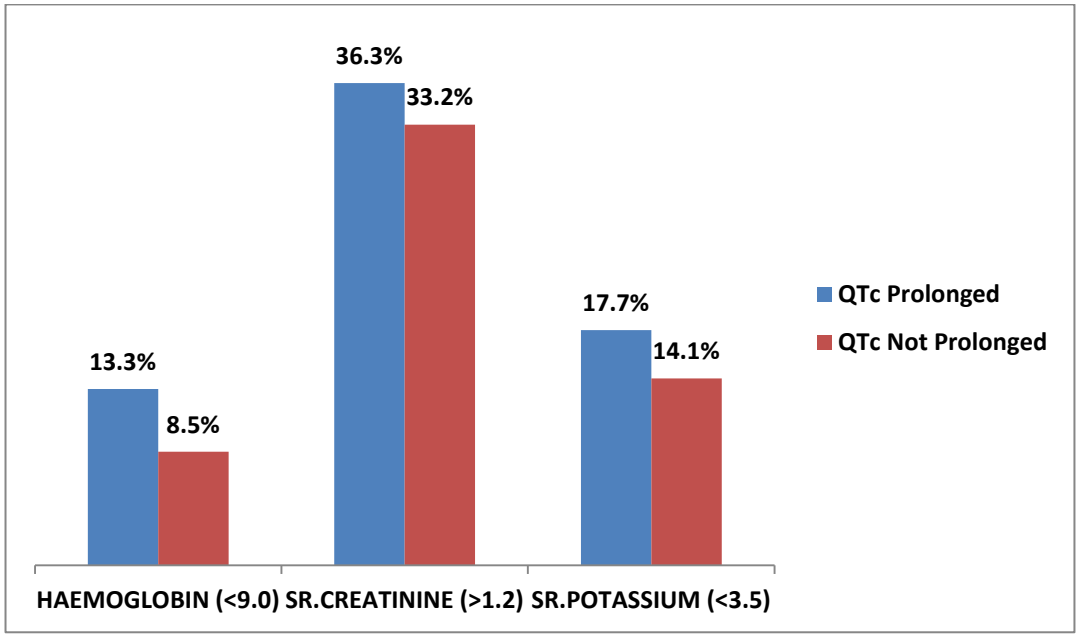
Figure 7: **Descriptive Statistics Of Pathological Parameters**



DISTRIBUTION OF HAEMOGLOBIN, CREATININE AND POTASSIUM ACCORDING TO QTC

Parameters	Prolonged		Not Prolonged		p value
	N	%	N	%	
HAEMOGLOBIN (<9.0)	15	13.3%	17	8.5%	0.191
SR.CREATININE (>1.2)	41	36.3%	66	33.2%	0.577
SR.POTASSIUM (<3.5)	20	17.7%	28	14.1%	0.393
Total	113	100.0%	199	100.0%	

FIGURE: DISTRIBUTION OF HAEMOGLOBIN, CREATININE AND POTASSIUM ACCORDING TO QTC



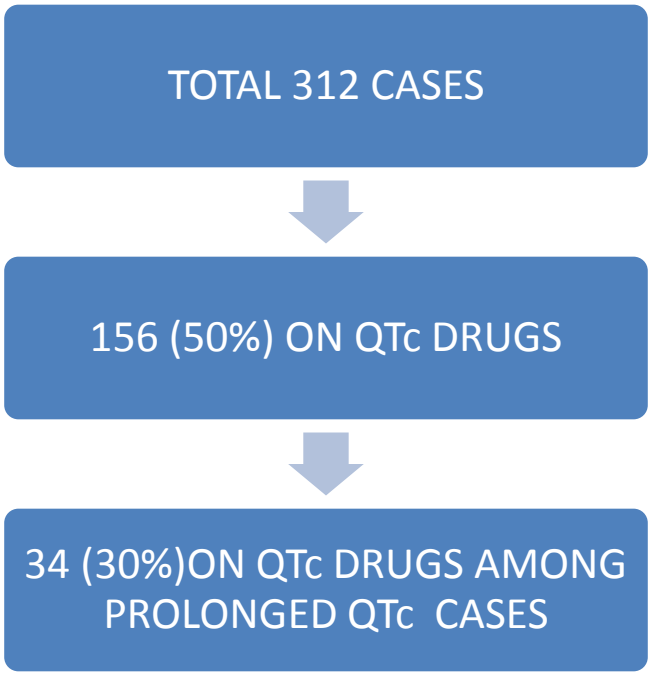

TOTAL 312 CASES
156 (50%) ON QTc DRUGS
34 (30%)ON QTc DRUGS AMONG PROLONGED QTc CASES

TABLE 8: DISTRIBUTION OF CASES ACCORDING TO ECG VARIATION

ST.SEGMENT	N	%
DEPRESSION	30	9.6
ELEVATION	56	17.9
ISOELECTRIC	222	71.2
NO CHANGES	2	0.6
SAWTOOTHED FLUTTER WAVES	1	0.3
T INVERSION IN V1 TO V3	1	0.3
Total	312	100

