“QT INTERVAL ABNORMALITIES IN ACUTE ISCHEMIC STROKE AND ITS CORRELATION WITH STROKE SEVERITY AND SUBTYPE”

Dr. Nandana J

DM NEUROLOGY THESIS

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A THESIS SUBMITTED BY

Dr. Nandana J

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES

AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE

REQUIREMENTS FOR THE AWARD

OF

DM NEUROLOGY

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DECLARATION BY THE STUDENT

CERTIFICATE

I Dr. Nandana J, hereby certify that I had personally carried out the work depicted in the thesis titled, "**QT INTERVAL ABNORMALITIES IN ACUTE ISCHEMIC STROKE AND ITS CORRELATION WITH STROKE SEVERITY AND SUBTYPE**". No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

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Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

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This is to certify that the dissertation entitled "QT INTERVAL ABNORMALITIES IN ACUTE ISCHEMIC STROKE AND ITS CORRELATION WITH STROKE SEVERITY AND SUBTYPE" is a bonafide research work done by **Dr Nandana J**, Senior resident in Department of Neurology, in partial fulfillment of the requirement of DM Neurology degree.

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LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1	AIS	Acute ischemic stroke
2	ECG	Electrocardiography
3	CVD	Cardiovascular diseases
4	NIHSS	National Institutes of Health Stroke Scale
5	mRS	Modified Rankin scale
6	TOAST	The Trial of Org 10172 in Acute Stroke Treatment
7	TIA	Transient ischemic attacks
8	SAH	Subarachnoid haemorrhage
9	ICH	Intracerebral haemorrhage
10	AF	Atrial fibrillation
11	QTd	QT interval dispersion
12	QTc	corrected QT interval
13	Tpe	Tpeak-Tend interval
14	ANS	Autonomic nervous system
15	CNS	Central nervous system
16	RR	R wave to R wave interval
17	POVD	Peripheral occlusive vascular disease
18	RBS	Random blood sugar
19	BP	Blood pressure
20	HDL	High-density lipoprotein
21	LDL	Low-density lipoprotein
22	TGL	Triglyceride

23	MCA	Middle cerebral artery
24	LAA	Large artery atherosclerosis
25	IMT	Intima media thickness
26	ms	Milliseconds

SYNOPSIS

Background and Purpose

The QT interval in ECG is susceptible to autonomic changes. Autonomic dysfunction, especially sympathetic hyperactivity, is well known in acute ischemic stroke (AIS) and the level of sympathetic activity may differ based on stroke subtype and severity. Even though there are studies highlighting the difference in dysautonomia and QT interval changes between ischemic and haemorrhagic strokes, so far to our knowledge, no studies have looked into the differential effect of ischemic stroke subtypes on QT interval changes. Our study aims to determine the incidence of QT interval abnormalities in acute ischemic stroke patients without any known cardiac comorbidities, and its correlation with stroke severity and subtype.

Materials and Methods

Ours was a single centre prospective observational study. 100 consecutive patients admitted to the Stroke unit at SCTIMST with a diagnosis of acute ischemic stroke were included in the study after applying inclusion and exclusion criteria, and were followed up for 3 months. The demographic details, clinical features (stroke severity by NIHSS and disability scores with mRS), stroke subtype (based on TOAST classification) and imaging data were collected. QT interval changes were recorded from ECG at admission, at 48 hours post admission and 3 month follow up. The data was analysed to find out the incidence and nature of QT interval abnormalities in acute ischemic stroke and, any potential association based on stroke subtype and/or severity.

Results

Overall, 59 %(n=59) of patients had a prolonged QTc noted on the admission ECG, while 40% patients had prolonged QTc after 48 hours and only 15% patients had prolonged QTc at 3 months. 52.5% patients with QTc prolongation at admission had large artery atherosclerotic disease (p value= 0.010). Among our patients, those with moderate (55.5%, n= 30) and severe

stroke at admission (95.5%, n= 21) had significant QTc prolongation at admission as compared to those with minor stroke (33.3% n =8) (p value <0.001). Patients with more disability ie. mRS scale of 3 to 6, at admission (p value <0.001), discharge (p value 0.013) and 3 month follow up (p value 0.004) had more QTc prolongation as compared to those with mRS score of 0 to 2. Admission QTc prolongation was also associated with severe stroke deficits at discharge and 3 month follow up (p value <0.05). In multivariate analysis, only functional disability at admission by mRS scoring remained to be associated with prolonged QTc at admission (odds ratio 4.303, 95% confidence interval 1.356-13.655). However, persistently prolonged QTc after 48 hours was associated with worse NIHSS (p value 0.002 and <0.001), and mRS score (p value <0.001 and 0.001), at discharge and 3 month follow up respectively as compared to those with normalisation of QTc after 48 hours, which was independent of stroke severity and disability at admission. 80% of patients with normalization of QTc at 48 hours had improvement of mRS score at discharge (p value <0.001). The 4 patients who had died had QTc prolongation of at admission as well as at 48 hours.

Conclusion

QTc-prolongation is common after AIS, and is associated with increased long-term morbidity and mortality. Our study explored the correlation of prolonged QTc with large artery atherosclerotic disease as well as stroke severity. The prolonged QTc at 48 hours was associated with worser neurological outcome at discharge as well as at 3months follow up. The differential incidence of QTc prolongation possibly indicates a variable autonomic dysregulation among patients with AIS, with regard to stroke subtype and severity.

INTRODUCTION

1. INTRODUCTION

The interconnection between the cardiovascular and nervous system has been described since beginning of the twentieth century (1). The existence of a 'brain-heart axis' has been postulated whereby the structural brain lesions by themselves result in electrocardiographic changes (ECG) (2), even without the evidence of primary heart disease(3) . However the ECG abnormality and cardiac arrhythmias which are identified in 50-70% of patients with acute stroke (4,5), are often underrecognized after strokes (6).Many people who suffer from stroke often have underlying cardiovascular diseases (CVD) such as hypertension, ischaemic heart disease, and atrial fibrillation (7). And these underlying CVD are associated with several pre-existing ECG anomalies. However irrespective of the presence or absence of a pre-existing cardiac disease, observing an abnormal ECG in an acute stroke patients more than doubled their mortality rate at 6 months (8).

The common ECG abnormalities are found following stroke include QT interval prolongation, ST segment as well as T wave changes (9).These abnormalities have been attributed to transient autonomic dysfunction especially sympathetic hyperactivity, which is well known in acute ischemic stroke and the level of sympathetic activity may differ based on stroke severity (10–12). Stroke severity is assessed based on National Institutes of Health Stroke Scale (NIHSS) (13) and Modified Rankin scale (mRS) (14).

It is well known that QT intervals on ECG are susceptible to autonomic influences (15). And the presence of prolonged QT interval has been shown to be associated with higher mortality in stroke (16); but there are no studies available on the differential effect of ischemic stroke subtypes and stroke severity on QT interval changes. Ischemic stroke is divided into five subtypes based on The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (17).

It will be logical to hypothesize that the sympathetic over drive may be related to stroke subtype and stroke severity. Hence corresponding QT interval changes will occur in ECG. It would be interesting to look for potential correlation of QT interval abnormalities with severity and subtype of acute ischemic stroke. This might also have therapeutic implications.

REVIEW OF LITERATURE

2. REVIEW OF LITERATURE

The presence of electrocardiographic changes in the acute phase of stroke have been reported since 1947 (18,19). Since then, several researchers have been published on ECG changes, either arrhythmia, repolarization or conduction abnormalities in patients with acute stroke, including ischemic stroke, transient ischemic attacks (TIA), subarachnoid haemorrhages (SAH) and intracerebral haemorrhages (ICH) (20). The ECG abnormalities seen in stroke reflects either the cause of stroke (e.g., cerebral embolism in a patient with atrial fibrillation), manifestations of a pre-existing cardiac disorder or they are direct consequences of stroke.

PREVALENCE

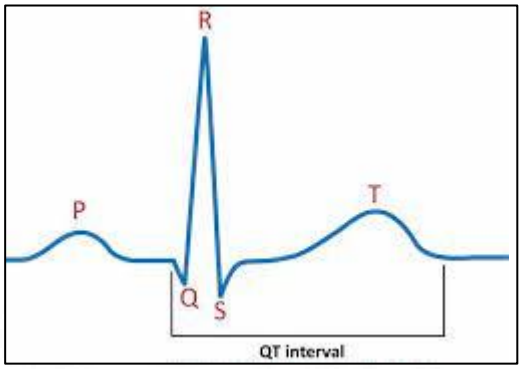
The abnormalities in ECG and cardiac arrhythmias are identified in 50-70% of patients with acute stroke (4,5).These changes are seen more commonly in patients with ICH (60–70%) and SAH (40–70%) than in patients with ischemic stroke (15–40%) (20). Nearly every type of ECG change which includes repolarization abnormalities (QT interval prolongation, increased QT interval dispersion (QTd) and ST-segment changes) and cardiac arrhythmias, such as ventricular premature beats, ventricular tachycardia and atrial fibrillation (AF) has been described in stroke (21).

QT prolongation is the most common stroke related ECG abnormality and it is found in about 71% of patients with SAH, 64% with ICH, and 38% of patients with ischemic stroke (4,22,23). The other common ECG abnormalities seen in patients with acute stroke include ST segment changes which occur in 22% to 35% (24) and new T wave abnormalities appear in approximately 15% (23).

QT INTERVAL

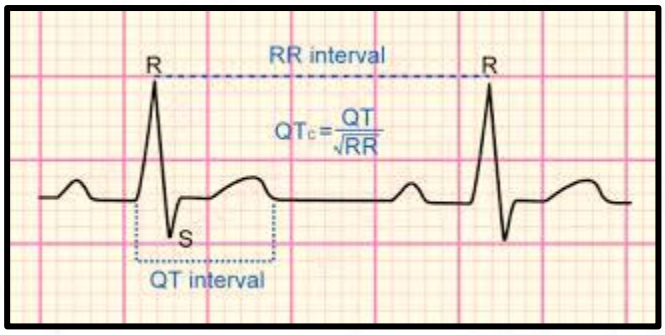
The QT interval is defined as the interval from the onset of QRS complex which is the earliest indication of ventricular depolarization, to the end of T wave which denotes the ventricular repolarization(25) (Figure 2.1).

FIGURE 2.1: QT INTERVAL



QT interval is a reflection of the sum of the ventricular action potential durations, and it is considered the 'outer' manifestation of the underlying cardiac action potential (26). Using the Bazett's formula, the corrected QT interval (QTc) for the heart rate can be calculated, where QTc = QT interval/√ RR interval in seconds (27) (Figure 2.2). The QTc interval is defined as prolonged, if QTc in lead II was > 0.440 seconds in males and > 0.460 seconds in females (28).

FIGURE 2.2: CORRECTED QT INTERVAL CALCULATION



In the study by Sultan et al.(29) , it was shown that the QTc interval was significantly prolonged in acute stroke than control group. It was significantly higher with larger infarct or large haemorrhage than smaller lesions and there was no significant difference between right and left sided stroke regarding QTc interval values. Tatschl et al (30) studied in 122 patients with acute stroke and showed that 31% of patients had QT prolongation. It was associated with insular involvement and prior stroke.

QTc-prolongation is also common after posterior circulation stroke. In the study by Henninger et al (31), 34 % of patients with posterior circulation stroke had a prolonged QTc noted on the admission ECG. There was a significant association noted between temporal lobe infarction and QTc ($p < 0.001$) in multivariable linear regression analyses after adjusting for demographics, preadmission medication uses and ECG parameters. The Exploratory analyses showed that patients with temporal lobe infarction had worse 30-day functional outcomes ($p = 0.022$), but no significant association between the QTc and 30-day functional outcome was seen.

QT DISPERSION (QTd)

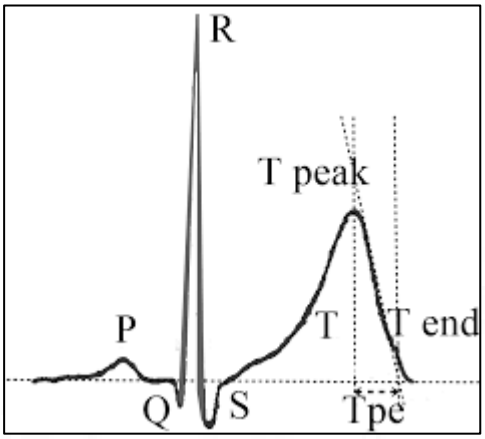
There exist significant differences in the duration of the QT interval when measured in the individual leads. Hence QT dispersion is calculated, which is the difference between the maximum and minimum QT intervals in a 12-lead ECG (32). It is considered as a marker of sudden cardiac death risk and arrhythmia(33), as well as a quantitative non-invasive method to determine myocardial repolarization inhomogeneities (34,35). The normal upper limit of Qtd is 50ms, which is age and sex independent (36).

In a study by Alabd et al (37), QT dispersion was found to be increased significantly in acute ischemic stroke especially in patients with insular involvement. However conflicting results have been reported on the prognostic value of QTd in patients following acute myocardial infarction (38,39) and stroke (40,41). Therefore, its association as well as predictive value in acute stroke still remains controversial.

TPEAK-TEND INTERVAL (Tpe)

The Tpe is the interval from the peak of the T wave to the end of the T wave measured in milliseconds, (Figure 2.3). It is an easy and assessable measure of transmural dispersion of repolarization, and is related to arrhythmogenesis (42). The normal upper limit of Tpe is 90ms (43).

FIGURE 2.3: TPe INTERVAL



INFLUENCE OF AUTONOMIC NERVOUS SYSTEM ON QT INTERVAL

In stroke several autonomic dysfunctions can occur which can adversely affect the prognosis, example, alteration in the arterial blood pressure, arrhythmias, and ischemic cardiac damage (44). Multiple and different anatomical regions of the brain have been suggested to be involved in this, but the exact pathogenesis and mechanism leading to these changes are not fully understood (45).

It is well known that QT intervals on ECG are susceptible to autonomic influences (15). Hence these autonomic changes which occur during acute ischemic stroke can lead to QT interval changes. The alterations in QT interval can be due to the effect of autonomic conditions on sinus node(46) that can cause a change in heart rate, which in turn influences the QT interval(27). In addition, these autonomic changes also have direct action on the ventricular myocardium which in turn affects the duration of cardiac repolarization (47).

The prolonged Qtd seen in stroke is also secondary to sympathetic hyperactivity which may mediate the occurrence of cardiac abnormalities. It is found to be associated with stroke patients who developed ventricular arrhythmias (48) as well as in those with an increase in serum catecholamine concentration (49).

FACTORS AFFECTING QT INTERVAL

Though the prolongation of QT interval can be because of either congenital or acquired abnormalities, the phenomenon probably involves a gene-environment interaction (50). Even though the congenital long QT syndromes are rare, they are characterized by lifelong, ambient QT prolongation and does carry a high risk of sudden death. A plethora of drugs and patient-specific risk factors for QTc-prolongation have been mentioned in the literature, and the risk is stated to increase with the number of risk factors (51).

The risk factors for QT prolongation includes (50–52):

1. Patient specific factors:
    - Age $\geq$ 65 years
    - Female gender
    - Smoking
2. Cardiovascular risk factors:
    - Ischemic cardiomyopathy
    - Arrhythmia
    - Systemic hypertension
3. ECG parameter:
    - Prolonged QTc at baseline
4. Comorbidities:
    - Thyroid disorders
    - Septic shock
    - Liver failure
5. Electrolyte imbalance:
    - Hypokalemia

- Hypocalcemia
- Hyponatremia
- Hypomagnesemia

6. QTc-prolonging medication:
    - ≥ 1 QTc-prolonging drug

Several drugs are notorious to cause QTc prolongation (50), and healthcare professionals should be aware about this side effects of these drugs. Table 2.1 mentions the important drugs that are known to cause QT prolongation.

Table 2.1: Drugs causing QT prolongation

Drugs causing QT prolongation		
Antiarrhythmics Amiodarone Disopyramide Dofetilide Ibutilide Procainamide Quinidine Sotalol	**Antipsychotics** Thioridazine Pimozide Ziprasidone Haloperidol	**Antidepressants** Amitriptyline Desipramine
Antibiotics Erythromycin Clarithromycin Sparfloxacin	**Antimalarials** Chloroquine Hydroxychloroquine	**Others** Bepridil Cisapride

MECHANISM FOR CEREBRAL INFLUENCES ON CARDIAC STRUCTURE AND FUNCTION

In the last few decades, there were several studies exploring the connection between the brain and heart, leading to the concept of “brain heart axis” (2). Neurocardiology refers to the pathophysiological interplay of the nervous and cardiovascular systems (53,54).

Central nervous system (CNS) mechanisms which are involved in cardiovascular autonomic control, maintains the homeostasis by close coordinated with respiratory and other regulatory mechanisms. CNS regulates the cardiovascular system by three general means (55): a) feedforward regulation, referred to as "central command," b) feedback or reflex regulation, and c) complex integrative mechanisms involving several relaying centers. The anterior cingulate cortex, insula amygdala, hypothalamus, parabrachial nucleus, periaqueductal grey matter and the medulla have an important role in modulating the cardiac function (2). These structures through the parasympathetic and sympathetic nervous system modulate the cardiac activity in the responses to stress, emotional events as well as in the homeostatic reflexes (56).

The presence of transient autonomic nervous system (ANS) dysfunction with predominant sympathetic activity is described in the hyperacute phase of stroke (57). This was demonstrated by Orlandi et al. (57) in his study of 44 patients suffering a stroke in whom the dynamic ECG on admission revealed that 31 (70.5%) out of the 44 patients already had arrhythmia. These were observed in 9 (75%) out of 12 haemorrhagic patients ($P < 0.05$) as compared to 22 (68.8%) of the 32 ischaemic ones. Arrhythmias were seen in 16 (76.2%) out of 21 cases with right hemisphere lesions and in 12 (63.2%) out of 19 cases of left hemisphere lesions ($P<0.05$). Arrhythmia was still present in 19 (43.2%) patients after 3 days and only in 2 (6.5%) patients after 7 days. The spectral analysis of heart rate variability, evaluation of arterial blood pressure and the levels of catecholamine in the blood and 24-h urine was also studied. The spectral analysis parameters on admission and after 3 days were significantly ($P < 0.05$) modified in patients with stroke plus arrhythmia as compared to patients with stroke alone and to control subjects, however no differences were observed on the seventh day. It was also noted that arterial hypertension and high levels of catecholamine decreased from the third day onwards.

