

**Research Article**

## Association of prolonged QTc interval with severity of liver cirrhosis

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### ABSTRACT

**Objectives:** To detect the association of prolonged QTc interval with severity of liver cirrhosis

**Materials & Methods:** This case series study was conducted at Department of Medicine, Abbas Institute of Medical Sciences, Muzaffarabad Azad Kashmir from March 2017 to September 2017. Total 97 patients of liver cirrhosis were selected for this study. Association

**Results:** Mean age of patients was  $47.55 \pm 10.88$  years. Total 53 (54.6%) patients were male and 44 (45.4%) patients were females. Mean duration of disease was  $1.799 \pm 2.131$  years. Majority of patients i.e. 67.01% were presented with moderate disease according to MELD score. Results had shown prolonged QTc interval ( $>450$  msec) in 54.64% while 45.36% patients had shown no QTc interval prolongation. Severity of liver cirrhosis was significantly associated (P value  $< 0.001$ ) with prolonged QTc interval.

**Conclusion:** Frequency of prolonged QTc interval in liver cirrhosis patients was relatively high (54.6%) and significantly associated with severity of the disease.

**Keywords:** chronic liver disease, cirrhotic cardiomyopathy, MELD score, encephalopathy.

### INTRODUCTION

Cirrhosis represents the final common histologic pathway for a wide variety of chronic liver diseases. The term cirrhosis was first introduced by Laennec in 1826. It is derived from the Greek term scirrhus and refers to the orange or tawny surface of the liver seen at autopsy.<sup>1</sup> Cirrhosis is defined histologically as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. The progression of liver injury to cirrhosis may occur over weeks to years. Indeed, patients with hepatitis C may have chronic hepatitis for as long as 40 years before progressing to cirrhosis.<sup>2</sup> Many complications can occur as a result of

cirrhosis, out of which ascites, portal hypertension and varices are well-known.<sup>1</sup> The effects of cirrhosis on cardiovascular and circulatory system are not well studied.<sup>3</sup> Historically, liver cirrhosis has not been associated with any cardiac abnormalities, despite the fact that a hyperdynamic circulation has been described in patients with cirrhosis more than 50 years ago.<sup>4</sup> The use of new investigative modalities has shown several lines of evidence of impaired cardiac contractility and performance in patients with cirrhosis and has led to the introduction of the new clinical entity 'cirrhotic cardiomyopathy'.<sup>5-6</sup> It includes hypertrophy of the myocardium, leading to a stiffer ventricle

and hence diastolic dysfunction and normal systolic function at rest but systolic incompetence under conditions of stress.<sup>6-7</sup> The electrocardiographic QT interval reflects ventricular repolarization. Its prolongation provides substrate for ventricular arrhythmias. QT interval prolongation is one of the electrophysiological indicators of cirrhotic cardiomyopathy.<sup>8</sup> It is hypothesized that this abnormality occurs due to cardiotoxins reaching the heart due to portosystemic shunting.<sup>9</sup> QT interval is affected by heart rate, so the disease specific formula was used for QT correction. This is known as QT cirrhosis formula.<sup>8</sup>

#### OPERATIONAL DEFINITIONS:

- **Liver Cirrhosis:** Diagnosis of cirrhosis was made on the basis of presence of any three of these physical findings i.e.
  - **Palmar erythema:** reddening of the palms at the thenar and hypothenar eminences was considered as positive.
  - **Spider nevi:** central red spot and reddish extensions which radiate outwards like a spider's web beneath skin surface was deemed as positive.
  - **Splenomegaly:** palpable, enlarged spleen with > 11 cm in its largest dimension was considered positive.
  - **Ascites:** presence of fluid in peritoneal cavity on ultrasonography and on examination presence of shifting dullness and fluid thrill was considered as positive.
  - **Deranged clotting profile:** i.e. PT > 13 sec, INR > 1.2.
  - **Low serum albumin** i.e. <3.4g/dl.
  - **Abdominal ultrasound:** coarse echotexture and irregular borders of liver.
- **Prolonged QTc Interval:** It is the time elapsing from the beginning of the QRS complex to the end of the T wave in an electrocardiogram and was calculated by following formula;  $QTc = QT \times RR^{-1/3}$ .

It was considered as prolonged when its value

was > 450 msec.

- **Severity of Liver cirrhosis:** Severity of liver cirrhosis was assessed by using the Model for End-Stage Liver Disease (MELD) scoring system. MELD uses the patient's values for S/Bilirubin, S/Creatinine, and the international normalized ratio for prothrombin time (INR). It was calculated by following formula:

$$MELD = 3.78[\text{serum bilirubin (mg/dL)}] + 11.2[\text{INR}] + 9.57[\text{serum creatinine (mg/dL)}] + 6.43.$$

- **Moderate disease:** MELD score = 11-19.
- **Severe disease:** MELD score > 19.