FIGURE 8 : DISTRIBUTION OF CASES ACCORDING TO ECG VARIATION

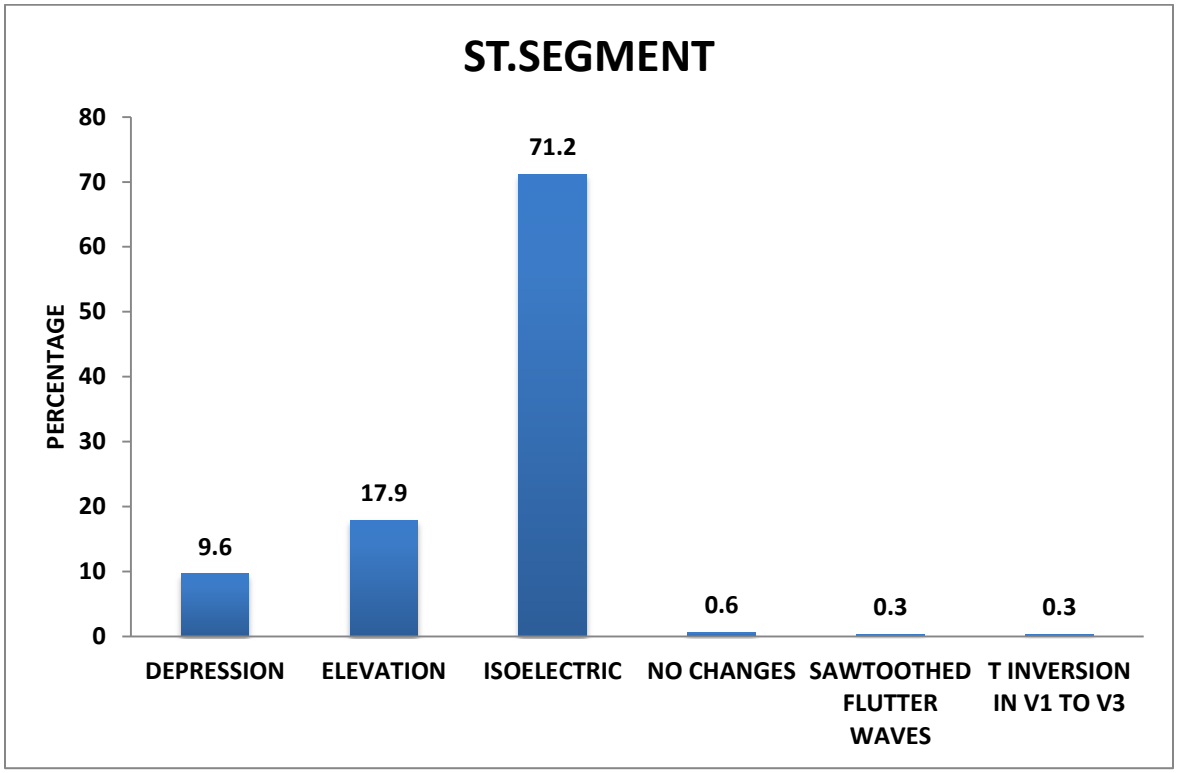


TABLE 9: DISTRIBUTION OF CASES ACCORDING TO SYSTEM INVOLVED

Out of 312 patients study group 112 patients(35.9%) were presented with the complaints of central nervous system ,137 patients (43.9%)had presented with the involvement of cardiovascular system ,66 patients(21.2%) presented with involvement of respiratory system ,28 patients(9%) had presented with symptoms of gastrointestinal system involvement,35 aptients (11.2%)had presented with renal emergencies and 10 patients (3.2%)had presented with endocrine involvement.

SYSTEM INVOLVED	N	%
CNS	112	35.9
CVS	137	43.9
GI/HEPATOBILIARY	28	9.0
RS	66	21.2
RENAL	35	11.2
ENDO	10	3.2

FIGURE 9: DISTRIBUTION OF CASES ACCORDING TO SYSTEM INVOLVED

Out of 312 patients

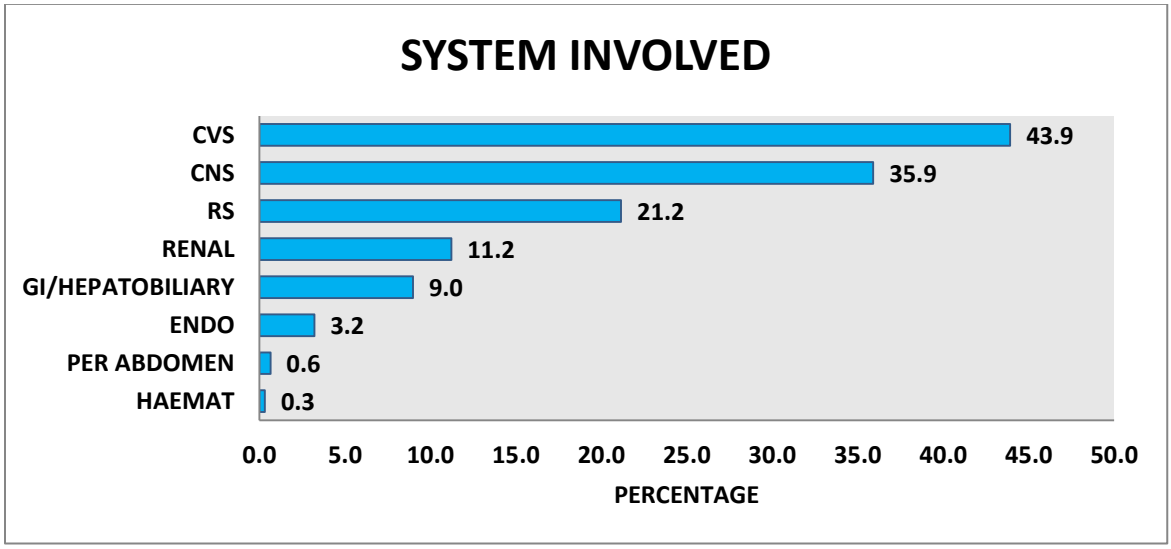
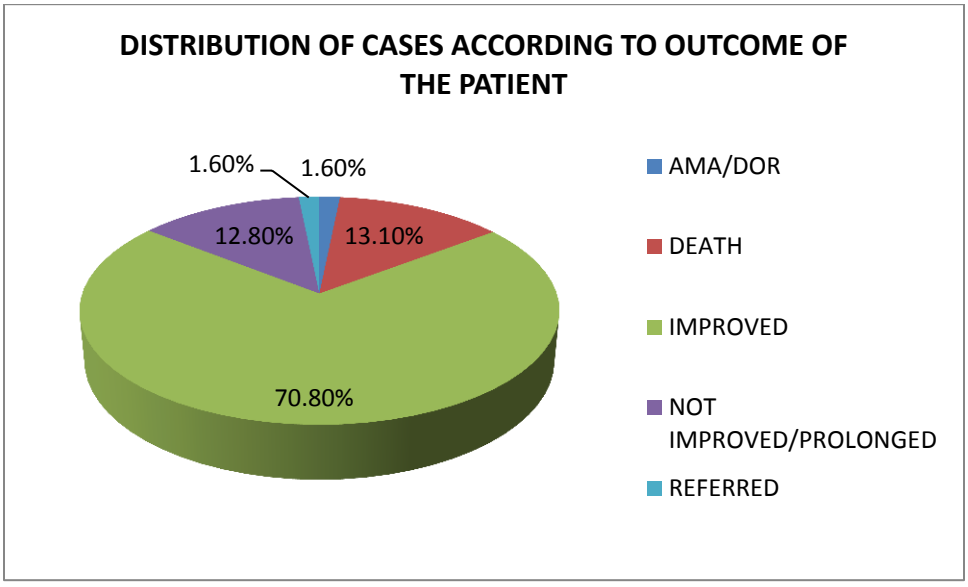