The "laterality hypothesis" has been postulated in cardiac control also where in the right insular cortex damage is considered the origin of sympathetic discharges leading to the cardiac alterations, while the parasympathetic activity may increase as a consequence of left insular cortex damage(58). Strittmatter et al. (59) investigated the location-dependent difference in cardio-autonomic function in patients with left hemisphere, right hemisphere as well as vertebrobasilar ischaemic stroke. It was seen that an initial increase in sympathetic function occurred in all 3 groups with a spontaneous decrease in norepinephrine in left hemisphere ($p < 0.01$) and vertebrobasilar stroke ($p < 0.05$) only. The norepinephrine level was significantly higher in right hemispheric stroke ($p < 0.05$). Thus, the alterations in autonomic function were

paralleled with a sustained elevation in cardiovascular parameters mainly in right hemispheric stroke.

EFFECT OF STROKE SEVERITY AND SUBTYPE ON QT INTERVALS

The severity of stroke is assessed based on two scoring system.

1. NIHSS score (National Institutes of Health Stroke Scale) (13): It is a simple, reliable and effective tool for measuring acute stroke-related neurologic impairments. The score ranges from 0 to 42 and is the sum of 15 individually evaluated elements. Based on NIHSS score, stroke severity is categorized as minor stroke, 1–4; moderate stroke, 5–15; and severe stroke, >15 (60).
2. mRS score (Modified Rankin scale) (14): The score ranges from 0 to 6 and covers the entire range of functional outcome in stroke patients from no symptoms to death.

The ECG measures of ventricular repolarization, such as QTc, Tp-e and Tp-e/QTc, were studied in acute ischemic stroke (AIS) patients to predict the probability of ventricular arrhythmia (61). Ahn et al., showed that prolonged QTc interval (≥501 ms in men and ≥517 m in women: HR: 1.33, 95% CI: 1.00–1.80) was significantly associated with all-cause mortality even after adjusting for all clinically relevant variables, such as stroke severity (62).

The study by Korkmaz et al.(63) investigated the relationships between corrected cardiac electrophysiological balance value, which is measured by dividing the corrected QT interval by the QRS duration, and the NIHSS scores at admission and discharge in patients with AIS. 231 patients with AIS were evaluated and it was found that patients with NIHSS score ≥5 had higher heart rate, QT, QTc interval, Tpe interval, and cardiac-electrophysiological balance values as compared with those with NIHSS score of 1–4. The cardiac-electrophysiological balance value was found to be independently related to NIHSS scores ≥5 (OR 1.102, 95%CI 1.036–1.172, $p<0.001$). There was also correlation between cardiac electrophysiological balance and NIHSS scores at admission ($r=0.333$, $p<0.001$) and discharge ($r=0.329$, $p<0.001$) (63).

In an observational case control study by Hromádka et al, the prolonged QTc interval in AIS patients 48 hours after the index stroke correlated with NIHSS score at admission and mRS scores at discharge (64). But in the study by Stead et al., no relationship between prolonged

QTc and discharge mRS was found (16). A prospective cohort study on QT dispersion in AIS patients showed that QT dispersion did not predict short-term clinical outcome for mRS score (odds ratio [OR] = 1.001, 95% confidence interval [CI] .99-1.01, P = .85), NIHSS at discharge (OR = .994, 95% CI .98-1.01, P = .30), or discharge disposition (OR = 1.001, 95% CI .99-1.01, P = .81) (65). However the US Third National Health and Nutrition Examination Survey suggested that the prolonged QTc interval predicts all-cause mortality in the general population (66).

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification is used for categorization of subtypes of ischemic stroke which is based on the aetiology of stroke. This is as follows (17) :

1.Large artery atherosclerosis

This can be extracranial or intracranial disease

2.Small artery occlusion (lacunar)

3.Cardioembolism

4.Other demonstrated cause

Prothrombotic disorders, nonatherosclerotic vasculopathies

5.Undetermined cause (cryptogenic)

≥2 conflicting causes found

Diagnostic studies were negative

Incomplete evaluation for cause

So far to our knowledge, no study has looked into the correlation between QT interval changes and stroke subtypes based on TOAST classification. However, the relationship between QT interval and intima media thickness (IMT) of the carotid arteries was studied by Strohmer et al (67) in general population undergoing cardiovascular screening. Significant correlations between QT/QTc and internal carotid artery IMT (r=0.14-0.16) were found in males. In women a statistically significant relationship was found between the QT interval and common carotid artery IMT (r=0.15, P=0.006). This demonstrated that QT and QTc prolongation are in part associated with IMT of carotid arteries, which is a risk marker of subclinical atherosclerosis (68). Festa et al (69) also demonstrated a significant relation of QTc interval to carotid

atherosclerosis in nondiabetic subjects, that was stronger in women.IMT of the common carotid artery correlated significantly with QTc interval duration (r=50.15 for QT60 and r=50.14 for QTc), whereas no relationship between IMT of the internal carotid artery and QT interval was found (r= 520.01). The increased catecholamine levels that prolong the QT interval (70) and are also associated with development of atherosclerosis (71) and this may, therefore be the mediator for any association between QT interval and incident cardiovascular events.

Among the participants in the Multi-Ethnic Study of Atherosclerosis (MESA), Beinart et al. studied the association between baseline QT interval and incident cardiovascular events (72).Cardiovascular events occurred in 291 participants over a mean follow-up of 8.0 ± 1.7 years. Each 10 ms increase in the baseline QTc was associated with incident heart failure (HR,95% confidence interval (CI): 1.25 [1.14 to 1.37]), CVD events (HR, 95% CI: 1.12 [1.05 to 1.20]),and stroke (HR, 95% CI: 1.19 [1.07 to 1.32]) after adjustment for CVD risk factors and potential confounders, with no interaction with sex or ethnicity.

IMPLICATION OF ELECTROCARDIOGRAM ABNORMALITIES

Over the last decade, there is increasing evidence about the brain-heart interaction with major potential implications in the treatment of cardiovascular diseases (54). Stroke can induce ECG abnormalities and a variety of cardiac arrhythmias that can sometimes lead on to sudden death. Hence these findings have major clinical as well as therapeutical implications in acute stroke patients (54). A prolonged QTc interval at the time of admission has been shown to be associated with an increased risk of early death in patients with acute ischemic stroke, with the estimated survival at 90 days was 70.5% and 87.1% in patients with a prolonged QTc and in those patients without a prolonged interval (16). This association was statistically significant even after adjusting for age and NIHSS score (RR 1.7; 95% CI 1.0-2.9; P = .043). The hemispheric lateralization in autonomic control should also be taken into account while managing patients with stroke because of an increased susceptibility to cardio-autonomic dysfunction in patients with right hemispheric stroke(59).

ECG changes has been extensively studied in SAH(73), in which it was shown that ischemic ECG abnormalities are associated with poor neurologic outcomes, but not with the all-cause mortality(74). Kawasaki et al. (75) reported an ECG scoring system based on the presence of

Q waves, ST depression, and inverted T waves, where in an ECG score of 6 or higher was a significant predictor of adverse neurologic outcomes and in-hospital mortality.

The prolonged QTc interval was found to be associated with stroke risk (76).Among the 10 643 subjects studied by Ishikawa et al (76) who had prolonged QTc on ECG, there were a total of 375 stroke events during the mean follow-up period of 128.7±28.1 months. The persons with prolonged QTc (hazard ratio, 2.13; 95% confidence interval, 1.22–3.73) had an increased risk of stroke even after adjustment for ECG LVH (hazard ratio, 1.71; 95% confidence interval, 1.22–2.40). The multivariate-adjusted Cox proportional hazards analysis demonstrated that the subjects with prolonged QTc intervals but not ECG-LVH (1.2% of all subjects; incidence, 10.7%; hazard ratio, 2.70, 95% confidence interval, 1.48–4.94) and those with ECG-LVH (incidence, 7.9%; hazard ratio, 1.83; 95% confidence interval, 1.31–2.57) had an increased risk of stroke events, compared with those with neither a prolonged QTc interval nor ECG-LVH.

Stroke and TIAs are frequently caused by congestive heart failure and/or cardiac arrhythmias (77,78). And among the arrhythmias, it has been shown that AF in particular may result in cognitive disorders due to hippocampal atrophy which can precede the occurrence of TIAs or stroke (79–81). Hence cognition as well as the measures of structural brain integrity should be considered in the evaluation of novel treatments for AF.

The impact of cardiac autonomic derangement on functional outcome after a 60 day rehabilitation program in patients with ischemic stroke was studied by Bassi et al (44). In this study 85 patients underwent 24-hour Holter monitoring were taken and it was demonstrated that age [odds ratio (OR) 1.09, 95% CI 1.04–1.19, P=0.002], stroke severity (OR 1.12, 95% CI 1.01–1.34, P=0.004), Barthel Index score (OR 0.92, 95% CI 0.87–0.98, P=0.01) and Rankin Scale score (OR 3.88, 95% CI 2.13–7.56, P=0.02) on admission, as well as lower values of the standard deviation of normal-to-normal R wave to R wave (RR) intervals (OR 9.67, 95% CI 2.58–18.67, P=0.006) were independent predictors of an unfavorable functional outcome. Assessment of heart rate variability before a rehabilitation program may thus provide additional information on the functional recovery in stroke.

OBJECTIVES OF THE STUDY

3. AIMS AND OBJECTIVES OF THE STUDY

The aim of this study was to determine the incidence of QT interval abnormalities in acute ischemic stroke and, any potential association based on stroke subtype and/or severity.

Primary objective:

- To find the incidence and type of QT interval abnormalities in acute ischemic stroke

Secondary objective:

- To determine whether QT interval abnormality correlates with stroke severity
- To determine whether QT interval abnormality correlates with stroke subtype

METHODOLOGY

4. METHODOLOGY

STUDY DESIGN: Hospital based prospective observational study.

SUBJECT/PARTICIPANT SELECTION

Patients admitted to the Stroke/Neurology services at SCTIMST from 01/01/2021 to 01/06/2022 with a diagnosis of acute ischemic stroke within 24 hours of onset of symptom was taken up for study and were followed up for 3 months. The consecutive patients who fulfilled the inclusion and exclusion criteria were recruited for the study. All the patients were recruited after obtaining informed consent from patient/care giver.

NUMBER:

The sample size was 100.Sample size determination was done and the number required for this study was calculated (with reference to a study by Tatschl et al (30)) with P =31% , 95% CI 23.1% - 39.7%.Anticipating lesser prevalence of QT prolongation in our study after applying exclusion criteria, keeping absolute precision of 10% around 31%, the sample size needed is 83.Applying 20% oversampling (+16.6) and hence sample size needed is 99.6 , which was rounded up to 100.

ELIGIBILITY:

Inclusion Criteria:

- Patients aged 18 years or more
- Patients with acute ischemic stroke (within 24 hours of onset of stroke)
- Patients who give consent for participation in the study

Exclusion Criteria:

- Age <18 years
- Patients with TIA
- Ischemic stroke with onset > 24hrs

- Haemorrhagic strokes or h/o prior intracranial haemorrhage
- Patients with concomitant acute coronary syndrome (in preceding 7 days)
- Patients with history of heart disease: Coronary artery disease (h/o Myocardial infarction, coronary artery bypass grafting or angioplasty, angina, abnormal stress test, abnormal coronary angiogram, ECG changes of previous MI (82)), cardiomyopathy (hypertrophic or dilated cardiomyopathy), valvular heart disease, congenital long QT syndrome, heart failure, cardiac pacemaker
- Patients on drugs affecting QT interval (class Ia and class III antiarrhythmics including Amiodarone, Sotalol, antimalarials, digoxin, theophylline, lithium carbonate, phenothiazines, tricyclic antidepressant, levodopa, erythromycin stearate, beta blockers, calcium channel blocker)
- Patients with electrolyte imbalance (abnormal serum potassium, calcium and magnesium levels) or thyroid dysfunction.
- Patients with ECG showing acute ischemic changes with elevated cardiac enzymes, and patients with pre-existent conduction abnormalities or arrhythmias.
- Fever or recurrent hypoglycaemia

RECRUITMENT:

Recruitment of patients was done by the principal investigator and co-principal investigators. Hospital records were reviewed for eligibility. All patients who were eligible was recruited for the study.

DATA COLLECTION PROCEDURES:

Patients attending to neurology, stroke services at SCTIMST with diagnosis of acute ischemic stroke were taken up in the study, after applying inclusion and exclusion criteria. The information regarding clinical, demographic & risk factors was collected. Baseline neurological and disability status at presentation to Neurology services was documented using NIHSS and modified Rankin's scale respectively. The stroke subtype (based on TOAST classification) was deciphered out from standard stroke work up (CT/MRI brain, CTA/MRA/DSA, Echo, Holter etc).

12 lead ECGs taken at 25 mm/s paper speed and 10 mm/mV amplitude admission and at 48 hours post admission was evaluated for QT interval abnormalities – QT interval, QTc interval, QT dispersion, T wave peak to T wave end (Tpe), U wave. QT interval was calculated manually using callipers in milliseconds from the earliest onset of the QRS complex to the end of the T wave. The end of the T wave was defined as the return of the descending limb to the TP baseline when not followed by a U wave or if distinct from the following U wave. Three consecutive QT intervals were measured and mean was taken. QTc interval was ascertained using the Bazett's formula (27). QTc = QT interval (seconds) / √RR interval (seconds). QT dispersion was manually assessed difference between the longest (QTmax) and the shortest (QTmin) QT intervals within the 12-lead ECG. T wave peak to T wave end (Tpe) was assessed manually by callipers. Tpe was measured in milliseconds from the peak of the T wave to the end of the T wave in V5, followed by leads V4 and V6 if lead V5 was not suitable. If the T-wave amplitude is <1.5 mm in a particular lead, that lead was excluded from analysis.

Imaging CT/MRI brain was done for all patients as part of stroke work up and was documented. The patient was followed up after 3 months and the data regarding neurological outcome and disability status using the NIHSS and mRS score along with an ECG of the patient to assess the QT intervals was collected at 3 months.

DATA ANALYSIS:

The data was analysed with the help of computer software MS Excel and SPSS 21 for windows (Armonk, NY: IBM Corp). The data is presented as percentages or mean +/- standard deviation as defined appropriate for qualitative and quantitative variables respectively. Univariate analysis was undertaken to examine relationship of various factors. Crude odds ratio with 95% confidence interval was reported. The Chi-square test/ Fisher's exact test was applied to evaluate statistical significance. Multivariate analysis/ logistic regression was used to evaluate the independent and joint effect of the variable of interest on the outcome. A p value of <0.05 is considered statistically significant.

RESULTS

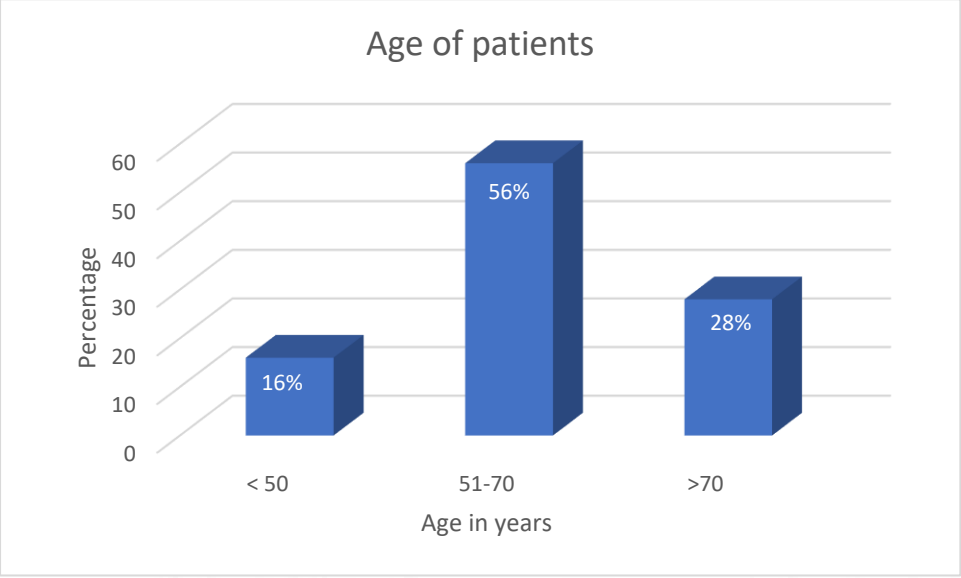
5. RESULTS

We had 100 patients with Acute Ischemic Stroke (AIS) presenting within 24 ours of onset of symptoms, who were admitted and evaluated in stroke unit and were followed up for 3 months.

COHORT CHARACTERISTICS

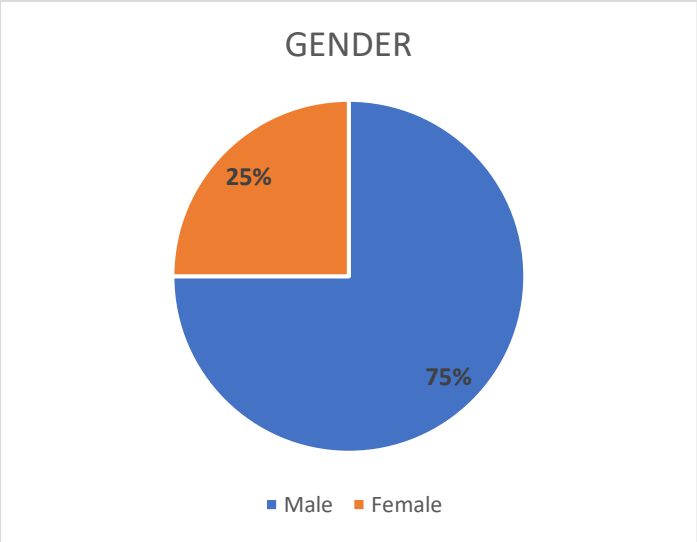
Mean age of the cohort was 63 ± 11.7 years. The majority of patients (n=56) were in the age group 50-70 years while 16 were below 50 years of age and 28 were above 70 years (Figure 5.1).

FIGURE 5.1: AGE OF PATIENTS



In our study, there were 75 males and 25 females (Figure 5.2).