TABLE 10: DISTRIBUTION OF CASES ACCORDING TO OUTCOME OF THE PATIENT

Out of 312 patients out come was observed till the discharge,221 patients (70%)were improved ,around 41 patients died(13.1%),40 patients (12.8%)had prolonged stay or worsend and 10 patients(3.2%) were referred or went against medical advice

OUTCOME OF THE PATIENT	N	%
AMA/DOR	5	1.6
DEATH	41	13.1
IMPROVED	221	70.8
NOT IMPROVED/PROLONGED	40	12.8
REFERRED	5	1.6
Total	312	100

FIGURE 10: DISTRIBUTION OF CASES ACCORDING TO OUTCOME OF THE PATIENT



DISTRIBUTION OF CASES ACCORDING TO DURATION

Among 312 patients duration of stay was observed ,132 patients were discharged after 4-7 days,76 patients were stayed for a period of 2-3 days,66 patients were stayed for 7-10 days,22 patients discharged after 10 days,and around 16 patients were discharged with in a day

TABLE 13: DISTRIBUTION OF CASES ACCORDING TO DURATION

DURATION	N	%
≤24 HRS	16	5.1
2-3 DAYS	76	24.4
4-7 DAYS	132	42.3
7-10 DAYS	66	21.2
>10 DAYS	22	7.1
Total	312	100.0

FIGURE 11: DISTRIBUTION OF CASES ACCORDING TO DURATION

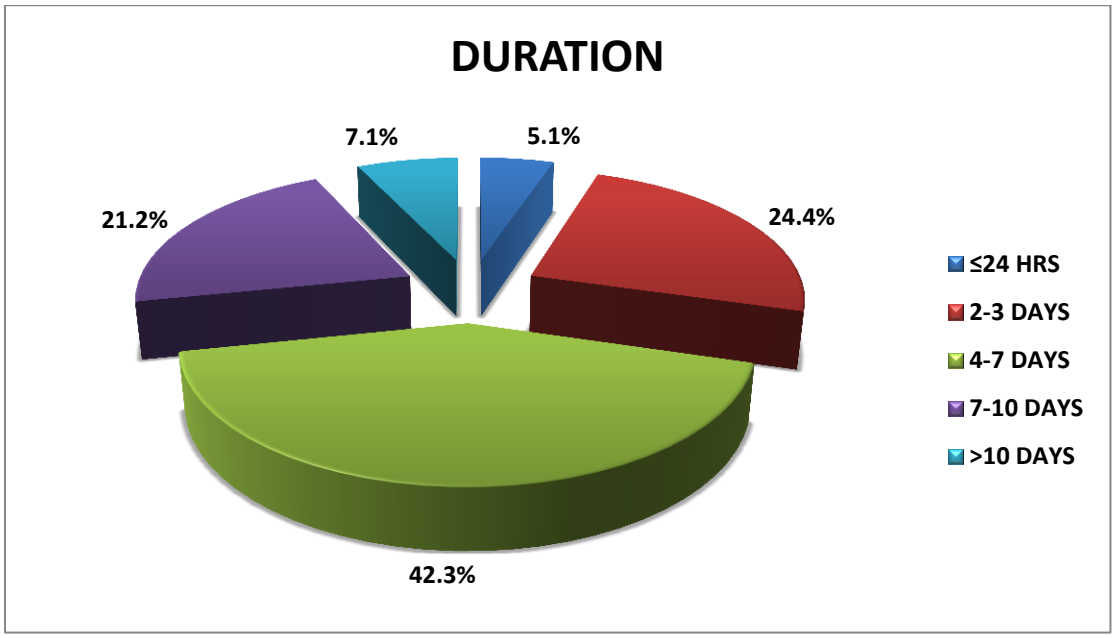


TABLE 11: DESCRIPTIVE STATISTICS OF DURATION OF STAY

	Min	Max	Mean	SD
DURATION (day)	1	16	3.4	1.1

TABLE 12: DISTRIBUTION OF CASES ACCORDING TO QTc

Total 312 patients were studied for the QTc interval prolongation with in 24 hrs of admission .113 patients had prolonged QTc interval which is more than 0.44 sec in males and more than 0.46 in females.shortest was 0.24 sec and longest was 0.74 with a mean of 0.44 sec