FIGURE 5.2: GENDER OF PATIENTS



RISK FACTOR PROFILE

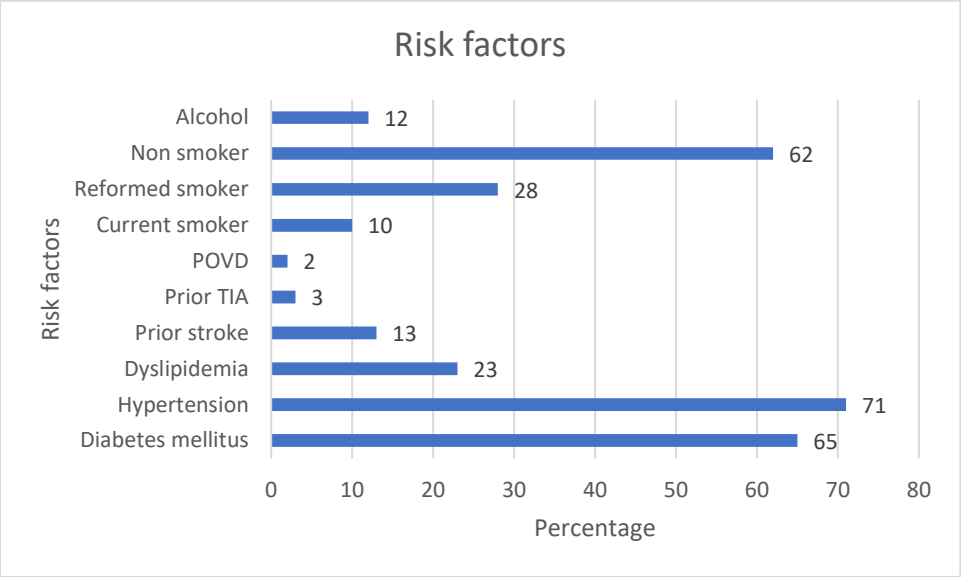
Among the subjects, 65% had diabetes, 71% had hypertension, 23% had dyslipidemia and 2% had peripheral occlusive vascular disease (POVD). The previous history of stroke and TIA was present in 13% and 3% respectively.

TABLE 5.1: RISK FACTOR PROFILE OF PATIENTS

Risk factor	Frequency (n=100)	Percentage
Diabetes mellitus	65	65
Hypertension	71	71
Dyslipidaemia	23	23
Prior stroke	13	13
Prior TIA	3	3
POVD	2	2
Smoking **Current smoker**	10	10
Stopped smoking >3 months	28	28
Non smoker	62	62
Alcohol	12	12

Among the subjects, 10% were smokers and 28% were reformed smokers while 62% were nonsmokers.

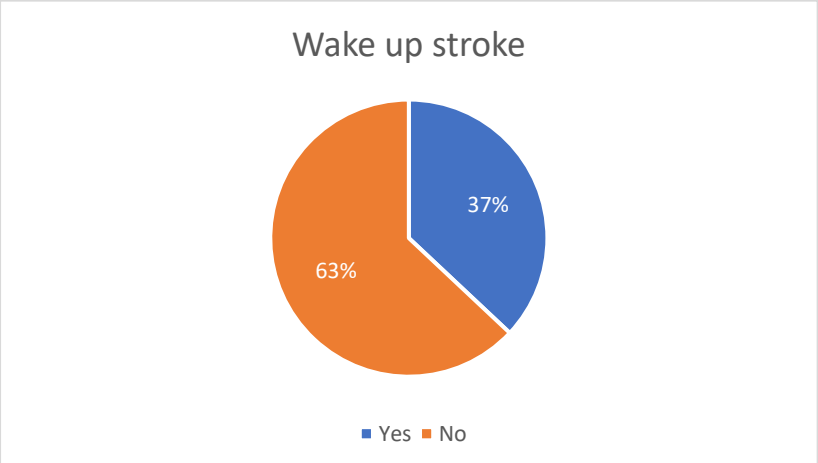
FIGURE 5.3: RISK FACTOR PROFILE OF PATIENTS



BIOCHEMICAL AND CLINICAL PARAMETERS

The mean time from symptom onset to admission to the hospital was 350.8 minutes (350.8 ± 302.6) (range 15-1400 minutes, SD= 302.6). 37 patients (37%) presented as wake up stroke with the mean time from last seen normal to admission to the hospital was 582.4 minutes (range 140-1350 minutes, SD =238.2).

FIGURE 5.4: PATIENTS WITH WAKE-UP STROKE



The mean blood sugar at the time of admission was 182.1 ± 70.1 mg/dl (range 95-400mg/dl). Table 5.2 shows the biochemical parameters of the patient at time of admission.

TABLE 5.2: CLINICAL AND BIOCHEMICAL PARAMETERS OF PATIENTS AT ADMISSION

PARAMETER	N	Mean ± SD	Range	Median	IQR
RBS (mg/dl)	100	182.1 ± 70.1	95 – 400	164.5	127.25 - 219.5
Systolic BP (mm Hg)	100	162.8 ± 26.3	110 – 240	160	150 - 180
Diastolic BP (mm Hg)	100	88 ± 17.6	60 – 172	90	70 - 100
Total cholesterol (mg/dl)	100	198.2 ± 45.6	89 – 339	195	176 - 227.25
HDL (mg/dl)	100	46.9 ± 13.3	13 – 90	46	38 - 54
LDL (mg/dl)	100	127.2 ± 39.2	39 – 235	126	109 - 147
TGL (mg/dl)	100	108.3 ± 41.2	48 – 236	103	72.75 - 129.75

N- number of patients, IQR- interquartile range , RBS- Random blood sugar, BP : blood pressure, HDL - High-density lipoprotein, LDL -Low-density lipoprotein, TGL- Triglyceride

Admission NIHSS was ranging from 0-23 with a mean of 9.8 ± 6.2. The patients were further subdivided based on NIHSS into minor (NIHSS less than 5), moderate (NIHSS 5-15) and severe stroke (NIHSS >15). The majority of patients, 54% (n=54), were having moderate stroke with NIHSS between 5-15 at the time of admission (Figure 5.5).

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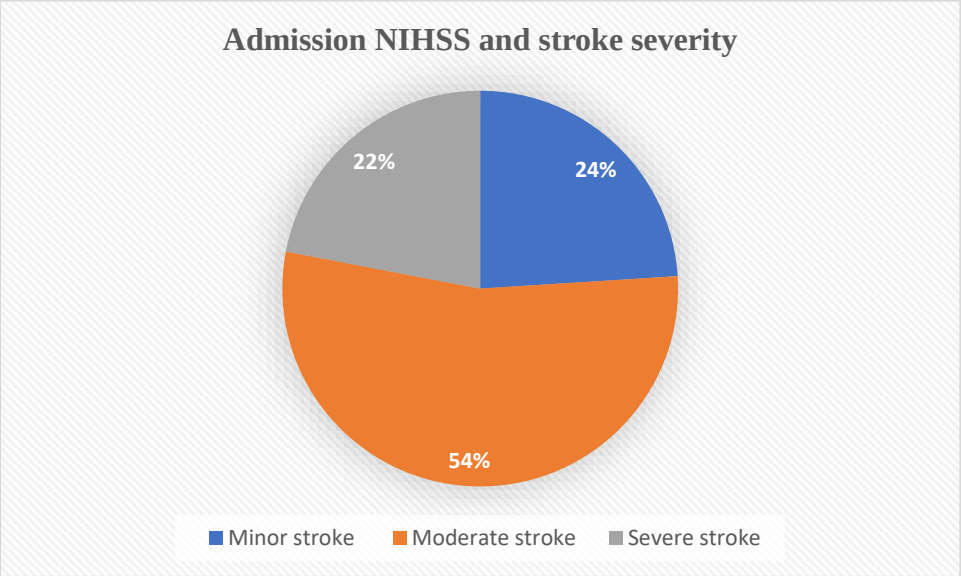
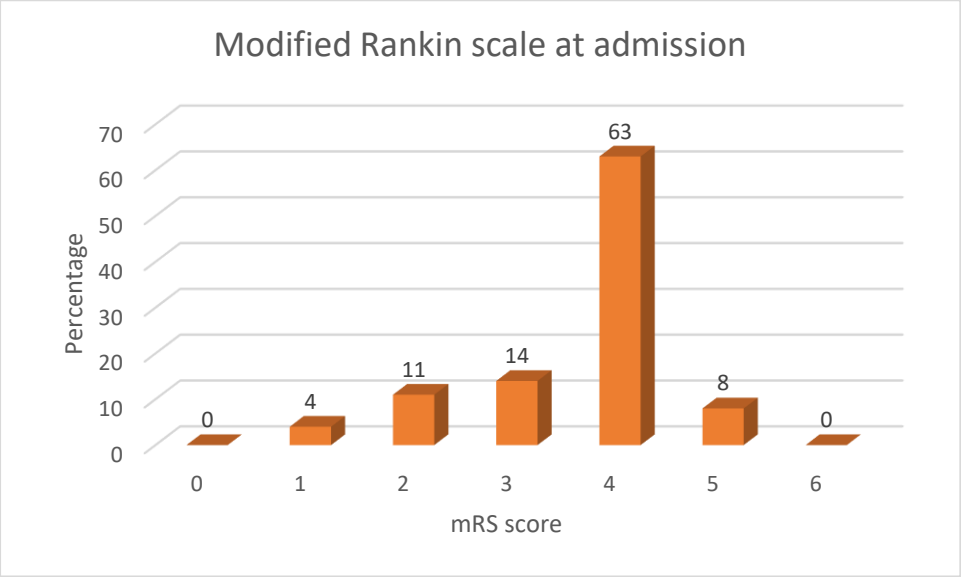
FIGURE 5.5: ADMISSION NIHSS SCORE AND STROKE SEVERITY



The functional disability of patients was scored according to modified ranking score (mRS). At admission, majority of patients (63%) had mRS score of 4, followed by 14%, 11%, 8% and 4% for mRS score of 3, 2, 5 and 1 respectively (Figure 5.6).

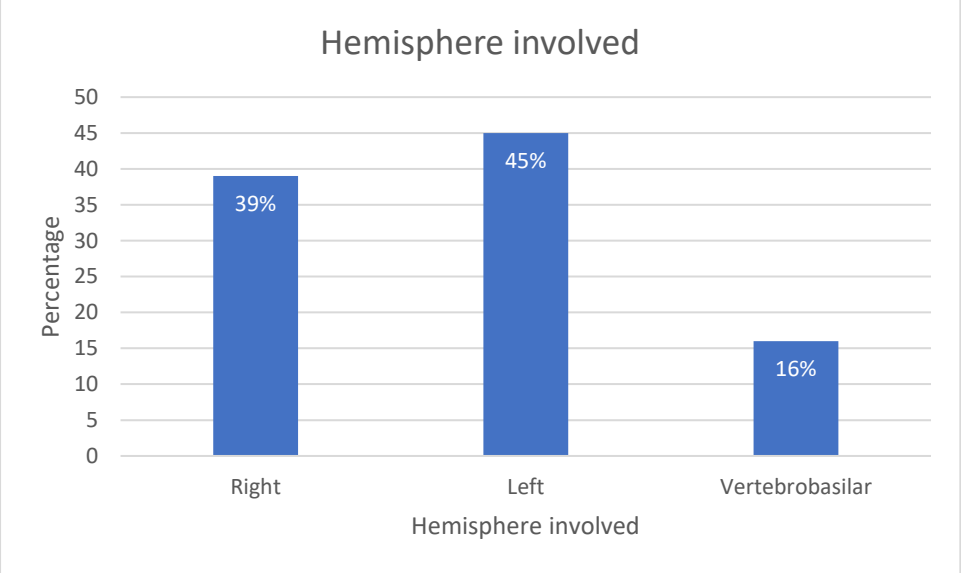
FIGURE 5.6: ADMISSION MODIFIED RANKIN SCALE



IMAGING FEATURES

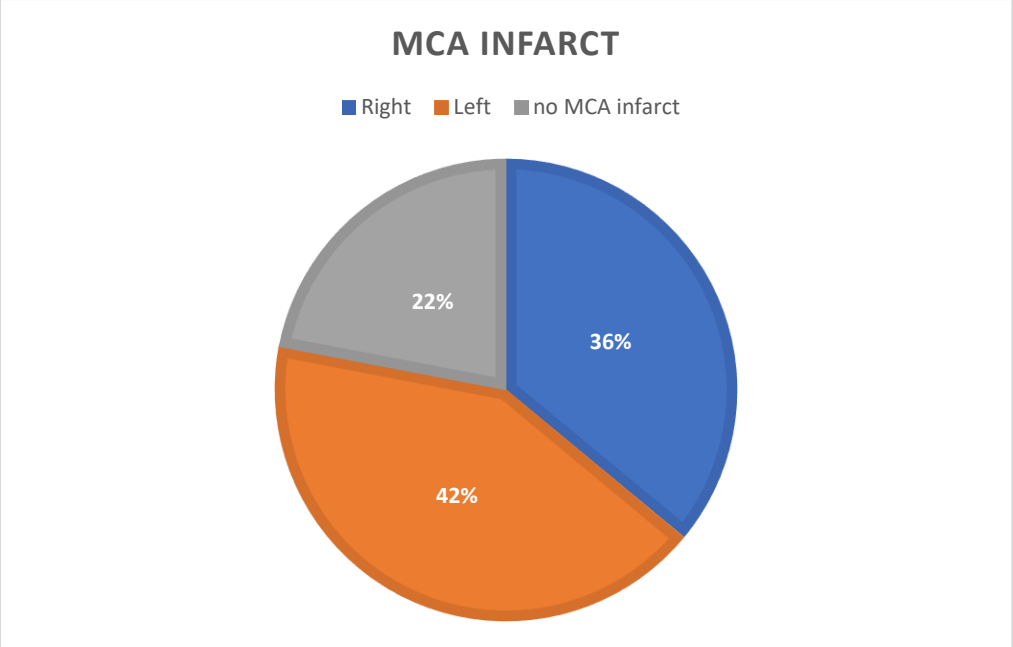
61 patients had MRI Brain and 39 patients had CT head imaging during evaluation. 39 % (n=39) had right hemispheric, 45% had left hemispheric, 16% had vertebrobasilar stroke, and none had bihemispheric stroke.

FIGURE 5. 7: HEMISPHERE INVOLVED



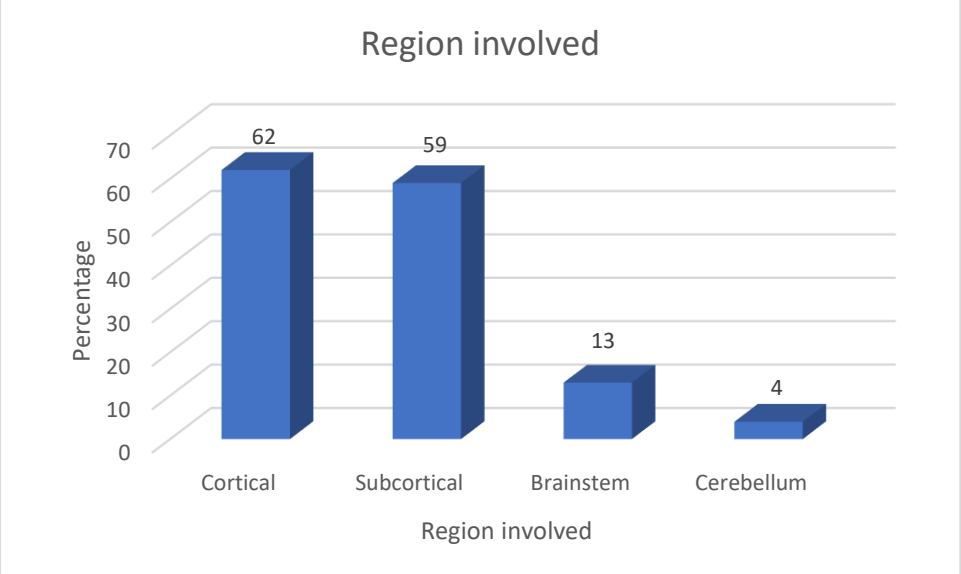
78 patients had Middle cerebral artery (MCA) infarcts, out of which 36 patients had right MCA and 42 patients had left MCA infarct.

FIGURE 5. 8: MCA INFARCT



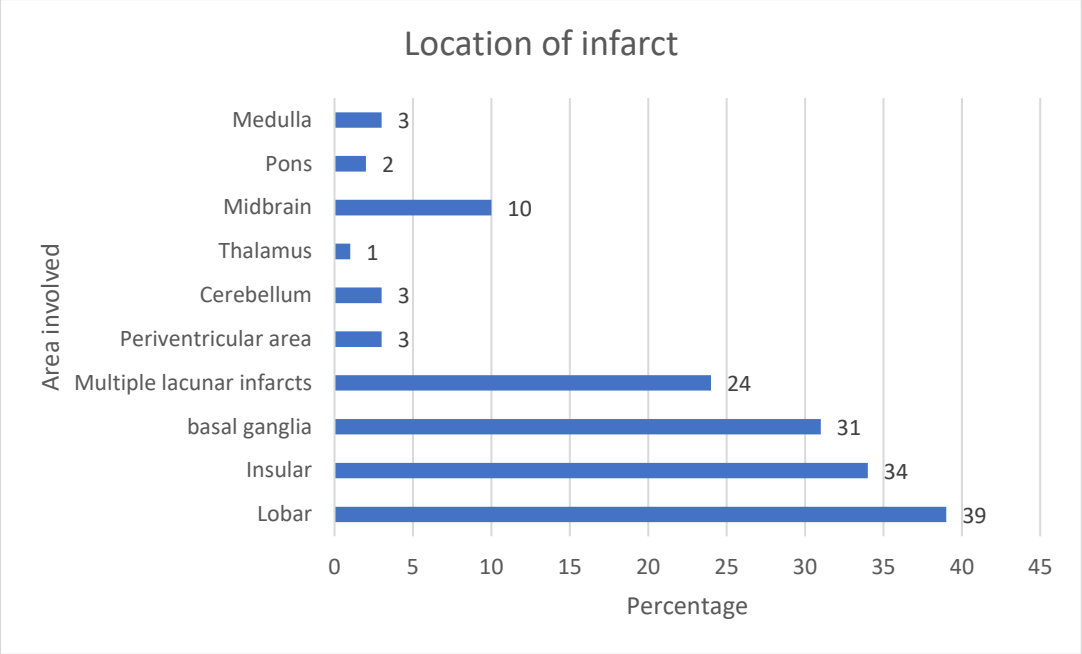
92 patients had single arterial territory infarct and 8 patients had multiple arterial territory infarcts. Among the infarct patterns, 46% had main artery territory infarct while 22% had branch occlusion, 18% had lacunar infarct, 6% had superficial watershed infarct and 8% had internal border zone infarct. 62 patients had cortical, 59 patients had subcortical, 13 patients had brainstem and 4 patients had cerebellar involvement (Figure 5.9). Among them, 31 patients had both cortical and subcortical involvement and 1 patient had both brainstem and cerebellar involvement.

FIGURE 5. 9: REGION NVOLVED



Most common location of infarct was lobar, as seen in 39% (n= 39 patients), followed by insula (34%), basal ganglia(31%) and multiple lacunar infarcts (24%). Among the brainstem infarcts, the most common was midbrain infarct seen in 10 % (Figure 5.10). 42% patients had a combination of regions with a combination of lobar, insula, subcortical structures, brainstem or cerebellum

FIGURE 5.10: LOCATION OF INFARCT

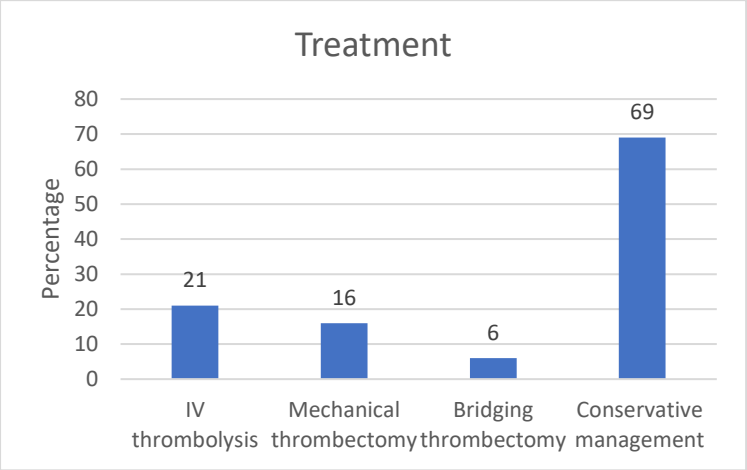


We had also studied the prevalence of chronic infarcts in the imaging. 32 patients had chronic infarcts with 20 patients (62.5%) having territorial and 12 patients (37.5%) had lacunar infarcts. 12% had Fazekas grade 1, 21% had Fazeka grade 2 and 5% had Fazeka grade 3 white matter changes while rest of the 62% did not have any white matter ischemic changes.

TREATMENT

21 % had received intravenous (IV) thrombolysis, 16% had underwent mechanical thrombectomy, and among them 6 patients received both intravenous thrombolysis followed by mechanical thrombectomy (bridging thrombectomy). The rest of 62% of patients were managed conservatively.

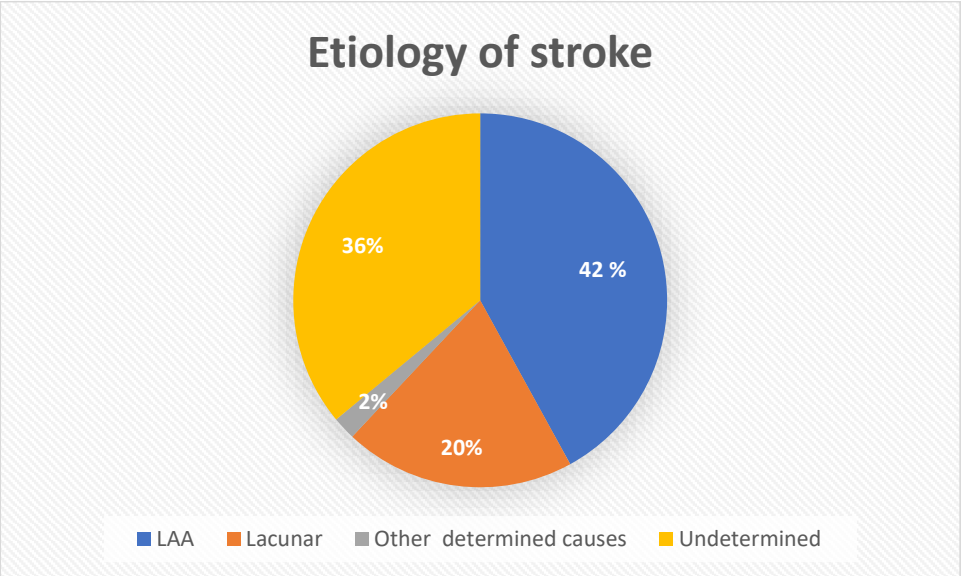
FIGURE 5. 11: TREATMENT RECEIVED



ETIOLOGY OF STROKE

The aetiology of stroke was classified based on the TOAST classification. Among the various stroke subtypes based on the etiology of stroke (Figure 5.12); the large artery atherosclerosis (LAA) constituted 42%, lacunar (small vessel occlusion) 20%, other determined causes 2%, and undetermined was 36%. 2 patients with other determined etiology had arterial dissection. The patients with cardioembolic etiology of stroke were excluded from our study.

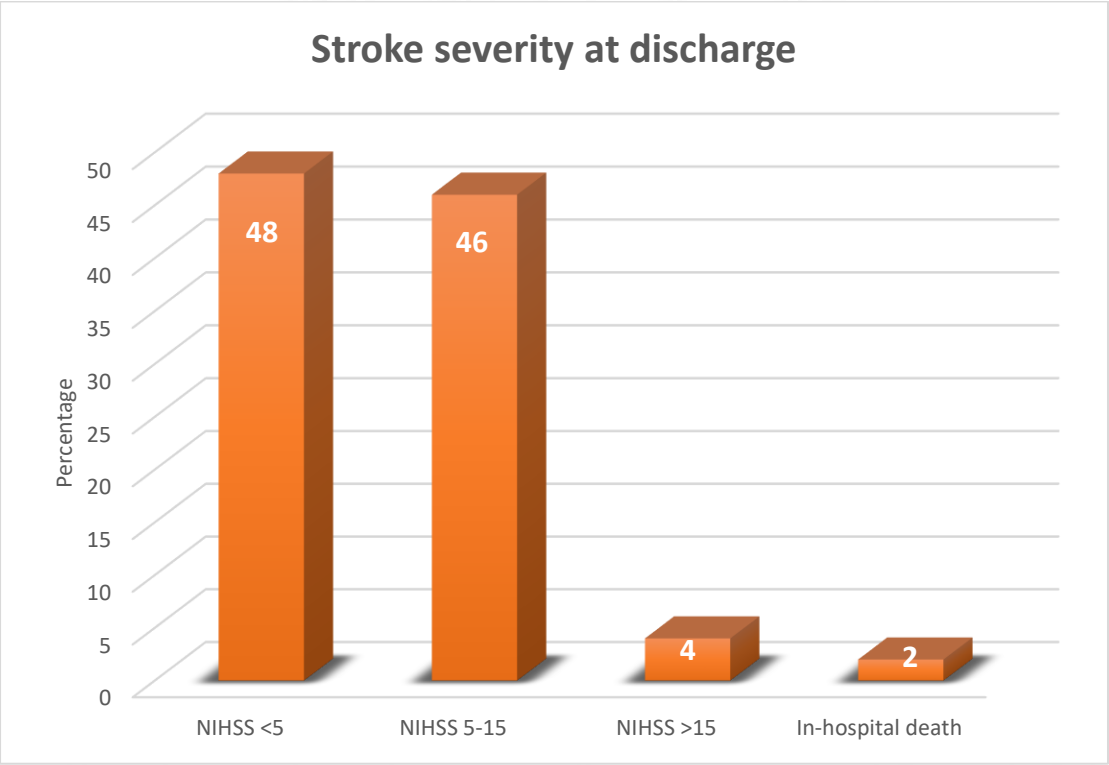
FIGURE 5.12: ETIOLOGY OF STROKE



STROKE SEVERITY

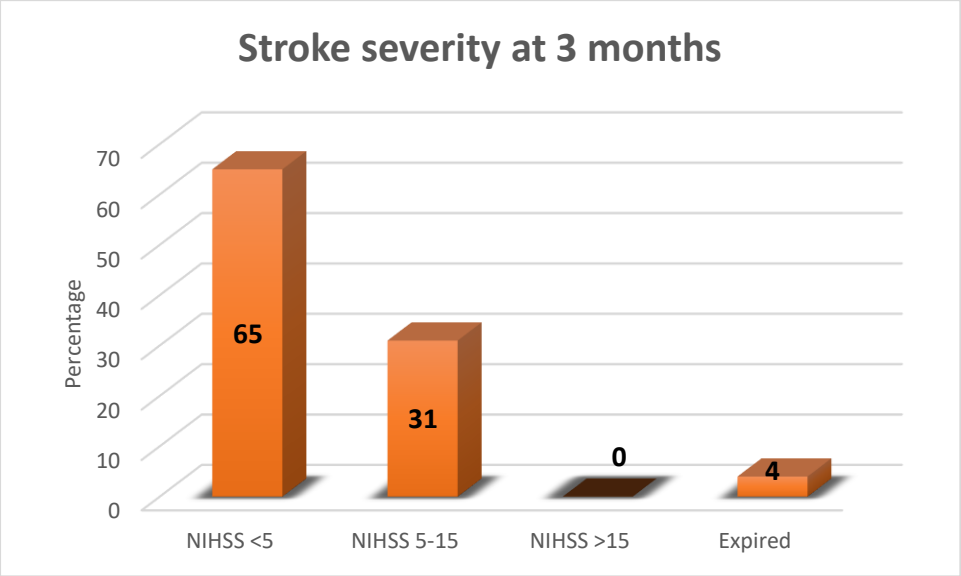
At discharge, the NIHSS was ranging from 0-24 with a mean of 5.9 ± 5.1. 48% (n=48) had NIHSS less than 5, 46 % had NIHSS score 5-15 and 4% had NIHSS >15. 2 patients have died during hospital stay.

FIGURE 5.13: STROKE SEVERITY AT DISCHARGE



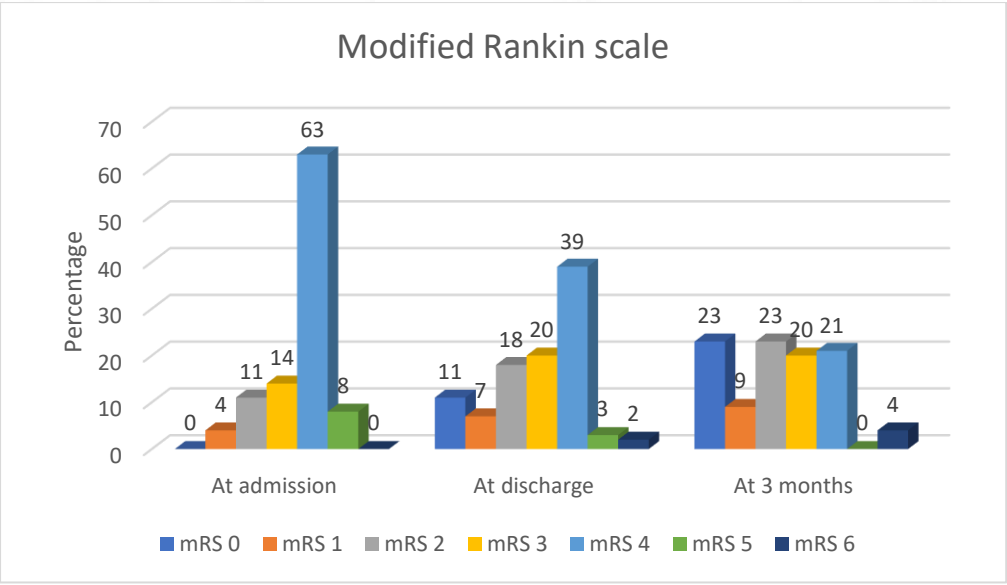
At 3 month follow up, the NIHSS was ranging from 0-14 with a mean of 3.6 ± 3.8. 65% (n=65) had NIHSS less than 5, 31 % had NIHSS score 5-15 and 0 had NIHSS >15. 2 patients have died during hospital stay and 2 patients died on 3 month.

FIGURE 5.14: STROKE SEVERITY AT 3 MONTHS FOLLOW UP



Among the study population, 47% and 49% of patient showed improvement of mRS score at discharge and at 3 month follow up. However, 8% of patients had worsening of neurological status during hospital stay. At discharge, 39% of patient had a mRS score of 4, followed by 20%, 18%, 7% and 3% for mRS score of 3, 2, 1 and 5 respectively. And at 3 month follow up, 23% of patient had a mRS score of 0 as well as 2, followed by 21%, 20%, 9% and none for mRS score of 4, 3, 1 and 5 respectively. A total of 4% of patients (n=4) had died, with 2 patients each died during hospital stay and on 3 month follow up.

FIGURE 5.15: MODIFIED RANKING SCALE OF PATIENTS



CARDIAC PARAMETERS

The mean time taken for ECG from the onset of symptoms was 373.1 ± 301.8 minutes (range 30 - 1420 minutes). The mean time taken for ECG from time of admission was 26.3 ± 22.8 minutes. The second ECG was taken 48 hours post admission for all the patients, and follow up ECG at 3 months. The various ECG parameters along with their mean, range and median is shown in Table 5.3.

TABLE 5.3: ECG PARAMETERS AT ADMISSION, 48 HOURS POST ADMISSION AND AT 3 MONTHS

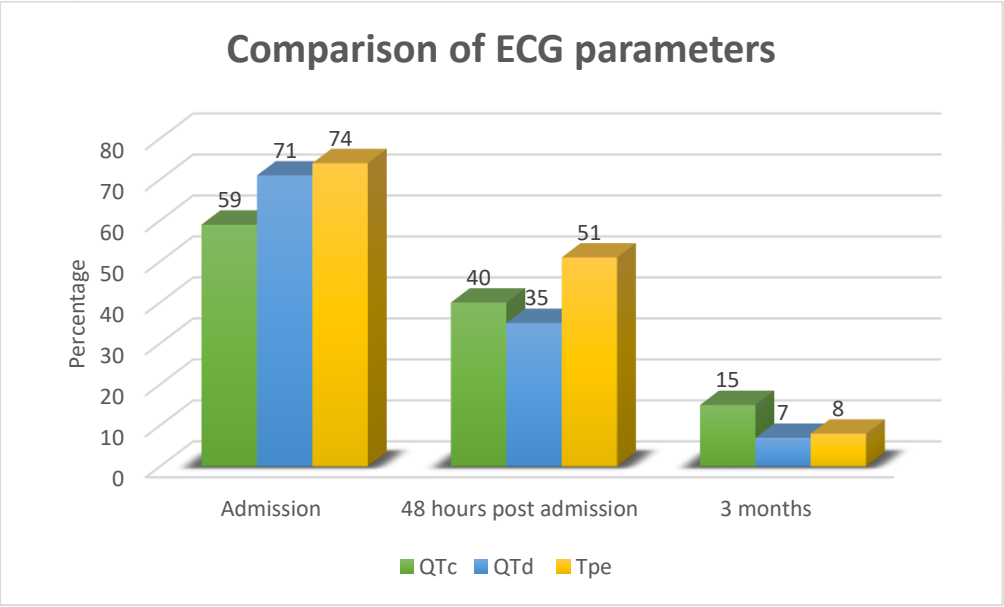
ECG parameter	N	Mean ± SD (milliseconds)	Range	Median	IQR
QT A	100	434.5 ± 54.1	360 - 640	435	400 - 460
QT PA	100	432.6 ± 50.6	360 - 680	420	400 - 460
QT 3m	96	405 ± 91.1	360 - 560	420	400 - 440
RR A	100	887.2 ± 152.4	400 - 1400	870	800 - 960
RR PA	100	922.5 ± 154.8	580 - 1400	880	805 - 1000
RR 3m	96	899.4 ± 229.9	640 - 1240	920	840 - 1020
QTc A	100	464.6 ± 57.7	365.1 - 682.2	447.8	426.4 - 480
QTc PA	100	452.8 ± 46.3	346.4 - 625.5	438.2	424.9 - 470.4
QTc 3m	96	437.7 ± 33.2	376.3 - 571.5	432.3	422.1 - 442.6
QTmax A	100	471 ± 67.4	380 - 800	460	420 - 500
QTmax PA	100	457.4 ± 53.8	340 - 700	440	420 - 480
QTmax 3m	96	442.9 ± 38.8	340 - 580	440	420 - 460
QTmin A	100	401.2 ± 52.6	320 - 620	380	360 - 435
QTmin PA	100	408 ± 51.2	320 - 660	400	380 - 440
QTmin 3m	96	400.9 ± 38.1	300 - 540	400	380 - 420
QTd A	100	70.2 ± 38.0	20 - 180	60	40 - 80

QTd PA	100	49.4 ± 19.6	20 - 140	40	40 - 60
QTd 3m	96	42 ± 9	20 - 80	40	40 - 40
Tpe A	100	104.6 ± 18.8	60 - 140	100	80 - 120
Tpe PA	100	92.8 ± 14.1	80 - 120	100	80 - 100
Tpe 3m	96	81.8 ± 6.9	60 - 120	80	80 - 80

N- number of patients, IQR- interquartile range; ECG parameters with A -at admission, PA- at 48 hours post admission, 3m- At 3 months follow up; RR- RR interval, QTc- corrected QT, QT max- maximum QT interval, QT min- minimum QT interval, QTd- QT dispersion.

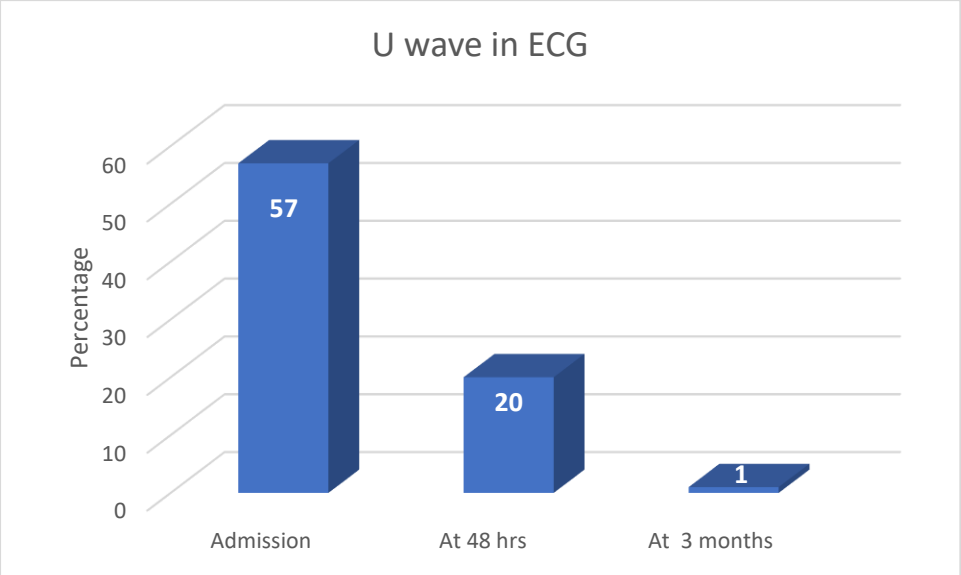
The mean QTc at admission was 464.6 ± 57.7 milliseconds (ms) (range 365.1 - 682.2 ms), and the mean QTc at 48hours post admission was 452.8 ± 46.3 ms (range 346.4 - 625.5 ms). The QTc was prolonged in 59 % (n =59) of patients at the time of admission, 40% at 48 hours and 15 % at 3 months follow up (Figure 5.16). QTd was prolonged in 71%, 35% and 7% at admission, 48 hours and 3 months follow up. Tpe interval was prolonged in 74%, 51% and 8 % at admission, 48 hours and 3 months respectively.