QTc	N	%
Prolonged	113	36.2
Not Prolonged	199	63.8
Total	312	100.0

DESCRIPTIVE STATISTICS OF QT

	Min	Max	Mean	SD
QT	0.20	0.68	0.4	0.1
QTc INTERVAL	0.24	0.74	0.44	0.1

FIGURE 12 : DISTRIBUTION OF CASES ACCORDING TO QTc

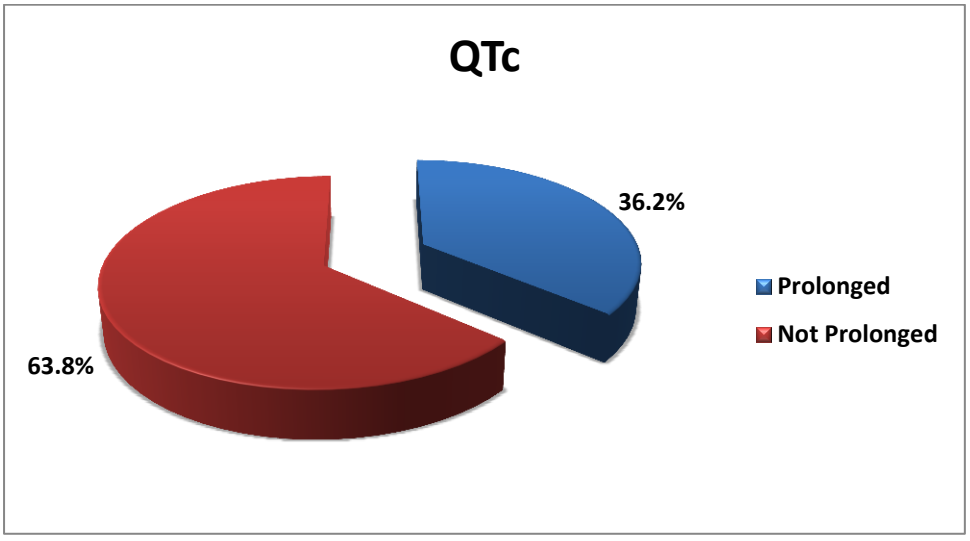


TABLE 13 : DISTRIBUTION OF SYSTEM INVOLVED ACCORDING TO QTc

QTc interval was analysed in a different systems and values were compared with different system. QTc interval of 112 patients with CNS involvement was observed 34 had prolonged out of 112. Cardiovascular system involvement was observed in 137 patients ,55 patients had prolonged QT interval .66 patients were admitted with respiratory emergency 27 patients had prolonged QT interval.35 renal emergencies were observed for QT prolongation only 9 had prolonged,28 patients presented with gastro intestinal emergencies in that 9 ptients had presented with prolonged QTc. 10 patients had endocrine emergencies like DKA ,5 patients had prolonged QTc

SYSTEM INVOLVED	QTc			
	Prolonged		Not Prolonged	
	N	%	N	%
CNS	34	30.1	78	39.2
CVS	55	48.7	82	72.6
GI/HEPATOBILIARY	9	8.0	19	16.8
RS	27	23.9	39	34.5
RENAL	9	8.0	26	23.0
ENDO	5	4.4	5	4.4

FIGURE 13 : DISTRIBUTION OF SYSTEM INVOLVED ACCORDING TO QTc

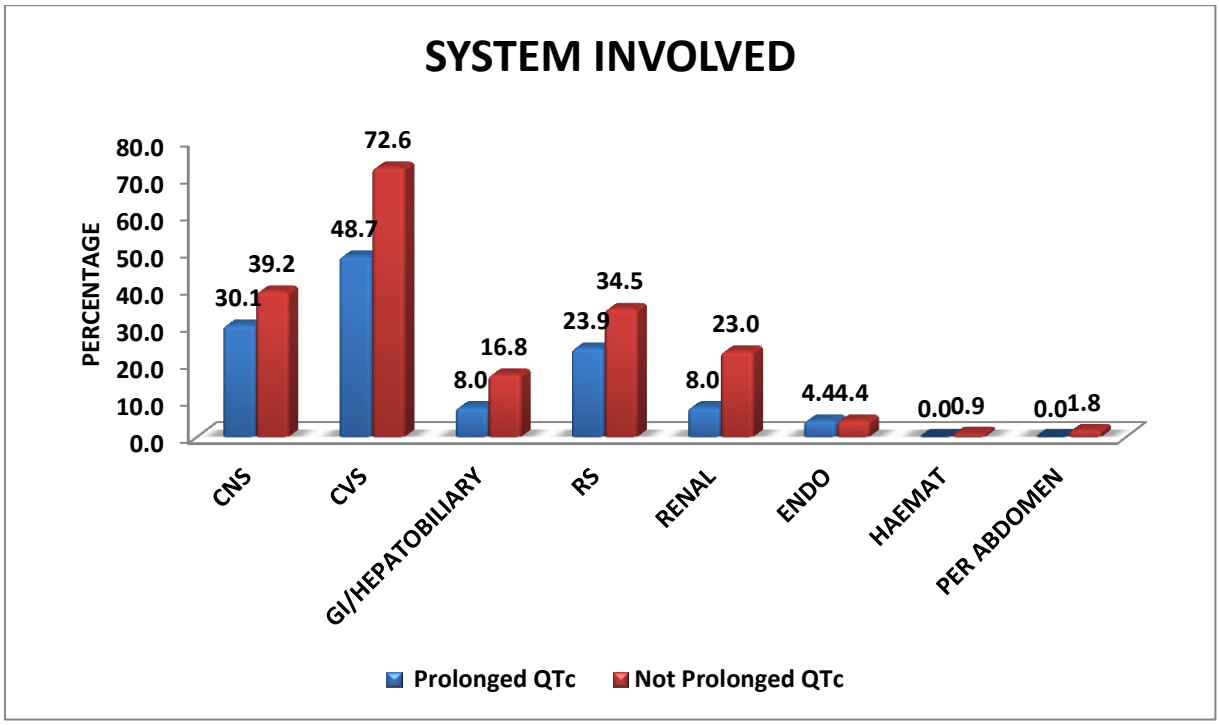


TABLE 14: DISTRIBUTION OF DURATION ACCORDING TO QTc

Among 312 patients duration of stay was compared with prolonged QTc interval.among 16 patients who stayed for less than 24 hrs QTc was prolonged in 5 patients.76 patients were discharged in 2-3 days 21 patients had prolonged QTc,132patients were discharged between 4-7 days of admission56 patients had prolonged QTc,66 patients had discharged between 7-10 days 26 had prolonged QTc and 23 patients were admitted for more than 10 days and QT was prolonged in 5 patients.