FIGURE 5.16: COMPARISON OF ECG PARAMETERS



The U wave was present in the ECG of 57 patients at time of admission, 20 patients at 48 hours and in 1 patient at 3 month follow up.

FIGURE 5.17: The presence of U wave in ECG



Echocardiogram was done for all patients. The mean LV end systolic dimension was 28.8 ± 5.7, range from 20 - 49 and the mean LV end diastolic dimension was 46 ± 7.5, range from 19 - 58. 63% patients had LV end systolic dimension less than 30, while rest had between 30-60. The mean ejection fraction was 63 ± 9 %, with range from 37 -80%. Among the patients 51 had underwent Holter study, which were all normal. And among them the mean duration of QRS was 165.2 ± 34.8 milliseconds (range 120 - 240). The mean of average heart rate, maximum and minimum heart rate was 73.2 ± 9.9, 113.2 ± 18.5, and 51.6 ± 8.6.

COMPARISON WITH QTc INTERVAL PROLONGATION

Various parameters were compared among those who had QTc prolongation at admission with those who did not had QTc prolongation at admission. Among patients with QTc prolongation at admission, 61% were in the age group of 51 – 70 years, and 71.2 % were males. Only 39% presented as a wake-up stroke. On comparison of various risk factors for stroke, QTc was

prolonged 53.8% patients with diabetes mellitus, 57.5% with hypertension, and 60.8% with dyslipidaemia, but these were not statistically significant (Table 5.4).

TABLE 5.4: Comparison of demographic profile and risk factors with QTc prolongation at admission

	QTc at admission prolonged				**Total**		χ^2	**df**	**p value**
	Yes		No						
	n	%	n	%	n	%			
Age in years									
< 50	7	11.9	9	22	16	16			
51-70	36	61	20	48.8	56	56			
>70	16	27.1	12	29.3	28	28	2.23	2	0.329
Gender									
Male	42	71.2	33	80.5	75	75			
Female	17	28.8	8	19.5	25	25	1.12	1	0.291
Wake up	23	39	14	34.1	37	37	0.24	1	0.622
Diabetes mellitus	35	59.3	30	73.2	65	65	2.04	1	0.153
Hypertension	41	69.5	30	73.2	71	71	0.16	1	0.690
Dyslipidaemia	14	23.7	9	22	23	23	0.04	1	0.835
Smoking									
Current smoker	5	8.5	5	12.2	10	10			
Stopped >3 months	14	23.7	14	34.1	28	28			
Non smoker	40	67.8	22	53.7	62	62	2.05	2	0.358
Alcohol	5	8.5	7	17.1	12	12	1.69	1	0.193
Prior stroke	9	15.3	4	9.8	13	13	0.65	1	0.421
Prior TIA	2	3.4	1	2.4	3	3	0.08	1	0.784
POVD	2	3.4	0	0	2	2	1.42	1	0.234

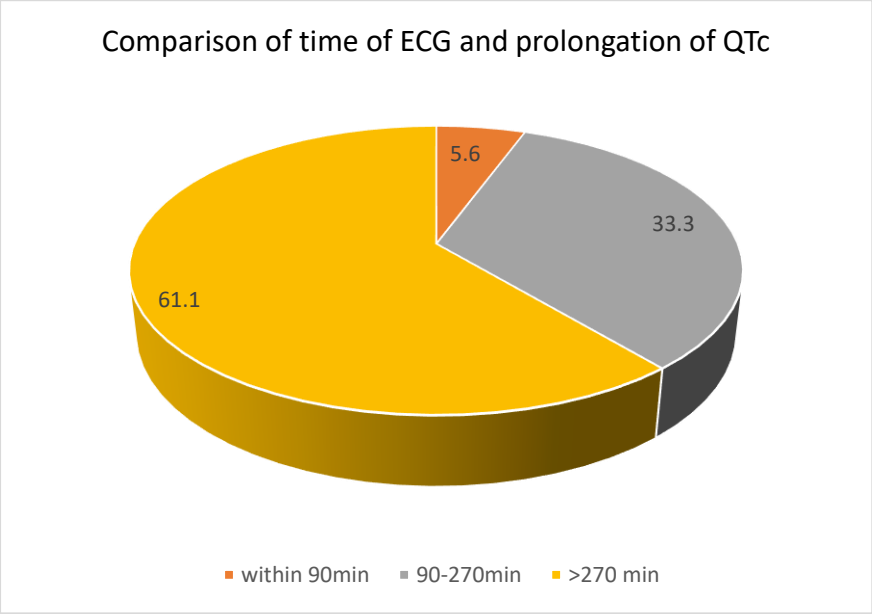
n- number of patients, CCB-calcium channel blocker, ACE-I -Angiotensin converting enzyme inhibitor, ARB – Angiotensin receptor blocker, TIA- Transient ischemic attack, POVD-Peripheral occlusive vascular disease

Patients who presented as wake up stroke, 62.1% (n=23) had QTc prolongation at admission (p value 0.622). And in the rest of the patients, with known time of symptom onset, 57.14% (n=36) had QTc prolongation at admission. Among them, 5.6% had ECG taken with 90min, 33.3% had ECG taken between 90-270min, and 61.1% had ECG taken after 270min (Figure 5.18). As compared to those without QTc prolongation, 48.1% had ECG taken between 90-270min and 44.4% had ECG taken after 270min from symptom onset (p value 0.451) (Table 5.5)

TABLE 5.5: Comparison of time of ECG taken with QTc prolongation at admission

	QTc at admission prolonged				Total		χ^2	df	p value
	Yes		No						
	n	%	n	%	N	%			
Time of ECG									
within 90min	2	5.6	2	7.4	4	6.3			
90-270min	12	33.3	13	48.1	25	39.7			
>270 min	22	61.1	12	44.4	34	54			
Total	36	100	27	100	63	100	1.73	2	0.451

FIGURE 5.18: COMPARISON OF TIME OF ECG FROM ONSET OF SYMPTOMS AND PROLONGATION OF QTc INTERVAL AT ADMISSION.



On comparing the imaging features (Table 5.6), patients with MCA territory infarct were found to have significant QTc prolongation. Among those with QTc prolongation 40.7% had Right sided MCA infarct, 45.8% had left MCA infarct and 13.6% did not have any MCA infarct (p = 0.049). 61 % patients with QTc prolongation had a territorial main artery pattern of infarct (p value = 0.007). Based on the region of infarct, 67.7% % of patients with cortical infarcts (p value = 0.023) and 80.6% of patients with cortical and subcortical region infarcts had QTc prolongation (p value = 0.003). The involvement of Insula was seen in 47.5% (n=28) patients

with QTc prolongation at admission as compared to 14.6% (n=6) patients without QTc prolongation (p value 0.001) and the involvement of basal ganglia was seen in 40.7% (n=24) patients with QTc prolongation at admission as compared to 19.5% (n=8) patients without QTc prolongation (p value 0.026). The patients with multiple area infarcts were also compared with prolongation of QTc interval, however no statistical significance was noted. The presence of chronic infarcts and white matter hyperintensities on imaging did not have any relation with the QTc prolongation at admission.

TABLE 5.6: Comparison of imaging characteristics with QTc prolongation at admission

	QTc at admission Prolonged				**Total**		χ^2	**df**	**p value**
	Yes		No						
	n	%	n	%	n	%			
HEMISPHERE									
Right	25	42.4	14	34.1	39	39			
Left	27	45.8	18	43.9	45	45			
Vertebrobasilar	7	11.9	9	22	16	16	1.98	2	0.372
MCA TERRITORY									
Right	24	40.7	12	29.3	36	36			
Left	27	45.8	15	36.6	42	42			
no MCA infarct	8	13.6	14	34.1	22	22	6.02	2	0.049
INFARCT PATTERN									
Single arterial territories	55	93.2	37	90.2	92	92			
Multiple arterial territories	4	6.8	4	9.8	8	8	0.29	1	0.589
INFARCT SUBTYPE									
Territorial Main artery	36	61	10	24.4	46	46			
Branch occlusion	10	16.9	12	29.3	22	22			
Superficial watershed	3	5.1	3	7.3	6	6			
Internal border zone	4	6.8	4	9.8	8	8			
Lacunar	6	10.2	12	29.3	18	18	14.09	4	0.007
REGION INVOLVED									
Cortical	42	71.2	20	48.8	62	62	5.16	1	0.023
Subcortical	39	66.1	20	48.8	59	59	3.00	1	0.083
Brainstem	6	10.2	7	17.1	13	13	1.02	1	0.313
Cerebellum	3	5.1	1	2.4	4	4	0.44	1	0.507
Cortical + Subcortical	25	42.4	6	14.6	31	31	8.70	1	0.003
Brainstem + cerebellum	1	1.7	0	0	1	1	0.70	1	0.402
LOCATION OF INFARCT									
Lobar	37	62.7	19	46.3	56	56	2.63	1	0.105

Insular	28	47.5	6	14.6	34	34	11.61	1	0.001
Basal ganglia	24	40.7	8	19.5	32	32	4.98	1	0.026
Periventricular	16	27.1	11	26.8	27	27	0.00	1	0.974
Cerebellum	3	5.1	1	2.4	4	4	0.44	1	0.507
Thalamus	1	1.7	3	7.3	4	4	1.99	1	0.158
Midbrain	2	3.4	0	0	2	2	1.42	1	0.234
Pons	4	6.8	7	17.1	11	11	2.62	1	0.106
Medulla	3	5.1	0	0	3	3	2.15	1	0.143
CHRONIC INFARCT	21	35.6	11	26.8	32	32	0.85	1	0.355
LOCATION OF CHRONIC INFARCT									
No infarct	38	64.4	30	73.2	68	68			
Territorial	14	23.7	6	14.6	20	20			
Lacunar	7	11.9	5	12.2	12	12	1.28	2	0.528
WMHI									
Grade 0	37	62.7	25	61	62	62			
Grade I	7	11.9	5	12.2	12	12			
Grade II	10	16.9	11	26.8	21	21			
Grade III	5	8.5	0	0	5	5	4.61	3	0.202

n- number of patients, WMHI- white matter hyperintensities

Most of the patients who underwent mechanical thrombectomy (n= 13, 81.2%) had QTc prolongation at admission (p value = 0.048) as compared to 66.5 % of patients treated with intravenous thrombolysis and 53.6% patient treated conservatively.

TABLE 5.7: Comparison of treatment received with QTc prolongation at admission

	QTc at admission Prolonged				**Total**		**χ^2**	**df**	**p**
	Yes		No						
	n	%	N	%	n	%			
Intravenous Thrombolysis	14	23.7	7	17.1	21	21	0.65	1	0.422
Mechanical thrombectomy	13	22	3	7.3	16	16	3.90	1	0.048
Bridging thrombectomy	5	8.5	1	2.4	6	6	1.56	1	0.211
Conservative management	37	62.7	32	78	69	69	2.66	1	0.103

Stroke subtype based on TOAST classification was compared with QTc prolongation at admission (Table 5.8), it was found that 73.8 % (n= 31) patients with large artery atherosclerotic disease had QTc prolonged at admission (p value= 0.010). 40% of patients with

lacunar stroke, 52.7% with undetermined cause had QTc prolongation at admission, which was not statistically significant. Among the patients with QTc prolongation at admission 52.5% had large artery atherosclerotic disease.

TABLE 5.8: Comparison of etiology of stroke with QTc prolongation at admission

	QTc at admission Prolonged				Total		χ^2	df	p value
	Yes		No						
	n	%	n	%	n	%			
Large artery atherosclerosis	31	52.5	11	26.8	42	42	6.57	1	0.010
Lacunar	8	13.6	12	29.3	20	20	5.43	1	0.066
Other determined causes	1	1.7	1	2.5	2	2	0.70	1	0.402
Undetermined	19	32.2	17	41.5	36	36	0.90	1	0.343

Patients with moderate (55.5%, n= 30) and severe stroke at admission (95.5%, n= 21) had significant QTc prolongation as compared to those with minor stroke (33.3% n =8); (p value <0.001). Even at discharge and on 3 month follow up, those patients with NIHSS score 5 to 15 (71.7% at discharge and 80.6% at 3 months) had significant QTc prolongation at admission as compared to those with NIHSS <5 (41.7% at discharge and 46.2% at 3 months) with p value of 0.003 at discharge and 0.001 at 3 months follow up. All the 4 patients with NIHSS >15 at discharge had significant QTc prolongation at admission, 2 of them died and 2 of them recovered on 3 month follow up.

In the mRS functional scale for stroke, those with more disability ie. mRS scale of 3 to 6, at admission (p value <0.001), discharge (p value 0.013) and 3 month follow up (p value 0.004) had more QTc prolongation as compared to those with mRS score of 0 to 2. 64.2% (n= 34) and 62.7% (n= 32) of patients who did not have improvement in mRS scale at discharge and at 3 months, had QTc prolongation at admission, even though it was not found to have statistical significance (p value = 0.266 and 0.437). 5 out of 8 patients who had worsening of neurological deficits during hospital stay had QTc prolongation at admission (p value = 0.834) (Table 5.9).

TABLE 5.9: Comparison of stroke severity with QTc prolongation at admission

	QTc at admission Prolonged				Total		χ^2	df	p
	Yes		No						
	n	%	n	%	n	%			
NIHSS at admission									
Minor stroke	8	13.6	16	39	24	24			
Moderate stroke	30	50.8	24	58.5	54	54			
Severe stroke	21	35.6	1	2.4	22	22	18.89	2	<0.001
NIHSS at discharge									
NIHSS <5	20	35.1	28	68.3	48	49			
NIHSS 5-15	33	57.9	13	31.7	46	46.9			
NIHSS >15	4	7	0	0	4	4.1	11.73	2	0.003
NIHSS at 3 months									
NIHSS <5	30	54.5	35	85.4	65	67.7			
NIHSS 5-15	25	45.5	6	14.6	31	32.3			
NIHSS >15	0	0	0	0	0	0	10.21	1	0.001
mRS at admission									
1	1	1.7	3	7.3	4	4			
2	2	3.4	9	22	11	11			
3	4	6.8	10	24.4	14	14			
4	47	79.7	16	39	63	63			
5	5	8.5	3	7.3	8	8	21.23	4	<0.001
mRS at discharge									
0	4	6.8	7	17.1	11	11			
1	2	3.4	5	12.2	7	7			
2	6	10.2	12	29.3	18	18			
3	14	23.7	6	14.6	20	20			
4	29	49.2	10	24.4	39	39			
5	2	3.4	1	2.4	3	3			
6	2	3.4	0	0	2	2	16.18	6	0.013
mRS at 3 months									
0	6	10.2	17	41.5	23	23			
1	5	8.5	4	9.8	9	9			
2	14	23.7	9	22	23	23			
3	16	27.1	4	9.8	20	20			
4	14	23.7	7	17.1	21	21			
6	4	6.8	0	0	4	4	17.31	5	0.004
mRS improved at discharge	25	42.4	22	53.7	47	47	1.24	1	0.266
mRS improved at 3 months	27	45.8	22	53.7	49	49	0.60	1	0.437
In hospital worsening	5	8.5	3	7.3	8	8	0.04	1	0.834

MULTIVARIATE ANALYSIS

In multivariate analysis, only functional disability at admission by mRS scoring remained to be associated with prolonged QTc at admission (odds ratio 4.303, 95% confidence interval 1.356-13.655).

TABLE 5.10: Multivariate analysis for association between various variables and prolongation of QTc at admission

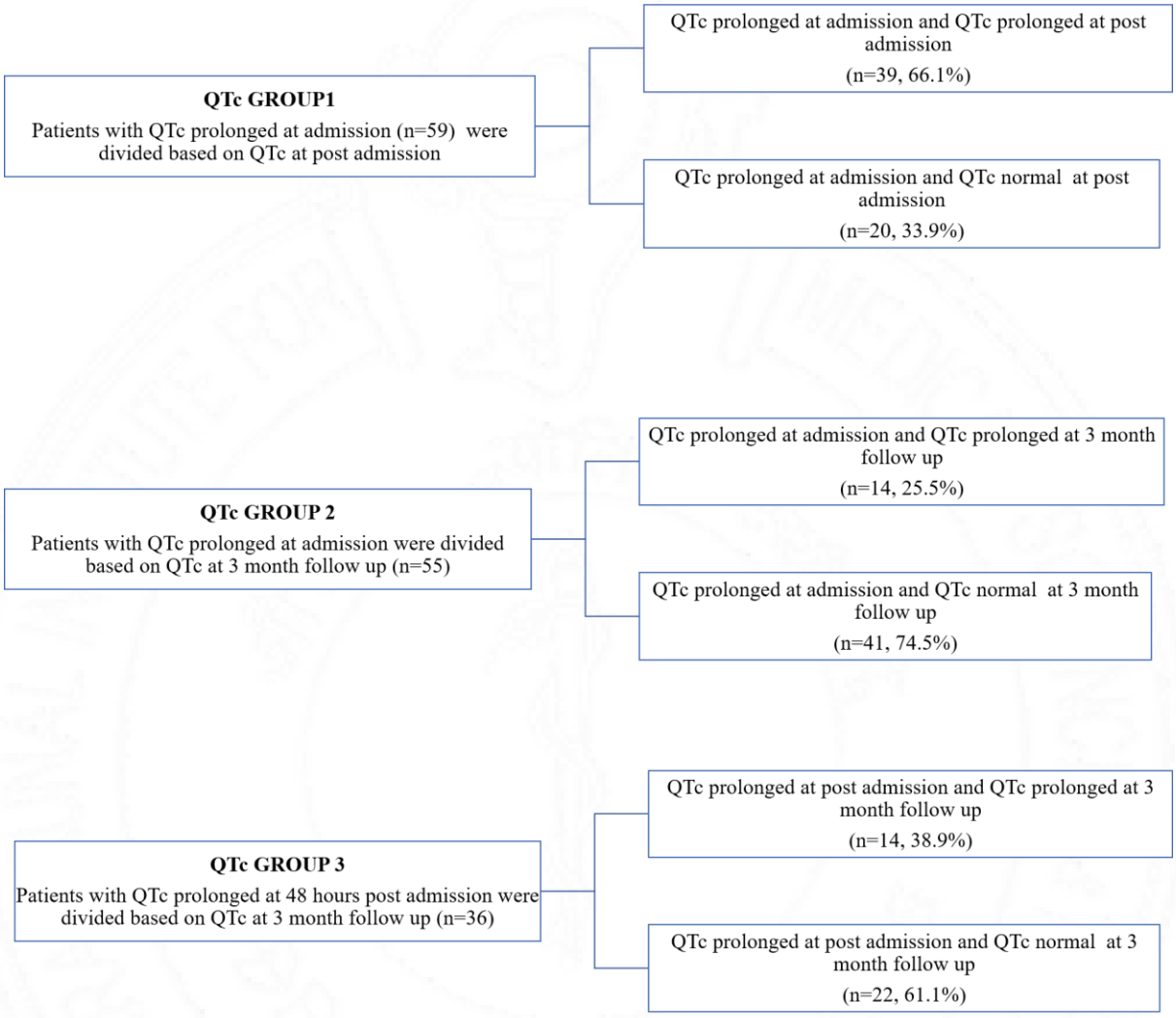
Variables	P value	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
NIHSS at admission	0.051	9.939	0.992	9.959
mRS at admission	0.013	4.303	1.356	13.655
MCA territory infarcts	0.244	2.127	0.598	7.566
Cortical	0.564	0.691	0.197	2.427
Cortical + subcortical involvement	0.719	1.367	0.249	7.506
Insula	0.404	1.933	0.676	8.96
Basal Ganglia	0.329	0.449	0.090	2.245
Large artery atherosclerotic disease	0.198	1.999	0.697	5.734

GROUPING OF PATIENTS WITH QTC PROLONGATION

We had also looked into the comparison with patients who had prolonged QTc values with stroke subtype and severity. The study subjects were grouped into 3 grouped based on the QTc prolongation at admission, 48 hours post admission and at 3 month follow up (Figure 5.19).

None of patients had a new QTc prolongation at 48 hours and 3 months as compared to baseline ECG. 4 patients who died were excluded from 3 month follow up analysis.

FIGURE 5.19: Groupwise division of patients with prolonged QTc interval



Among the patients who had persistent QTc prolongation at admission as well as at 48 hours post admission (Table 5.11), 46.5% and 38.5% had moderate and severe stroke at admission (p value 0.592). While on comparing with the NIHSS score at discharge, 70.3% patients (n =26) who had persistent QTc prolongation at 48 hours had with NIHSS score of 5 -15 as compared to majority of patients (65%, n= 13) with normal QTc at 48 hours who had minor

deficits with NIHSS score less than 5 (p value 0.002). All the 4 patients with NIHSS at discharge >15 had persistent QTc prolongation at 48 hours. Similar results were found with NIHSS score at 3 months, 68.6% of patients (n = 24) with persistent QTc prolongation at 48 hours had moderate deficits with NIHSS score of 5 -15 as compared to majority of patients (95%, n= 19) with normal QTc at 48 hours, who had minor deficits with NIHSS score less than 5 (p value <0.001).

Table 5.11: Comparison of variables with QTc group 1

	QTc Group I				Total		χ^2	df	p
	Yes		No						
	n	%	n	%	n	%			
Age in years									
< 50	7	17.9	0	0	7	11.9			
51-70	23	59	13	65	36	61			
>70	9	23.1	7	35	16	27.1	4.36	2	0.113
GENDER									
Male	26	66.7	16	80	42	71.2			
Female	13	33.3	4	20	17	28.8	1.15	1	0.284
NIHSS at admission									
Minor stroke	6	15.4	2	10	8	13.6			
Moderate stroke	18	46.2	12	60	30	50.8			
Severe stroke	15	38.5	6	30	21	35.6	1.05	2	0.592
NIHSS at discharge									
NIHSS <5	7	18.9	13	65	20	35.1			
NIHSS 5-15	26	70.3	7	35	33	57.9			
NIHSS >15	4	10.8	0	0	4	7	12.81	2	0.002
NIHSS at 3 months									
NIHSS <5	11	31.4	19	95	30	54.5			
NIHSS 5-15	24	68.6	1	5	25	45.5			
NIHSS >15	0	0	0	0	0	0	20.75	1	<0.001
mRS at admission									
1	1	2.6	0	0	1	1.7			
2	1	2.6	1	5	2	3.4			
3	3	7.7	1	5	4	6.8			
4	31	79.5	16	80	47	79.7			
5	3	7.7	2	10	5	8.5	0.97	4	0.914
mRS at discharge									

0	1	2.6	3	15	4	6.8			
1	1	2.6	1	5	2	3.4			
2	1	2.6	5	25	6	10.2			
3	5	12.8	9	45	14	23.7			
4	27	69.2	2	10	29	49.2			
5	2	5.1	0	0	2	3.4			
6	2	5.1	0	0	2	3.4	27.05	6	<0.001
mRS at 3 months									
0	2	5.1	4	20	6	10.2			
1	3	7.7	2	10	5	8.5			
2	4	10.3	10	50	14	23.7			
3	12	30.8	4	20	16	27.1			
4	14	35.9	0	0	14	23.7			
5	0	0	0	0	0	0			
6	4	10.3	0	0	4	6.8	21.56	5	0.001
mRS improved at discharge	9	23.1	16	80	25	42.4	17.54	1	<0.001
mRS improved at 3 months	16	41	11	55	27	45.8	1.04	1	0.308
Stroke subtype									
Large artery atherosclerosis	17	43.6	14	70	31	52.5			
Lacunar	7	17.9	1	5	8	13.6			
Other determined etiology	1	2.6	0	0	1	1.7			
Undetermined etiology	14	35.9	5	25	19	32.2	4.39	3	0.222
Large artery atherosclerosis	17	43.6	14	70	31	52.5	3.70	1	0.054
Lacunar	7	17.9	1	5	8	13.6	1.89	1	0.169
Undetermined etiology	14	35.9	5	25	19	32.2	0.72	1	0.396

We had also compared group 1 patients with their functional disability due to stroke. The majority of patients in this study had mRS score of 4 (79.7%) at admission, among them 31 patients had persistent QTc prolongation at 48 hours while 16 patients had normalization of QTc at 48 hours (p value 0.914). On evaluating the disability at discharge, the majority of patients with persistent QTc prolongation at 48 hours (69.2%, n =27) had mRS score of 4 as compared to 10% of patients with normalization of QTc at 48 hours who has mRS score of 4 (p value <0.001). It was also seen that all the patients with mRS score of 5 and 6 had persistent QTc prolongation at 48 hours. On 3 month follow up assessment, only 35.9% of patients with persistent QTc prolongation at 48 hours had mRS of 4 however it was found that among patients with normalization of QTc at 48 hours, 50% had mRS 2, 20% had mRS 0, 10% had mRS 1 and none had mRS of >3 (p value 0.001). On comparing with patients who had improvement of mRS score at discharge, it was found that 76.9% of patients who had persistent

QTc prolongation did not have any improvement as compared to 80% of patients with normalization of QTc at 48 hours who had improvement of mRS score at discharge (p value <0.001).

43.6% of patients with persistent QTc prolongation at 48 hours had large artery atherosclerotic disease and 35.9% had undetermined etiology for stroke (p value 0.222). 70% of patients with normalization of QTc at 48 hours had LAA as compared to 43.6% with prolonged QTc at 48 hours, however this was not statistically significant (p value 0.054).

The group 2 analyzed patients with QTC prolongation at admission and persistent QTc prolongation at 3 months suggesting possibility that they had a pre-existing QTc abnormality with those who had normalization of QTc at 3 months. However, in this population the comparison with NIHSS scores at admission, discharge and 3 month follow up as well the corresponding mRS score did not have any statistical significance (Table 5.12). 42.9 % patients with persistent QTc prolongation at 3 months had undetermined etiology for stroke as compared to 26.8% who had normalization of QTc at 3 months (p value 0.120). On comparing patients with LAA alone, only 28.6% of patient with persistent QTc at 3 months had LAA as the etiology as compared to 61% of patients with normalization of QTc at 3 months (p value 0.036).

Table 5.12: Comparison of variables with QTc group 2

	QTc Group II				**Total**		χ^2	**df**	**p**
	Yes		No						
	n	%	n	%	n	%			
Age in years									
< 50	3	21.4	4	9.8	7	12.7			
51-70	9	64.3	24	58.5	33	60			
>70	2	14.3	13	31.7	15	27.3	2.34	2	0.311
GENDER									
Male	11	78.6	28	68.3	39	70.9			
Female	3	21.4	13	31.7	16	29.1	0.54	1	0.465
NIHSS at admission									
Minor stroke	3	21.4	4	9.8	7	12.7			
Moderate stroke	6	42.9	23	56.1	29	52.7			
Severe stroke	5	35.7	14	34.1	19	34.5	1.47	2	0.479

NIHSS at discharge									
NIHSS <5	4	28.6	16	39	20	36.4			
NIHSS 5-15	9	64.3	23	56.1	32	58.2			
NIHSS >15	1	7.1	2	4.9	3	5.5	0.53	2	0.766
NIHSS at 3 months									
NIHSS <5	6	42.9	24	58.5	30	54.5			
NIHSS 5-15	8	57.1	17	41.5	25	45.5			
NIHSS >15	0	0	0	0	0	0	1.04	1	0.309
mRS at admission	0	0	1	2.4	1	1.8			
1	0	0	2	4.9	2	3.6			
2	3	21.4	1	2.4	4	7.3			
3	10	71.4	34	82.9	44	80			
4	1	7.1	3	7.3	4	7.3			
5	0	0	0	0	0	0	6.37	4	0.173
mRS at discharge	0	0	4	9.8	4	7.3			
0	0	0	2	4.9	2	3.6			
1	1	7.1	5	12.2	6	10.9			
2	3	21.4	11	26.8	14	25.5			
3	10	71.4	18	43.9	28	50.9			
4	0	0	1	2.4	1	1.8			
5	0	0	0	0	0	0	4.31	5	0.506
mRS at 3 months	1	7.1	5	12.2	6	10.9			
0	2	14.3	3	7.3	5	9.1			
1	3	21.4	11	26.8	14	25.5			
2	3	21.4	13	31.7	16	29.1			
3	5	35.7	9	22	14	25.5			
4	0	0	0	0	0	0			
5	0	0	0	0	0	0	2.08	4	0.722
mRS improved at discharge	4	28.6	21	51.2	25	45.5	2.16	1	0.142
mRS improved at 3 months	8	57.1	19	46.3	27	49.1	0.49	1	0.485
Stroke subtype									
Large artery atherosclerosis	4	28.6	25	61	29	52.7			
Lacunar	4	28.6	4	9.8	8	14.5			
Other determined etiology	0	0	1	2.4	1	1.8			
Undetermined etiology	6	42.9	11	26.8	17	30.9	5.83	3	0.120
Large artery atherosclerosis	4	28.6	25	61	29	52.7	4.40	1	0.036
Lacunar	4	28.6	4	9.8	8	14.5	2.97	1	0.085
Undetermined etiology	6	42.9	11	26.8	17	30.9	1.26	1	0.263

The group 3 analyzed patients with QTc prolongation at 48 hours post admission and persistent QTc prolongation at 3 months, with those who had normalization of QTc at 3 months. However, in this population also the comparison with NIHSS scores at admission, discharge

and 3 month follow up as well the corresponding mRS score did not have any statistical significance (Table 5.13). 42.9 % patients with persistent QTc prolongation at 3 months had undetermined etiology for stroke as compared to 27.3 % who had normalization of QTc at 3 months (p value 0.316).

Table 5.13: Comparison of variables with QTc group 3

	QTc Group III				Total		χ^2	df	p
	Yes		No						
	n	%	n	%	n	%			
Age in years									
< 50	3	21.4	4	18.2	7	19.4			
51-70	9	64.3	11	50	20	55.6			
>70	2	14.3	7	31.8	9	25	1.41	2	0.493
GENDER									
Male	11	78.6	13	59.1	24	66.7			
Female	3	21.4	9	40.9	12	33.3	1.46	1	0.227
NIHSS at admission									
Minor stroke	3	21.4	2	9.1	5	13.9			
Moderate stroke	6	42.9	12	54.5	18	50			
Severe stroke	5	35.7	8	36.4	13	36.1	1.17	2	0.556
NIHSS at discharge									
NIHSS <5	4	28.6	3	13.6	7	19.4			
NIHSS 5-15	9	64.3	17	77.3	26	72.2			
NIHSS >15	1	7.1	2	9.1	3	8.3	1.22	2	0.543
NIHSS at 3 months									
NIHSS <5	6	42.9	6	27.3	12	33.3			
NIHSS 5-15	8	57.1	16	72.7	24	66.7	0.94	1	0.334
NIHSS >15									
mRS at admission	0	0	1	4.5	1	2.8			
1	0	0	1	4.5	1	2.8			
2	3	21.4	0	0	3	8.3			
3	10	71.4	19	86.4	29	80.6			
4	1	7.1	1	4.5	2	5.6			
5	0	0	0	0	0	0	6.33	4	0.176
mRS at discharge	0	0	1	4.5	1	2.8			
0	0	0	1	4.5	1	2.8			
1	1	7.1	0	0	1	2.8			
2	3	21.4	2	9.1	5	13.9			
3	10	71.4	17	77.3	27	75			
4	0	0	1	4.5	1	2.8			

5	0	0	0	0	0	0	4.46	5	0.486
mRS at 3 months									
0	1	7.1	1	4.5	2	5.6			
1	2	14.3	1	4.5	3	8.3			
2	3	21.4	1	4.5	4	11.1			
3	3	21.4	9	40.9	12	33.3			
4	5	35.7	10	45.5	15	41.7			
5	0	0	0	0	0	0	4.44	4	0.350
mRS improved at discharge	4	28.6	5	22.7	9	25	0.16	1	0.693
mRS improved at 3 months	8	57.1	8	36.4	16	44.4	1.50	1	0.221
Stroke subtype									
Large artery atherosclerosis	4	28.6	12	54.5	16	44.4			
Lacunar	4	28.6	3	13.6	7	19.4			
Other determined etiology	0	0	1	4.5	1	2.8			
Undetermined etiology	6	42.9	6	27.3	12	33.3	3.54	3	0.316
Large artery atherosclerosis	4	28.6	12	54.5	16	44.4	2.34	1	0.126
Lacunar	4	28.6	3	13.6	7	19.4	1.22	1	0.270
Undetermined etiology	6	42.9	6	27.3	12	33.3	0.94	1	0.334

DISCUSSION

6. DISCUSSION

Our study is the first of its kind to demonstrate the correlation between baseline QTc interval in patients with AIS and the stroke subtype as well as the stroke severity and functional disability. Our study investigates the QTc interval changes during admission, 48 hours and 3 months follow up after an ischemic stroke and its relation to stroke subtype, severity and clinical outcome. We have excluded patients with prior cardiac disease as well as patients on medications that can prolong QT interval. We found that prolongation of QTc interval is associated with large artery atherosclerosis and an increase in stroke severity and poor functional outcomes in AIS patient, which was independent of age, gender, and cardiovascular risk factors.

The last few decades has seen the development of "neurocardiology" (54), which allows us to understand how the primary CNS pathology can affect the cardiovascular system. As the heart has important as well as florid autonomic innervation, it is expected that acute disturbances of the CNS may result in a wide spectrum of cardiac functional disorders. Several studies have shown that acute CNS insult such as stroke can this produce changes in the ECG (4,22). The QT intervals which are susceptible to autonomic influences (15) can thus be altered in acute stroke patients. These alterations in QT interval may be due to the influence of autonomic nervous system on the ventricular myocardium (47) which affects the duration of cardiac repolarization as well as on the sinus node (46) that affects the heart rate and thus the QT interval (27). The QT interval prolongation may also be attributed to a disturbed regional myocardial sympathetic activity (83) that can occur as a part of sympathetic hyperactivity occurring in acute stroke (84).

In our study, the mean QT and QTc interval at baseline of the study subjects were 434.5 ± 54.1 minutes and 464.6 ± 57.7 minutes. The QTc was prolonged in 59 % (n =59) of patients at the time of admission. This is similar to previous studies in which prolonged QTc was seen in in 38–71% of patients with acute stroke, thus constituting QTc prolongation as the most frequent single ECG abnormality in acute stroke (73,85). The reflex increase in blood pressure occurring in acute ischemic stroke due to dysautonomia and sympathetic overdrive returns to baseline in

majority of patients within 24hours(86,87). Therefore, for this study we presumed that the QT interval which is also a marker of autonomic dysfunction, might return to premorbid state within 48hours in most of the patients with AIS. However, in our study the QTc was prolonged in 40% (n= 40) of patients at 48 hours and 15 % at 3 months follow up. In study by Hromádka et al., 65.2% (n =45) patients had prolonged QTc at baseline and only 26.1% (n=18) patients had prolonged QTc after 48 hours (64).

The QT dispersion (QTd) which is also a marker of myocardial repolarization, is found to be increased significantly in patients with AIS (37). We found that QTd was prolonged in 71%, 35% and 7% of our patients at admission, 48 hours and 3 months follow up. Similarly in the study by Afzar et al,, on a 3-day follow up ECG, the QTd values of stroke patients decreased to non-stroke control values (88). We had also studied the Tpe interval in ECG, which was prolonged in 74%, 51% and 8 % at admission, 48 hours and 3 months respectively. Tpe as a new repolarization marker in AIS was studied by Emektar et al. (61), who demonstrated that Tpe was significantly prolonged in stroke patients as compared to control group and Tpe values reduced in the ECG on third day than ECG on first day (p value <0.05).

Among the other ECG changes, a prominent U wave was present in the ECG of 57 % of patients at time of admission, 20 % at 48 hours and 1 % at 3 month follow up. In an early study of 150 patients Golstein detected prominent U-waves in 28% of their patients with acute stroke(4). However in SAH in which most of the ECG abnormalities have been extensively studied, prominent U-waves were seen in 4% to 47% of patients (89).

DEMOGRAPHICS AND RISK FACTORS

We had 100 patients with AIS who were admitted in our stroke unit, with the mean age of the study population was 63 ± 11.7 years and 75% of patients were male. This is comparable with the mean age of stroke onset in India (i.e., 63 years) which is lower than that in Western countries (68 years in the USA and 71 in Italy) (90). Among the patients who had QTc prolongation at admission, 11.9% were of age < 50years, 61% were of age between 51-70 years and 27.1% were of age >70 years. No specific gender-based difference in QT interval prolongation was noted in the study subjects. Upper normal limits for QTc vary with age and sex, QTc is considered prolonged if > 0.440 seconds in males and > 0.460 seconds in females(28). This sex difference in QTc is attributed to the shortened QT interval seen in adolescent males (91),which is most likely the result of changes in sex-specific hormones, even

though the exact mechanism is unknown (92). Rautaharju (91) had suggested an age- and sex-specific criteria for the evaluation of QT prolongation, however validation in large ethnically diverse population is needed.