DURATION	QTc				p value
	Prolonged		Not Prolonged		
	N	%	N	%	
≤24 HRS	5	4.4%	11	5.5%	0.146
2-3 DAYS	21	18.6%	55	27.6%	
4-7 DAYS	56	49.6%	76	38.2%	
7-10 DAYS	26	23.0%	40	20.1%	
>10 DAYS	5	4.4%	17	8.5%	
Total	113	100.0%	199	100.0%	

FIGURE 14: DISTRIBUTION OF DURATION ACCORDING TO QTc

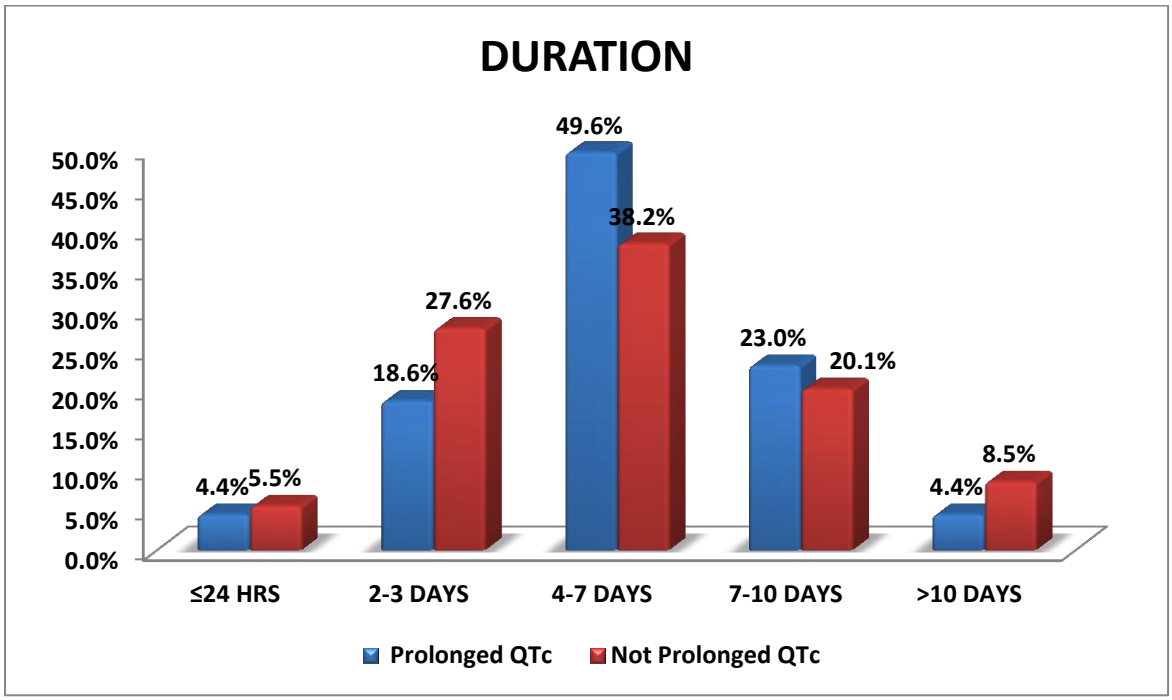
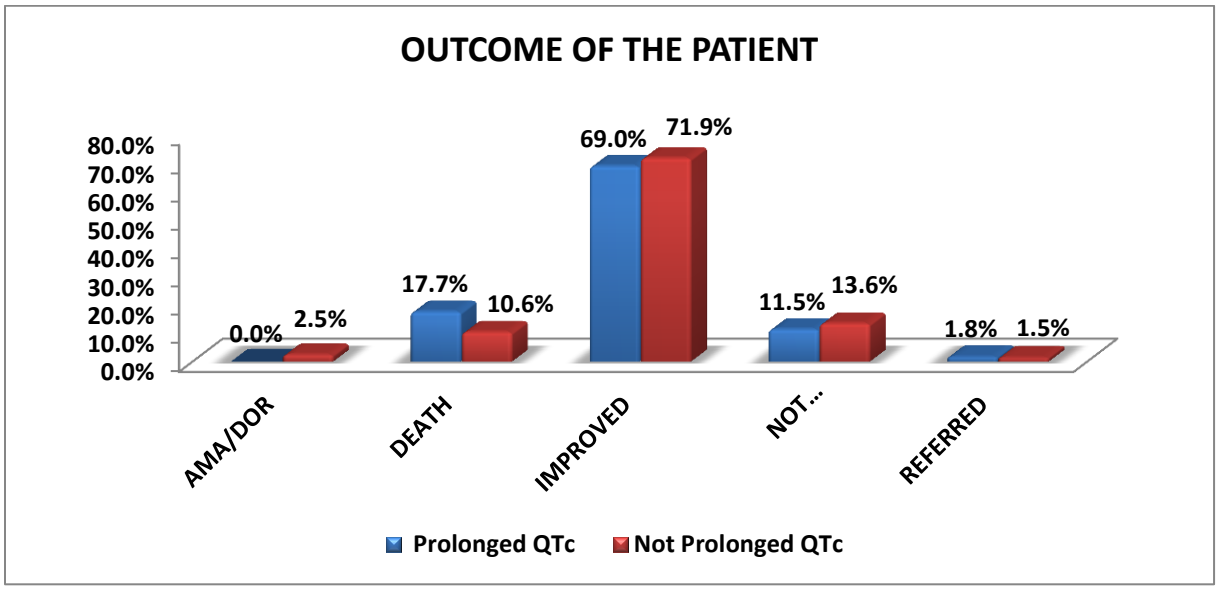


TABLE 15: DISTRIBUTION OF OUTCOME ACCORDING TO QTc

Out come of 312 patients were observed during the study and out come was compared with the QTc interval.41 patients were died during the study 20 had long QTc,worsened or unchanged outcome was observed in 40 patients and 13 had long QTc,221 patients were improved with 78 patients had prolonged QTc and 10 patients were referred or went against medical advice during study.

OUTCOME	QTc				p value
	Prolonged		Not Prolonged		
	N	%	N	%	
AMA/DOR	0	0.0%	5	2.5%	0.200
DEATH	20	17.7%	21	10.6%	
IMPROVED	78	69.0%	143	71.9%	
NOT IMPROVED/PROLONGED	13	11.5%	27	13.6%	
REFERRED	2	1.8%	3	1.5%	
TOTAL	113	100.0%	199	100.0%	

FIGURE 15: DISTRIBUTION OF OUTCOME ACCORDING TO QTc



DISCUSSION

Globally, emergency conditions are significant healthcare burden worldwide with rise in patient volumes over the last few decades. The lack of basic data about emergency care delivery and the incidence of emergency conditions has slowed down attempts to comprehend and improve emergency care.(64) Patients with chest pain and/or anginal equivalent symptoms the 2ndmost common reason of emergency departments (ED) visits among adults.(65) 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.(66), (67) However, there is scarce literature about the prevalence and determinants of QTc interval prolongation in patients admitted to emergency medical services.