Several CVD risk factors are associated with prolongation of QTc interval which includes smoking, diabetes mellitus, systemic hypertension, etc. (85,93). However, among the various CVD risk factors that we had studied including diabetes mellitus, systemic hypertension, dyslipidemia, smoking, alcoholism, POVD and prior history of stroke or TIA, none of them had significant correlation with QTc prolongation.

INFARCT LOCATION

Various structural as well as functional lesions of the brain have been associated with electrocardiographic changes (94) .And majority of studies have demonstrated that insula which plays an integral role in central autonomic control, can lead to various ECG changes including QT interval prolongation (30,94). The involvement of Insula was seen in 47.5% patients with QTc prolongation at admission as compared to 14.6% patients without QTc prolongation (p value 0.001). We had also observed that the involvement of basal ganglia was seen in 40.7% patients with QTc prolongation at admission as compared to 19.5% patients without QTc prolongation (p value 0.026), suggesting a possible role of basal ganglia involvement in control of autonomic activity (95). However, on multivariate analysis location of infarct was not found to be associated with QTc prolongation.

Strittmatter et al. (59) suggested that alterations in autonomic function were paralleled with a sustained elevation in cardiovascular parameters mainly in right hemispheric stroke. Henninger et al (31). showed that left sided temporal infarction was associated with significantly longer QTc interval as compared with right-sided infarction (QTc Bazett: 480 ± 26 ms vs. 429 ± 38 ms, $p < 0.01$). However, we did not observe any significant difference between QTc prolongation at baseline with right hemispheric, left hemispheric or vertebrobasilar stroke. This was similar to study by Sultan (29) in which no significant difference between right and left sided stroke were found with regard to QTc interval values. Simula et al. (96) showed that right MCA ischemic stroke resulted in prolongation of QT interval. In our patients with QTc prolongation at baseline, majority had MCA infarct (86.4%, p value 0.049) but no major difference between right and left MCA territory infarct was noted (40.7% and 45.8%).

A study on QTc-prolongation in patients with posterior circulation strokes found that 34 % of patients had a prolonged QTc on admission, and there was a significant association between temporal lobe infarction and QTc ($p < 0.001$) (31). We did not assess for any correlation of lobe wise involvement with QTc. However, we did not find any significant association between vertebrobasilar region infarcts and prolongation of QTc. Based on the region of infarct, 67.7% % of patients with cortical infarcts (p value = 0.023) and 80.6% of patients with cortical and subcortical region infarcts had QTc prolongation (p value = 0.003). Alabd et al.(37) studied QTd on first and third day of hospitalisation, and found no significant differences among the four territorial subgroups (ie. cortical, subcortical, brain stem and cerebellar infarctions), or between right and left hemispheric lesions. However, the 'first-day' QTd were significantly higher in patients with insular involvement than in those without such involvement.

STROKE SUBTYPE

We had explore the correlation between QT interval changes and stroke subtypes based on TOAST classification. We excluded patients with cardioembolic etiology of stroke as well as those with prior cardiac disease. Among the various stroke subtypes based on the etiology of stroke; the large artery atherosclerosis constituted 42%, lacunar (small vessel occlusion) 20%, other determined causes 2%, and undetermined was 36%. This is comparable with the prevalence of stroke subtypes in India (97), where 41% of strokes are caused due to LAA,18% lacunar, 10% to cardioembolic , 4% to other determined etiology and 27% due to undetermined causes.

73.8 % patients with large artery atherosclerotic disease had QTc prolonged at admission (p value= 0.010). 40% of patients with lacunar stroke and 52.7% with undetermined cause also had QTc prolongation at admission, but it was not statistically significant. Among the 59 patients with QTc prolongation at admission 52.5% had large artery atherosclerotic disease. Henninger et al. (31) in his study on posterior circulation stroke, found that cardioembolic cause was the most common etiology associated with QTc prolongation (36%, p 0.014) and 33 % had LAA (p value 0.027), however on multivariate analysis none of them had significance with QTc prolongation.

We had also found that among the patients who had QTc prolongation at admission, 61% of patients with normalization of QTc at 3 months had LAA as etiology as compared to 28.6% of patient with persistent QTc at 3 months, which was found to be statistically significant. This may be due the the acute insult in a LAA which might have lead to QTc prolongation at time of admission in AIS, that later normalised in majority of patients by 3months.

Several studies have demonstrated QTc prolongation as a risk marker of subclinical atherosclerosis(67,69) and QTc prolongation subsequently can be predictive of future atherosclerotic vascular events such as stroke (85) . Strohmer et al found significant correlation between QT interval and intima media thickness (IMT) of the carotid arteries in general population undergoing cardiovascular screening (67). Significant correlations between QT/QTc and internal carotid artery IMT (r=0.14-0.16) were found in males. In women a statistically significant relationship was found between the QT interval and common carotid artery IMT (r=0.15, P=0.006). Festa et al (69) also demonstrated a significant relation of QTc interval to carotid atherosclerosis in nondiabetic subjects, that was stronger in women.IMT of the common carotid artery correlated significantly with QTc interval duration (r=50.15 for QT60 and r=50.14 for QTc), whereas no relationship between IMT of the internal carotid artery and QT interval was found (r= 520.01). The probable mediator for this association might be the increased catecholamine levels that prolong the QT interval (70) and which are also associated with development of atherosclerosis (71). However acute prolongation of QTc interval as a part of AIS due to large artery atherosclerotic disease has not been explored. The possibility that the sympathetic hyperactivity and catecholamine surge that occur was part of AIS can lead to prolongation of QTc interval (10,84). Paroxysmal sympathetic hyperactivity as an initial manifestation of acute large vessel occlusion was demonstrated by Yin et al.(98) in his case series of posterior circulation stroke, in whom the symptoms of paroxysmal sympathetic hyperactivity did not recur after the recanalization of vessels by endovascular treatment. However, further studies are needed in future for understanding the exact mechanism involved.

STROKE SEVERITY AND OUTCOME

Among our patients, those with moderate (55.5%, n= 34) and severe stroke at admission (95.5%, n= 21) had significant QTc prolongation as compared to those with minor stroke

(33.3% n =8) (p value <0.001). A prior study found correlation between the increase in QTd and severity of stroke as measured by the NIHSS. It was shown that the NIHSS score changed 3.1 units in the same direction (95% CI: 2.0, 4.2) for every 10 ms change in QTd (99). Korkmaz et al.(63) demonstrated that both QT and QTc were substantially longer in patients with NIHSS ≥5. But none of them were found to be independent predictors of high NIHSS scores.

Even at discharge and on 3 month follow up, those patients with NIHSS score 5 to 15 had significant QTc prolongation at admission as compared to those with NIHSS <5. All the 4 of our patients with NIHSS >15 at discharge had significant QTc prolongation at admission. This was similar to a prior study that demonstrated the increased cardiac-electrophysiological balance levels (iCEB), which is determined on ECG by dividing the QT interval by QRS duration, as an independent predictor of NIHSS ≥5 and it correlated with both the NIHSS scores at admission and discharge (63).

A prolonged QTc was associated with worser functional disability with the mRS score from 3 to 6, at admission, discharge as well on 3 month follow up. However, Stead et al. showed no relationship between prolonged QTc and discharge mRS (16). And a prospective cohort study on QT dispersion in AIS patients showed that QT dispersion did not predict short-term clinical outcome for mRS score (p value 0.85), NIHSS at discharge (p value 0 .30), or discharge disposition (p value 0.81) (65). As seen in our study population, a prolonged QT interval in patients with acute stroke was associated with a significantly greater risk of all-cause mortality within 3 months (16).

Among the patients who had QTc prolongation, those who had persistent QTc prolongation at 48 hours post admission had significantly worser NIHSS score at discharge as well as at 3 months follow up. However, there was no association found between persistent QTc prolongation at 48 hours and admission NIHSS score. Similarly, significant association was seen between prolonged QTc at 48 hours and the functional disability. The majority of patients with persistent QTc prolongation at 48 hours had a mRS score of 4 or more at discharge as well as at 3 months, however no such association was seen with mRS score at admission. Also those with persistent QTc prolongation at 48 hours was found to be associated with a poorer recovery as evidenced by lack of improvement in the mRS score at discharge. This was similar to the study by Hromádka et al, in which the baseline QTc was not associated with neurological

outcome. However, the prolonged QTc after 48 hours was found to be associated with worse mRS at discharge. The patients who deceased during hospitalization as compared with survivors had more frequently prolonged QTc after 48 hours(64).

STRENGTH OF OUR STUDY

- We had conducted a prospective study and followed up our patients for 3 months as well as obtained their ECG at 3-time frames, ie. at admission, 48hours post admission and on 3 month follow up
- We had excluded the patients with concomitant cardiac comorbidities, those taking medications known to cause QTc prolongation as well as patients with electrolyte imbalance.
- 50% of the study population had undergone Holter study, which ruled out the presence of any cardiac arrhythmias.

LIMITATIONS OF OUR STUDY

- This study is limited by the small number of patients
- We do not have a pre-stroke ECG for comparison
- As the consecutive AIS patients from a single institution were enrolled, the results may be limited in their relevance to a larger population as well as produce a susceptibility to selection bias
- The disproportionate age and sex distribution observed in our patients may have affected the QTc interval as well as the clinical characteristics in patients with stroke
- Lastly, as in other epidemiologic studies, residual confounding remains a possibility, although we adjusted for several factors which may affect the QTc interval.

CONCLUSION

7. CONCLUSION

- The QTc interval in an acute ischemic stroke patient is a dynamic parameter.
- We have found significant high incidence of QTc prolongation in patients being admitted with acute ischemic stroke, which was maximum at the time of admission.
- We observed the predictive role of prolonged QTc on stroke severity as well as the functional neurological outcome.
- The prolonged QTc at 48 hours was associated with worser neurological outcome at discharge as well as at 3months follow up as compared to the prolonged QTc at admission which found to be associated with stroke severity and worser functional disability at the time of admission.
- Patients who deceased during hospital stay as well as on follow up had persistent QTc prolongation at 48 hours.
- Among the etiology of stroke, a significant association was found between the large artery atherosclerotic disease and prolonged QTc interval suggesting an interplay of the autonomic fluctuations as well as a common pathogenic mechanism.
- The sympathetic over drive related to stroke subtype and stroke severity might have possibly led to corresponding QT interval changes in the ECG.
- Our study has explored the correlation of prolonged QTc with stroke severity and subtype. Thus, shedding light on the patient population who has to be keenly observed for QTc prolongation, which has an implication in selecting medication as well as avoiding electrolyte disturbances in them.
- However, further prospective studies including a larger sample size and longer observation period is warranted to assess for potential therapeutic implications of our findings.

REFERENCES

8. REFERENCES

1. Cushing H. The blood-pressure reaction of acute cerebral compression, illustrated by cases of intracranial hemorrhage: a sequel to the Mutter lecture for 1901. Place of publication not identified: publisher not identified; 1903. 27 p.
2. Manea MM, Comsa M, Minca A, Dragos D, Popa C. Brain-heart axis--Review Article. J Med Life. 2015;8(3):266–71.
3. Togha M, Sharifpour A, Ashraf H, Moghadam M, Sahraian MA. Electrocardiographic abnormalities in acute cerebrovascular events in patients with/without cardiovascular disease. Ann Indian Acad Neurol. 2013;16(1):66–71.
4. Goldstein DS. The electrocardiogram in stroke: relationship to pathophysiological type and comparison with prior tracings. Stroke. 1979;10(3):253–9.
5. Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllylä VV. Circadian rhythm of heart rate variability is reversibly abolished in ischemic stroke. Stroke. 1997 Nov;28(11):2150–4.
6. Ruthirago D, Julayanont P, Tantrachoti P, Kim J, Nugent K. Cardiac Arrhythmias and Abnormal Electrocardiograms After Acute Stroke. The American Journal of the Medical Sciences. 2016 Jan 1;351(1):112–8.
7. Wira CR, Rivers E, Martinez-Capolino C, Silver B, Iyer G, Sherwin R, et al. Cardiac complications in acute ischemic stroke. West J Emerg Med. 2011 Nov;12(4):414–20.
8. M B. Electrocardiographic findings and prognosis in ischemic stroke. Neurology India. 2003 Oct 1;51(4):500.
9. Ramani A, Shetty U, Kundaje GN. Electrocardiographic abnormalities in cerebrovascular accidents. Angiology. 1990 Sep;41(9 Pt 1):681–6.
10. Sander D, Klingelhöfer J. Stroke-Associated Pathological Sympathetic Activation Related to Size of Infarction and Extent of Insular Damage. CED. 1995;5(6):381–5.
11. Barron SA, Rogovski Z, Hemli J. Autonomic consequences of cerebral hemisphere infarction. Stroke. 1994 Jan;25(1):113–6.
12. Sander D, Klingelhöfer J. Changes of circadian blood pressure patterns and cardiovascular parameters indicate lateralization of sympathetic activation following hemispheric brain infarction. J Neurol. 1995 May;242(5):313–8.

13. Adams HP, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology. 1999 Jul 13;53(1):126–31.
14. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988 May;19(5):604–7.
15. Magnano AR, Holleran S, Ramakrishnan R, Reiffel JA, Bloomfield DM. Autonomic nervous system influences on qt interval in normal subjects. Journal of the American College of Cardiology. 2002 Jun 5;39(11):1820–6.
16. Stead LG, Gilmore RM, Bellolio MF, Vaidyanathan L, Weaver AL, Decker WW, et al. Prolonged QTc as a Predictor of Mortality in Acute Ischemic Stroke. Journal of Stroke and Cerebrovascular Diseases. 2009 Nov 1;18(6):469–74.
17. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993 Jan;24(1):35–41.
18. Byer E, Ashman R, Toth LA. Electrocardiograms with large, upright T waves and long Q-T intervals. Am Heart J. 1947 Jun;33(6):796–806.
19. Burch GE, Meyers R, Abildskov JA. A new electrocardiographic pattern observed in cerebrovascular accidents. Circulation. 1954 May;9(5):719–23.
20. Cheung RTF, Hachinski V. Cardiac Effects of Stroke. Curr Treat Options Cardiovasc Med. 2004 Jun;6(3):199–207.
21. Ma S. Cardiopulmonary aspects of acute neurologic diseases. Neurologic intensive care. 1993;103–19.
22. Yamour BJ, Sridharan MR, Rice JF, Flowers NC. Electrocardiographic changes in cerebrovascular hemorrhage. Am Heart J. 1980 Mar;99(3):294–300.
23. Lavy S, Yaar I, Melamed E, Stern S. The Effect of Acute Stroke on Cardiac Functions as Observed in an Intensive Stroke Care Unit. Stroke. 1974 Nov;5(6):775–80.
24. Valeriano J, Elson J. Electrocardiographic changes in central nervous system disease. Neurol Clin. 1993 May;11(2):257–72.
25. Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a

scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009 Mar 17;53(11):982–91.

26. Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, et al. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society Scientific Statement on Noninvasive Risk Stratification Techniques for Identifying Patients at Risk for Sudden Cardiac Death. A scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. J Am Coll Cardiol. 2008 Sep 30;52(14):1179–99.
27. C BH. An analysis of the time-relations of electrocardiograms. Heart. 1920;7:353–70.
28. Ward DE. Prolongation of the QT interval as an indicator of risk of a cardiac event. Eur Heart J. 1988 May;9 Suppl G:139–44.
29. Sultan HI. The relationship between prolonged QT interval and acute stroke in Tikrit teaching hospital. :6.
30. Tatschl C, Stöllberger C, Matz K, Yilmaz N, Eckhardt R, Nowotny M, et al. Insular involvement is associated with QT prolongation: ECG abnormalities in patients with acute stroke. Cerebrovasc Dis. 2006;21(1–2):47–53.
31. Henninger N, Haussen DC, Kakouros N, Selim M, Searls DE, Kumar S, et al. QTc-prolongation in posterior circulation stroke. Neurocrit Care. 2013 Oct 1;19(2):167–75.
32. Jain H, Avasthi R. Correlation between dispersion of repolarization (QT dispersion) and ventricular ectopic beat frequency in patients with acute myocardial infarction: a marker for risk of arrhythmogenesis? Int J Cardiol. 2004 Jan;93(1):69–73.
33. Day CP, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. Br Heart J. 1990 Jun;63(6):342–4.
34. Zabel M, Portnoy S, Franz MR. Electrocardiographic indexes of dispersion of ventricular repolarization: an isolated heart validation study. J Am Coll Cardiol. 1995 Mar 1;25(3):746–52.
35. Mozos I, Hancu M, Jost N, Cristescu A. Multipolar QRST isointegral maps and QT dispersion in old myocardial infarction. Acta Physiol Hung. 2010 Mar;97(1):11–21.

36. Macfarlane PW, McLaughlin SC, Rodger JC. Influence of Lead Selection and Population on Automated Measurement of QT Dispersion. Circulation. 1998 Nov 17;98(20):2160–7.
37. Alabd AA, Fouad A, Abdel-Nasser R, Nammas W. QT interval dispersion pattern in patients with acute ischemic stroke: Does the site of infarction matter? Int J Angiol. 2009;18(4):177–81.
38. Zaputović L, Mavrić Z, Zaninović-Jurjević T, Matana A, Bradić N. Relationship between QT dispersion and the incidence of early ventricular arrhythmias in patients with acute myocardial infarction. Int J Cardiol. 1997 Dec 19;62(3):211–6.
39. Zabel M, Klingenheben T, Franz MR, Hohnloser SH. Assessment of QT Dispersion for Prediction of Mortality or Arrhythmic Events After Myocardial Infarction. Circulation. 1998 Jun 30;97(25):2543–50.
40. Chao CC, Wang TL, Chong CF, Lin YM, Chen CC, Tang GJ, et al. Prognostic value of QT parameters in patients with acute hemorrhagic stroke: a prospective evaluation with respect to mortality and post-hospitalization bed confinement. J Chin Med Assoc. 2009 Mar;72(3):124–32.
41. Huang CH, Chen WJ, Chang WT, Yip PK, Lee YT. QTc dispersion as a prognostic factor in intracerebral hemorrhage. Am J Emerg Med. 2004 May;22(3):141–4.
42. Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT, et al. T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol. 2008;41(6):567–74.
43. Koca H, Koç M. What is the Normal Value of Tpe Interval and Corrected Tpe Interval? Acta Medica. 2020 Dec 31;51:10–5.
44. Bassi A, Colivicchi F, Santini M, Caltagirone C. Cardiac autonomic dysfunction and functional outcome after ischaemic stroke. Eur J Neurol. 2007 Aug;14(8):917–22.
45. Hilz MJ, Schwab S. Stroke-Induced Sudden-Autonomic Death. Stroke. 2008 Sep;39(9):2421–2.
46. Browne KF, Zipes DP, Heger JJ, Prystowsky EN. Influence of the autonomic nervous system on the Q-T interval in man. Am J Cardiol. 1982 Nov;50(5):1099–103.
47. Shimizu W, Tsuchioka Y, Karakawa S, Nagata K, Mukai J, Yamagata T, et al. Differential effect of pharmacological autonomic blockade on some electrophysiological properties of the human ventricle and atrium. Br Heart J. 1994 Jan;71(1):34–7.