Sudden cardiac arrest (SCA) in the ED is being increasingly seen in younger age groups. There exists a great need for improving prehospital care as well as control of risk factors to decrease the incidence and improve the outcome in medical emergency patients.(68) Cardiac monitoring methods such as 12-lead electrocardiography (ECG) and bedside monitors, enable physician to identify arrhythmias, myocardial ischemia, and QT-interval measurements in real time.(69), (70) This study was conduct to evaluate the QTc interval in medical emergency patients and their in-hospital outcomes. Since ECG is available and relatively non-invasive and cheap, knowledge of $QT_C$is of immense benefit in patient management.(71)

In our study, the total number of patients enrolled were 312, of which 67.6% were males and 32.4% was female patients. The mean age of the patients enrolled in our study was

53.5 (±19.2) years, with minimum age 18 and maximum age 99 years. The major presenting symptom reported in our study was breathlessness 26.9%. In the patients attending the ED, the system involved were CNS 35.9%, CVS, 43.9%, GI/hepato-biliary 9%, respiratory system 21.2%, renal 21.2%, endocrinology 3.2% and hematology 0.3%. The distribution of patients as per ABG were: acidosis 21.8%, alkalosis 10.3%, CO2 retention in 1.9% cases.

Cardiac monitoring is a useful, noninvasive diagnostic tool to monitor the wide array of patient conditions in the ED. To assist clinicians in determining which patients need monitoring, experts in electrocardiology and cardiac monitoring convened to develop practice standards forECG monitoring during hospital stay.(72), (73) These practice standards encompass all areas of hospital cardiac monitoring, including arrhythmia, myocardial ischemia, and QT interval monitoring. Guidelines reflect expert opinions based on clinical experience and research; however, data for best practices for hospital cardiac monitoring are limited.(73)

The risk assessment for QT prolongation of in- hospital patients is based on their medication profile, demographic risk factors, electrolyte disturbances, and monitoring of the corrected QT (QTc) interval. Large population studies have shown a relation between QTc and all- cause mortality, cardiac mortality, and sudden cardiac death.(74),(72)A normal corrected QT (QT_c) for women is less than 0.46 seconds and for men is less than 0.45 seconds. A QT_c of greater than 0.50 seconds in either gender positively correlates with a higher risk for TdP. The duration of QT_c is a reliable risk indicator of cardiac events. Therefore, patients with long QT syndrome and associated ventricular arrhythmias should receive QT monitoring in the ED (class I recommendation).(73), (75)

In our study the mean QTc interval observed was 0.5 (±0.1) with range of minimum 0.24 to maximum 0.74.The importance of QT monitoring in the ED cannot be underestimated because ED patients are uniquely at risk for developing TdP owing to their vast array of chief complaints and high acuity. Specific patient characteristics are associated with development of TdP and should be considered during triage and risk stratification.(75) Practice guidelines recommend measuring patients' QT/QT_c interval at baseline and documenting repeat measures at least once every 8 hours.(73) Patients in the ED may initially require QT/QT_c monitoring more frequently, especially if receiving medications known to prolong the QT interval.

The prevalence of QTc prolongation is higher in patients brought to ED owing to presence of acute ailments. Frequently they have one or more of risk factors and are on poly-drug therapy. In this study the prevalence of prolonged QTc interval was 36.2%, which was similar to earlier studies by Birda et al. and Seftchick MW et al.(76), (77) In the study done by Birda et al the prevalence of QTc prolongation was 34.1%. In this study QTc prolongation was observed in 17.7% patients who succumb to the disease, 69% patients with improvement, 11.5 % who did not improve, and 1.8% referred patients. Whereas in a study by Birda et al, there was no difference in hospital mortality at subgroup analysis. Patients with markedly prolonged QTc interval had significantly more episodes of in-hospital ventricular tachycardia and hospital mortality.(76)In a recent study, the most frequent ECG abnormality (42%) was prolonged QTc interval. (78)High prevalence of Prolonged QTc (35%) was also reported by George TK et al in medical ICU at admission. (79)

The cardiovascular systems (CVS) involvement according to QTc prolongation was found in 48.7% cases.In our study ST segment changes observed were as follows: depression 9.6%, elevation 17.9%, isoelectric 71.2%, saw tooted flutter waves 0.3%, T inversion inV1 to V3 0.3% and no change in 0.6%. In all the patients the rhythms was regular and regional wall motion abnormality was found in 15.1%. LVEF was found to be less than 45% in 10.5% of study patients. The QTc interval was prolonged in 100% patients with early transmural ischemia. When compared with clinically accepted indexes of transmural ischemia (i.e., STD and STE [≥1 mm] it is the earliest noted ECG abnormality.(80)The corrected QT interval (QTc) is prolonged in the setting of acute coronary artery disease.(81)

Our results show QTc prolongation in 30.1% patients with CNS involvement. QTc-prolongation is common after posterior circulation stroke and is also associated with temporal lobe infarction.(82)Our finding demonstrated QTc prolongation in 8% of patients having renal involvement and with mean sr. creatinine 1.9 (±2.3). The QTc prolongation was also observed in 36.3% patients with sr. creatinine > 1.2. Hemodialysis patients have tendency to have higher values of QTc.(20)QT interval prolongation is a predictor of sudden cardiac death due to ventricular arrhythmias, which may account for 1.4% to 25% of deaths in end-stage renal disease (ESRD).(83)

QTc prolongation was seen in 4.4% of patients having endocrine involvement. In our study 34 % patients were diabetic. Overt hypothyroidism is associated with many cardiac manifestations, such as prolongation of QRS and QT intervals. QT prolongation and increased QTd have been shown to be directly related to TSH level in overt hypothyroidism.(84) Paradoxically, hyperthyroidism can also lead to QT prolongation. In

adults with hyperthyroidism, QTc is prolonged compared with controls that tends to normalize with treatment of hyperthyroidism.(85) QTc prolongation observed at baseline in type 2 diabetic (T2D) was significantly associated with QTc prolongation during severe hypoglycemia (SH) in patients with T2D, indicating the need of QTc monitoring and measures to be taken to avoid SH.(86).Prolongation of the QTc has been described in a few children receiving ketogenic diets. But cardiac effects of ketosis have not otherwise been investigated. Prolonged QTc occurs frequently during DKA and is correlated with ketosis.(87)But the findings regarding the QT and QTc interval durations are a little bit controversial in type 1 diabetes.(88), (89)

Alcoholic liver disease may lead to QT interval prolongation and is associated with an adverse prognosis, especially sudden cardiac death.(90)In our study QT interval prolongation was observed in 8.0% of patients with gastrointestinal and hepatobiliary diseases. Thus, QT measurement should be included in the initial assessment of alcoholic patients.

Prolonged QTc (corrected QT) interval and torsades de pointes (TDP) are associated with hypocalcemia, hypomagnesemia, hypokalemia, possibly alkalosis and may result in syncope and sudden cardiac death. In this study QTc prolongation was observed in patients with mean Sr. potassium 4.2 (±0.9). The QTc prolongation was observed in 17.7% patients with sr. potassium < 3.5. QTc duration is highly sensitive to hypokalemia, particularly in women. Methadone prolongs QTc remarkably compared to other non-cardiologic medicines. QTc>500 with normal QRS often signifies profound illness and substantial mortality risk, though not necessarily imminent TdP.(91) Hypokalemia is associated with lengthening of QT interval in psychiatric patients on admission(92)and it

is a strongly recommended as screening test. Drugs known to prolong the QT_c interval should be discontinued immediately. Serum potassium and/or magnesium should be replaced if the patient is hypokalemic or hypomagnesemic.

The QTc prolongation was observed in patients with mean hemoglobin (Hb) 12.2 (±3.6) and 13.3% patients with Hb <9.0. In a South Korean nationwide cohort it was found that anemia was associated with an augmented risk of sudden cardiac arrest (SCA) after accounting for concomitant conditions. The correlation between anemia and SCA could be because of might be explained by an increase in arrhythmic risks, such as QTc prolongation. A negative correlation between QTc prolongation and Hb level was observed in men, and a trend was observed in women.(93)

Numerous drugs have been associated with QT prolongation and over the last decade a number of drugs have been withdrawn from the market or restricted because of reports of QT prolongation and TdP.(94)In this study out of the 312 patients, 156 (50%) were on drugs with potential to cause QTc prolongation. Among these 156 patients, 43(30%) had QTc prolongation. Another study reporting comparable prevalence of QTc proportion had significant number of patients on drugs with potential of prolonging QT interval. (79) Study by Tisdale *et al* observed that among patients with a prolonged QTc at admission 18 (35%) received a QT prolonging drug.(95) In other studies 34.7% of the population with a prolonged QTc received a QT prolonging drug.(96) It was noted that an additional QT prolongation of >60 ms occurred in 57.1% of these patients. The study by Kozik and Wung documented that 59% received a drug with known QT prolonging action.(97)Some evidence indicates that concomitant administration of ≥ 2 QTc interval–prolonging drugs may increase the risk. Conditions that lead to elevated plasma concentrations of QTc

interval–prolonging drugs increase the risk of drug-induced TdP. These include pharmacokinetic drug interactions, inadequate dose adjustment if the drug has renal elimination and QTc interval–prolonging drugs in patients with acute kidney injury or chronic kidney disease.(98)

In respiratory system disorder, mortality of COPD patients is associated with QTc interval. (99)The study by Taooka Y et al showed that QTc interval (> 0.44 seconds) is one of the potential prognostic factors for pneumonia in elderly patients.(100)In our study QTc prolongation observed in 23.9% with respiratory system involvement.

During present study, the mean duration of stay in the emergency department was 3.4 (±1.1) days ranging from minimum 1 day to maximum 16 days. The duration of QTc prolongation was ≤24 hrs. in 4.4% of patients, 2.-3 days in 18.6% of patients, 4-7 days in 49.6% of patients, 7-10 days in 23.% of patients, and > 10 days in 4.4% of patients. In study by Bidra et al the median duration of hospital stay was 6 days. (13)Whereas,George TK et al (79)documented the mean duration of stay in the Intensive care unit (ICU) as 7 days and hospital stay of 13 days. The duration of ICU stay was comparable between normal QTc vs prolonged QTc group, 7.2 and 7.3 days respectively. In our study too, the duration of ICU stay for QTc prolonged group was not significantly different as compared to normal QTc group.

The QT prolongation due to existing cardiovascular disorder has been shown to have association with poor ICU outcomes.However earlier studies demonstrated mixed results in terms of outcome in hospital admissions with prolonged QTc interval. (101), (102), (103), (104)The outcome of the patient observed was, discharge against medical advice in 1.6%, death in 13.1%, improvement in 70.8%, prolonged illness in 12.8% and referral of

1.6%. In our study QTc prolongation resulted in mortality in 17.7% patients,and there was improvement in 69% patients. About 11.5 % patients had worsening and 1.8% patients were referred. Our results were in congruence with find of study by Bidra et al.(105) The results of Bidra et al show discharge at recovery in 76%, hospital death in 18.25%, leave against medical advice in 4.9% and two patients (0.76%) absconded. Our patient mortality rate was lower than the results of Anderson et al (all-cause mortality 39%) for patients with QT prolongation. The probable reason of findings by Anderson et al could be higher rate of ventricular arrhythmias patients in their cohort.(106)Seftchick MW et al reported structural heart disease, renal failure, and stroke as the most common comorbidities. About 44% of patients with any degree of QTc prolongation were discharged from the ED. Furthermore, 23% of patients with QTc intervals ≥ 500 ms were discharged from the ED, including 16 patients with QTc intervals greater than or equal to 500 ms and QRS durations less than 120 ms (16/60; 27%;). Five percent of the patients with QTc prolongation died in the ED or during hospitalization; none had QTc prolongation or torsades de pointes listed as a cause of death.(107) It is seen that in acutely ill patients the prevalence of a prolonged corrected QT interval (QTc) is much higher than one might expect. Though the underlying causes may be correctible.

CONCLUSION

To conclude, a high prevalence of QTc prolongation was present in patients admitted to our medical emergency department along with high incidence of risk factors. Therefore, it is critical that emergency department staff should not only be cognizant of drugs prolonging QTc, but must also thoroughly elicit related patient history that may contribute to QTc prolongation and monitor patients with risk factor for better patient outcomes.