48. Sato K, Kato M, Yoshimoto T. QT intervals and QT dispersion in patients with subarachnoid hemorrhage. J Anesth. 2001;15(2):74–7.
49. Randell T, Tanskanen P, Scheinin M, Kyttä J, Ohman J, Lindgren L. QT dispersion after subarachnoid hemorrhage. J Neurosurg Anesthesiol. 1999 Jul;11(3):163–6.
50. Al-Khatib SM, LaPointe NMA, Kramer JM, Califf RM. What Clinicians Should Know About the QT Interval. JAMA. 2003 Apr 23;289(16):2120–7.
51. Ames D, Camm J, Cook P, Falkai P, Gury C, Hurley R, et al. Minimizing the Risks Associated with Significant QTc Prolongation in People with Schizophrenia: A Consensus Statement by The Cardiac Safety in Schizophrenia Group. Australas Psychiatry. 2002 Jun 1;10(2):115–24.
52. Vandael E, Vandenberk B, Vandenberghe J, Willems R, Foulon V. Risk factors for QTc-prolongation: systematic review of the evidence. Int J Clin Pharm. 2017 Feb 1;39(1):16–25.
53. Ritz K, van Buchem MA, Daemen MJ. The heart-brain connection: mechanistic insights and models. Neth Heart J. 2013 Feb;21(2):55–7.
54. van der Wall EE, van Gilst WH. Neurocardiology: close interaction between heart and brain. Neth Heart J. 2013 Feb;21(2):51–2.
55. Ruffinazzi M, Dusi V. Central Nervous System Management of Autonomic Cardiovascular Control. In: Govoni S, Politi P, Vanoli E, editors. Brain and Heart Dynamics [Internet]. Cham: Springer International Publishing; 2020 [cited 2022 Dec 20]. p. 1–27. Available from: https://doi.org/10.1007/978-3-319-90305-7_65-1
56. Ja P, Ee B. Neural control of the heart: recent concepts and clinical correlations. Neurology [Internet]. 2014 Jul 15 [cited 2022 Dec 20];83(3). Available from: https://pubmed.ncbi.nlm.nih.gov/24928126/
57. Orlandi G, Fanucchi S, Strata G, Pataleo L, Landucci Pellegrini L, Prontera C, et al. Transient autonomic nervous system dysfunction during hyperacute stroke. Acta Neurol Scand. 2000 Nov;102(5):317–21.
58. Oppenheimer S. The anatomy and physiology of cortical mechanisms of cardiac control. Stroke. 1993 Dec;24(12 Suppl):I3-5.
59. Strittmatter M, Meyer S, Fischer C, Georg T, Schmitz B. Location-Dependent Patterns in Cardio-Autonomic Dysfunction in Ischaemic Stroke. ENE. 2003;50(1):30–8.

60. Kogan E, Twyman K, Heap J, Milentijevic D, Lin JH, Alberts M. Assessing stroke severity using electronic health record data: a machine learning approach. BMC Med Inform Decis Mak. 2020 Jan 8;20:8.
61. Emektar E, Çorbacıoğlu ŞK, Korucu O, Ramadan S, Uzunosmanoğlu H, Kan E, et al. The evaluation of a new marker of transmyocardial repolarization parameters in ischemic stroke patients; Tpeak–Tend (Tp-e), Tp-e/QTc. Acta Neurol Belg. 2017 Jun 1;117(2):461–7.
62. Ahn SH, Lee JS, Kim YH, Yun MS, Han JH, Kim SY, et al. Prognostic Significance of Prolonged Corrected QT Interval in Acute Ischemic Stroke. Front Neurol. 2021 Dec 20;12:759822.
63. Korkmaz Y, Hayıroğlu Mİ, Selçuk M, Çiçek V, Doğan S, Atmaca MM, et al. Evaluation of cardiac-electrophysiological balance according to National Institutes of Health Stroke Scale score at admission and discharge in acute ischemic stroke patients: A pilot study. Rev Assoc Med Bras (1992). 68(10):1441–6.
64. Hromádka M, Seidlerová J, Rohan V, Baxa J, Šedivý J, Rajdl D, et al. Prolonged Corrected QT Interval as a Predictor of Clinical Outcome in Acute Ischemic Stroke. J Stroke Cerebrovasc Dis. 2016 Dec;25(12):2911–7.
65. Lederman YS, Balucani C, Steinberg LR, Philip C, Lazar JM, Weedon J, et al. Does the Magnitude of the Electrocardiogram QT Interval Dispersion Predict Stroke Outcome? J Stroke Cerebrovasc Dis. 2019 Jan;28(1):44–8.
66. Soliman EZ, Shah AJ, Boerkircher A, Li Y, Rautaharju PM. Inter-relationship between electrocardiographic left ventricular hypertrophy and QT prolongation as predictors of increased risk of mortality in the general population. Circ Arrhythm Electrophysiol. 2014 Jun;7(3):400–6.
67. Strohmer B, Pichler M, Iglseder B, Paulweber B. Relationship of QT interval duration with carotid intima media thickness in a clinically healthy population undergoing cardiovascular risk screening. J Intern Med. 2005 Mar;257(3):238–46.
68. Ludwig M, von Petzinger-Kruthoff A, von Buquoy M, Stumpe KO. [Intima media thickness of the carotid arteries: early pointer to arteriosclerosis and therapeutic endpoint]. Ultraschall Med. 2003 Jun;24(3):162–74.

69. Festa A, D'Agostino R, Rautaharju P, O'Leary DH, Rewers M, Mykkänen L, et al. Is QT Interval a Marker of Subclinical Atherosclerosis in Nondiabetic Subjects? Stroke. 1999 Aug;30(8):1566–71.
70. Baumert M, Lambert GW, Dawood T, Lambert EA, Esler MD, McGrane M, et al. QT interval variability and cardiac norepinephrine spillover in patients with depression and panic disorder. Am J Physiol Heart Circ Physiol. 2008 Sep;295(3):H962–8.
71. Bauch HJ, Grünwald J, Vischer P, Gerlach U, Hauss WH. A possible role of catecholamines in atherogenesis and subsequent complications of atherosclerosis. Exp Pathol. 1987;31(4):193–204.
72. Beinart R, Zhang Y, Lima JAC, Bluemke DA, Soliman EZ, Heckbert SR, et al. The QT interval is associated with incident cardiovascular events: the MESA study. J Am Coll Cardiol. 2014 Nov 18;64(20):2111–9.
73. Kopelnik A, Zaroff JG. Neurocardiogenic Injury in Neurovascular Disorders. Critical Care Clinics. 2006 Oct 1;22(4):733–52.
74. Zaroff JG, Rordorf GA, Newell JB, Ogilvy CS, Levinson JR. Cardiac outcome in patients with subarachnoid hemorrhage and electrocardiographic abnormalities. Neurosurgery. 1999 Jan;44(1):34–9; discussion 39-40.
75. Kawasaki T, Azuma A, Sawada T, Sugihara H, Kuribayashi T, Satoh M, et al. Electrocardiographic score as a predictor of mortality after subarachnoid hemorrhage. Circ J. 2002 Jun;66(6):567–70.
76. Ishikawa J, Ishikawa S, Kario K. Prolonged Corrected QT Interval Is Predictive of Future Stroke Events Even in Subjects Without ECG-Diagnosed Left Ventricular Hypertrophy. Hypertension. 2015 Mar;65(3):554–60.
77. Verheugt FWA. Antithrombotic therapy in heart failure. Neth Heart J. 2012 Apr;20(4):176–8.
78. van der Wall EE. New insights in prevention, diagnosis and treatment of stroke: its relation with atrial fibrillation. Neth Heart J. 2012 Apr;20(4):141–2.
79. Smit MD, Van Gelder IC. Risk-benefit ratio assessment for stroke prevention in intermediate risk atrial fibrillation patients: will TEE-based aspirin treatment fill the gap? Neth Heart J. 2011 May;19(5):212–3.

80. Dinh T, Baur LHB, Pisters R, Kamp O, Verheugt FWA, Smeets JLRM, et al. Feasibility of TEE-guided stroke risk assessment in atrial fibrillation-background, aims, design and baseline data of the TIARA pilot study. Neth Heart J. 2011 May;19(5):214–22.
81. Goette A, Braun-Dullaeus RC. Atrial fibrillation is associated with impaired cognitive function and hippocampal atrophy: silent cerebral ischaemia vs. Alzheimer's disease? European Heart Journal. 2008 Sep 1;29(17):2067–9.
82. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018 Oct 30;72(18):2231–64.
83. Abildskov JA. Adrenergic effects of the QT interval of the electrocardiogram. Am Heart J. 1976 Aug;92(2):210–6.
84. Dütsch M, Burger M, Dörfler C, Schwab S, Hilz MJ. Cardiovascular autonomic function in poststroke patients. Neurology. 2007 Dec 11;69(24):2249–55.
85. Soliman EZ, Howard G, Cushman M, Kissela B, Kleindorfer D, Le A, et al. Prolongation of QTc interval and risk of stroke: the REasons for Geographic and Racial Differences in Stroke (REGARDS). J Am Coll Cardiol. 2012 Apr 17;59(16):1460–7.
86. Sare GM, Geeganage C, Bath PMW. High blood pressure in acute ischaemic stroke--broadening therapeutic horizons. Cerebrovasc Dis. 2009;27 Suppl 1:156–61.
87. Semplicini A, Calò L. Administering antihypertensive drugs after acute ischemic stroke: timing is everything. CMAJ. 2005 Mar 1;172(5):625–6.
88. Afsar N, Fak AS, Metzger JT, Van Melle G, Kappenberger L, Bogousslavsky J. Acute Stroke Increases QT Dispersion in Patients Without Known Cardiac Diseases. Archives of Neurology. 2003 Mar 1;60(3):346–50.
89. Rudehill A, Olsson GL, Sundqvist K, Gordon E. ECG abnormalities in patients with subarachnoid haemorrhage and intracranial tumours. J Neurol Neurosurg Psychiatry. 1987 Oct;50(10):1375–81.
90. Banerjee TK, Das SK. Fifty years of stroke researches in India. Ann Indian Acad Neurol. 2016;19(1):1–8.
91. Rautaharju PM, Mason JW, Akiyama T. New age- and sex-specific criteria for QT prolongation based on rate correction formulas that minimize bias at the upper normal limits. International Journal of Cardiology. 2014 Jul 1;174(3):535–40.

92. Vink AS, Clur SAB, Wilde AAM, Blom NA. Effect of age and gender on the QTc-interval in healthy individuals and patients with long-QT syndrome. Trends in Cardiovascular Medicine. 2018 Jan 1;28(1):64–75.
93. Fauchier L, Maison-Blanche P, Forhan A, d'Hour A, Lépinay P, Tichet J, et al. Association between heart rate–corrected QT interval and coronary risk factors in 2,894 healthy subjects (the DESIR study). American Journal of Cardiology. 2000 Sep;86(5):557–9.
94. Oppenheimer S. Cerebrogenic cardiac arrhythmias: Clin Auton Res. 2006 Feb 1;16(1):6–11.
95. Pazo JH, Belforte JE. Basal Ganglia and Functions of the Autonomic Nervous System. Cell Mol Neurobiol. 2002 Dec 1;22(5):645–54.
96. Simula S, Muuronen AT, Taina M, Jäkälä P, Sipola P, Vanninen R, et al. Effect of middle cerebral artery territory ischemic stroke on QT interval. J Stroke Cerebrovasc Dis. 2014 Apr;23(4):717–23.
97. Kaul S, Sunitha P, Alladi S, Kannan M, Uma M, Reddy J. Subtypes of Ischemic Stroke in a Metropolitan City of South India (One year data from a hospital based stroke registry). Neurology India. 2003 Jan 1;50 Suppl:S8–14.
98. Yin J, Wang W, Wang Y, Li G, Kong Y, Li X, et al. Case Report: Stroke Chameleon: Acute Large Vessel Occlusion in the Posterior Circulation With Paroxysmal Sympathetic Hyperactivity as the First Manifestation. Frontiers in Neuroscience. 2022 [cited 2022 Dec 28];16.
99. Lazar J, Busch D, Wirkowski E, Clark LT, Salciccioli L. Changes in QT dispersion after thrombolysis for stroke. Int J Cardiol. 2008 Apr 10;125(2):258–62.

ANNEXURES

9. ANNEXURES

a. PROFORMA

Baseline data

1.	Serial no	
2.	Age	
3.	Gender	
4.	Date of admission	
5.	Time between first symptom and admission	
6.	Wake up stroke If yes, Time between last seen normal and admission	
7.	Admission NIHSS	
8.	Admission mRS	
9.	Diabetes Mellitus	
10	Hypertension If yes-medications Betablockers CCB Alpha blockers ACE-I ARB Diuretics More than one	
11	Dyslipidemia	
12	Smoking	Current/ex->3 months/never
13	Alcohol	
14	Prior Stroke	
15	Prior TIA	
16	POVD	
17	Admission blood sugar	
18	Admission systolic BP	
19	Admission diastolic BP	
20	Admission body temperature	
21	Fasting Cholesterol	
22	HDL	
23	LDL	
24	TGL	

Imaging data

1	Type of imaging	CT/MRI
2	Hemisphere involved: Right/left/ bilateral/vertebrobasilar	
3	MCA infarct: Right/left/not MCA infarct	
4	Infarct pattern Single versus multiple arterial territories Territorial Main artery/Branch occlusion Superficial watershed Internal borderzone Lacunar Multiple embolic	Y/N
5	Area involved Cortical Subcortical Brainstem Cerebellum Mention the exact location: Lobar /Insular involvement/ basal ganglia and thalamus/ Multiple lacunar infarcts / Periventricular area/ Brainstem / cerebellum	
6	chronic infarcts territorial lacunar both	
7	WMHI Fazekas grade 0/1/2/3	

ECG

		Admission	48hours Post admission
1	Time between ECG and stroke onset		
2	QT interval in seconds		
3	RR interval in seconds		
4	longest QT interval (QTmax) in seconds		
5	shortest QT interval (QTmin) in seconds		
6	T wave peak to T wave end (Tpe) in milliseconds		
7	U wave		
8	LVH –voltage criteria		
9	Ischemia like changes ST segment changes T wave abnormalities		
10	Any other changes if present, mention		

Other Cardiac investigations

1	Echo, if done mention findings LV end systolic dimension LV end diastolic dimension RWMA EF Mitral regurgitation (grade 0-1) RV systolic pressure Any clot Vegetation Any structural heart disease	Y/N
2	24-hour Holter, if done mention the findings Ventricular ectopics % Supraventricular ectopics % AF% Any AV block (yes/no), if yes then type QRS duration (mean) Average HR (heart rate) Maximum HR Minimum HR	Y/ N

Treatment

1	Intravenous thrombolysis	
2	Mechanical thrombectomy	
3	Combination (bridging thrombectomy)	
4	Conservative	
5	Any of the following medications given during hospital stay Beta blockers Calcium channel blockers ACEI Macrolide antibiotics Digoxin Ionotropes	
6	Discharge diagnosis-TOAST 1.LAA 2.Cardioembolic 3.lacunar 4.other determined causes-specify 5. undetermined etiology	
7	NIHSS at discharge	
8	mRS at discharge	

At 3 months follow up

1	NIHSS	
2	mRS	

	ECG	3 months
1.	QT interval in seconds	
2.	RR interval in seconds	
3.	longest QT interval (QTmax) in seconds	
4.	shortest QT interval (QTmin) in seconds	
5.	T wave peak to T wave end (Tpe) in milliseconds	
6.	U wave	
7.	LVH –voltage criteria	
8.	Ischemia like changes ST segment changes T wave abnormalities	
9.	Any other changes if present, mention	

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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1567/OCTOBER-2020 30.11.2020

Dr. Nandana J
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Nandana,

Thank you for submitting documents related to your proposal titled "**QT INTERVAL ABNORMALITIES IN ACUTE ISCHEMIC STROKE AND ITS CORRELATION WITH STROKE SEVERITY AND SUBTYPE** (IEC/1567)" to the IEC for review.

The following documents were reviewed:

Original submission

1. *Checklist*
2. *Thesis proposal*
3. *IEC application form with signed declaration by investigators dated 04/05/2020*
4. *Forwarding letter from HOD, Dr.Sanjeev Thomas dated 12/08/2020*
5. *Covering letter to the Chairman by Dr.Sajith S dated nil*
6. *Proforma*
7. *TAC clearance certification dated 07/07/2020*
8. *Patient information sheet in English*
9. *Patient information sheet in Malayalam*
10. *Informed consent form with declaration by PI in English*
11. *Informed consent form with declaration by PI in Malayalam*
12. *Signed CV of PI Dr.Nandana J with TCMC number*
13. *Signed CV of Co-PI Dr.Sajith Sukumaran with TCMC number*
14. *Signed CV of Co-PI Dr.Arun Gopalakrishnan with TCMC number*
15. *Covering letter addressed to the chairman dated 12/08/2020*

Revised submission on 18/11/2020

1. *Revised checklist*
2. *Revised project proposal*
3. *IEC application form with signed declaration dated 04/05/2020*
4. *Covering letter to IEC chairperson endorsing the submission by HOD Dr.Sanjeev Thomas dated 12/08/2020*
5. *Covering letter to the Chairperson endorsing the submission by Dr.Sajith Sukumaran dated 15/11/2020*
6. *Proforma*
7. *TAC clearance certification dated 07/07/2020*
8. *Revised patient information sheet in English*
9. *Revised patient information sheet in Malayalam*
10. *Revised consent form in English*
11. *Revised consent form in Malayalam*
12. *Declaration by PI in English*
13. *Unclear document in machine language (possibly the Malayalam declaraion by PI)*
14. *Signed CV of PI Dr.Nandana J with TCMC number*
15. *Signed CV of Co-PI Dr.Sajith Sukumaran with TCMC number*
16. *Signed CV of Co-PI Dr.Arun Gopalakrishnan with TCMC number*
17. *Covering letter addressed to Chairman IEC dated 15/11/2020*

The following members of the Students Sub-Committee of the Institutional Ethics Committee participated in the discussions held between August 23-October 29, 2020 at the offices and residences of the members

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
5.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

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Originality Assessment

Overall Similarity: **7%**

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