SUMMARY

In our study, the total number of patients enrolled were 312, of which 67.6% were males and 32.4% was female patients.

The mean age of the patients enrolled in our study was 53.5 (±19.2) years, with minimum 18 to maximum 99 years.

The major presenting symptom in our study was breathlessness 26.9%.

In our study ST segment changes observed were as follows: depression 9.6%, elevation 17.9%, isoelectric 71.2%, saw tooted flutter waves 0.3%, T inversion inV1 to V3 0.3% and no change in 0.6% cases.

In the patients attending the ED, the system involved in cohort were CNS 35.9%, CVS, 43.9%, GI/hepato-biliary 9%, respiratory system 21.2%, renal 21.2%, endocrinology 3.2% and hematology 0.3%.

In all the patients the rhythm was regular and regional wall motion abnormality was found in 15.1%

LVEF was reported as 45% in 10.5% of patients.

The distribution of patients as per ABG were: acidosis 21.8%, alkalosis 10.3%, CO2 retention and 1.9% cases.

The outcome of the patient observed was, discharge against medical advice in 1.6%, death in 13.1%, improvement in 70.8%, prolonged illness in 12.8% and referral of 1.6%

The mean duration of stay in the emergency department was 3.4 (±1.1) days with minimum 1 to maximum 16 days.

The mean QTc interval observed was 0.5 (±0.1) with minimum 0.24 to maximum 0.74.The QTc prolongation was observed in 36.2% of patients.

The systems involved according to QTc prolongation were CNS 30.1%, CVS 48.7%, GI/hepatobiliary 8.0%, respiratory 23.9%, renal 8%, and endocrinological 4.4%

The duration of QTc prolongation was ≤24 hrs. in 4.4%, 2.-3 days in 18.6%, 4-7 days in 49.6%, 7-10 days in 23%, and > 10 days in 4.4% of patients.

QTc prolongation observed among cohortwas17.7% hospital death, improvement in 69%, no improvement in11.5 %, and 1.8% patient referals.

In this study out of the 312 patients, 156 (50%) were on drugs which had potential to cause QTc prolongation and of 156 patients, 43(30%) had QTc prolongation.

The QTc prolongation was observed in patients with mean Hb 12.2 (±3.6), sr. creatinine 1.9 (±2.3) and sr. potassium 4.2 (±0.9).

The QTc prolongation was observed in 13.3% patients with Hb <9.0, 36.3% patients with sr. Creatinine > 1.2 and 17.7% patients with Sr. potassium < 3.5.

LIMITATIONS OF THE STUDY

Firstly, we did not evaluate the diurnal QTc variability circadian although reported circadian QTc changes are conflicting. Secondly, the risk score that could have helped in clinical decision-making were not considered.As risk factors are important for the development of QTc interval prolongation/TdP, quantification of risk may be helpful in targeting patients at greatest need of intervention/monitoring. A risk score for predicting the development of QTc interval prolongation in patients hospitalized in cardiac care units has been developed and validated. Thirdly, continuous ECG monitoring was not evaluated as in our case continuous monitoring data was not captured, therefore we might have missed out other prolonged QT intervals or arrhythmias.

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ETHICAL CLERANCE CERTIFICATE

CONSENT FORM

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned,_____ , S/O D/O W/O _____, aged ____years, ordinarily resident of _____ do hereby state/declare that

_____

Research Centre has examined me thoroughly on _____ at _____ (place) and it has been explained to me in my own language that I am suffering from _____ disease (condition) and this disease/condition mimic following diseases. Further Doctor _____ informed me that he/she is conducting dissertation/research titled "left atrial volume index as a predictor of early in-hospital major cardiovascular events in acute coronary syndrome" under the guidance of requesting my participation in the study. Apart from routine treatment procedure, the pre-operative, operative, post-operative and follow-up observations will be utilized for the study as reference data.

Doctor has also informed me that during conduct of this procedure like adverse results may be encountered. Among the above complications most of them are treatable but are not anticipated hence there is chance of aggravation of my condition and in rare circumstances it may prove fatal in spite of anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study help in evaluation of the results of the study which is useful reference to treatment

of other similar cases in near future, and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made photographs video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Shri/Smt _____ under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient:

Signature of doctor:

Witness: 1.

2.

Date:

Place:

THE STUDY OF PROLONGED QTc INTERVAL AS A PREDICTOR OF OUTCOMES IN PATIENTS ADMITTED AS MEDICAL EMERGENCIE

Name: CASE NO:

Age: IP NO:

Sex: DOA:

Religion: DOD:

Occupation:

Residence:

Presenting complaints:

History of present illness:

Past History:

Family History:

Personal History:

Diet/appetite

Sleep

Bladder and bowel habits:

Smoking/Tobacco chewing/Alcohol

General Physical Examination:

Vitals

PR :

BP :

RR :

Temp:

Hair:

Eyes:

Pupils:

Nose:

Ears:

Oral Cavity:

Upper Limbs:

Chest:

Abdomen:

Genitilia:

Lower Limbs:

Skin:

SYSTEMIC EXAMINATION

Cardiovascular System

Central Nervous System

Respiratory system

Abdomen

INVESTIGATIONS

HAEMATOLOGY –

Haemoglobin	gm %
Total WBC counts	Cells/mm^3
Differential counts -	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Monocytes	%
Basophils	%
ESR	mm after 1 hour

BIOCHEMISTRY–

Random blood sugar(mg/dl)	
Blood urea(mg/dl)	
Serum creatinine (mg/dl)	
Serum sodium (mmol/dl)	
Serum potassium (mmol/dl)	

URINE EXAMINATION -

Albumin	
Sugar	
Microscopy	

ECG-

	ECG
Standardization	
Rate	
Rhythm	
P wave	
PR interval	
QRS complex	
QRS configuration	
QRS duration	
QRS Axis	
ST Segment	
T wave	
QT	
QTc	
Arrythmias	
Ectopics	
Heart blocks	

Ecg diagnosis:

DIAGNOSIS:

OUTCOME