#### Materials and methods:

This case series study was conducted at Department of Medicine, Abbas Institute of Medical Sciences, Muzaffarabad Azad Kashmir from March 2017 to September 2017. Total 97 patients with liver cirrhosis with age 20-60 years either male or female were selected. Patients having any other cause of prolonged QT interval including diabetes mellitus, electrolyte imbalance like hyperkalemia and anti-arrhythmic drugs, patients having valvular heart disease and ischemic heart disease, patients with congenital prolonged QT interval, patients having history of alcoholism and patients taking loop diuretics for last one week were excluded from the study.

Baseline laboratory investigations i.e. complete blood count, prothrombin time with international normalized ratio (INR), liver function tests, serum creatinine, blood urea, serum sodium, potassium, calcium and phosphate levels were done in every patient. Anti HCV and HBsAg status of all patients were checked to determine whether the etiology was viral or otherwise. Ultrasound imaging for hepatobiliary system was carried out. After this, a twelve lead ECG was carried out in all patients and QT interval was calculated manually. QT interval was calculated from start of Q wave till the end of

T wave. All values were corrected by using disease specific formula (QT cirrhosis) i.e.  $QTc = QT \times RR^{-1/3.02}$ . Prolonged QT interval was defined as value  $> 450$  msec (0.45 sec). Collected data was analyzed through computer software SPSS 16.0. Mean and standard deviation was calculated for quantitative variables i.e. age and duration of disease. Frequency and percentage was calculated for qualitative variables i.e. gender, etiology of disease (viral/non-viral), severity of liver cirrhosis (moderate to severe) and prolonged QTc interval (yes/no). Effect modifiers like age, gender, duration of disease, etiology of disease (viral/non-viral) and severity of disease were controlled through stratification. Post-stratification chi square was applied and p value  $\leq$  was considered as significant.

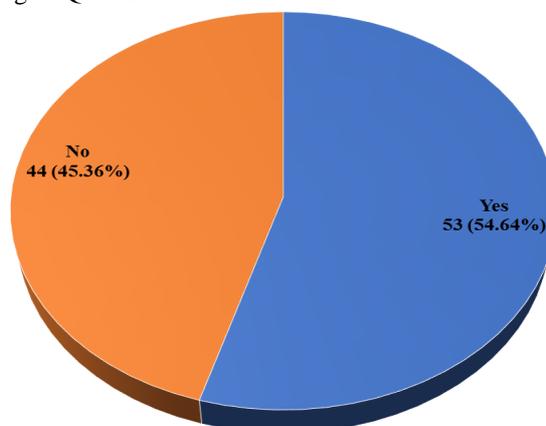
### RESULTS

Age range in this study was from 20 to 60 years with mean age of  $47.55 \pm 10.88$  years. All the selected patients were then undergone ECG for QTc interval measurement and results had shown prolonged QTc interval ( $>450$  msec) in 53 (54.64%) while 44 (45.36%) patients had shown normal QTc interval as shown in Figure I. Mean QTc interval was  $476.34 \pm 52.37$  msec.

Out of 53 male patients, Prolonged QTc Interval was noted in 28 (52.83%) patients and among the 44 female patients, Prolonged QTc Interval was noted in 25 (56.82%)

patients. Insignificant association between Prolonged QTc Interval and gender was noted with p value 0.694. (Table 1) Patients were divided into 4 age groups i.e. age group 20-30 years, age group 31-40 years, age group 41-50 years and age group 51-60 years. Total 10 patients belonged to age group 20-30 years followed by 20 patients to age group 31-40 years, 30 patients to 41-50 years and 37 patients belonged to 51-60 years and Prolonged QTc Interval was noted in 04 (40.0%), 10 (50.0%), 20 (66.67%) and 19 (51.35%) respectively in all age groups. But insignificant association between age group and Prolonged QTc Interval was noted with p value 0.399. (Table 2) Total 44 patients were found with  $>6$  months - 1 year duration of disease and Prolonged QTc Interval was noted in 16 (36.36%). Total 53 patients were found with  $>1$  year duration of disease and Prolonged QTc Interval was noted in 16 (30.19%). Insignificant ( $P = 0.520$ ) association of duration of disease with Prolonged QTc Interval was noted. (Table 3) Total 65 patients were found with moderate cirrhosis and Prolonged QTc Interval was noted in 25 (38.46%) patients. Among 32 patients with severe cirrhosis, Prolonged QTc Interval was noted in 28 (87.5%) patients. Statistically significant ( $P = 0.001$ ) association between Prolonged QTc Interval and severity of cirrhosis was noted. (Table 4)

**Figure 1:** Frequency of prolonged QTc interval



**Table 1:** Stratification for gender

Gender	Frequency	Prolonged QTc Interval		P-value
		Yes	No	
Male	53	28 (52.83%)	25 (47.17%)	<b>0.694</b>
Female	44	25 (56.82%)	19 (43.18%)	

**Table 2:** Stratification for age

Age	Frequency	Prolonged QTc interval		P-value
		Yes	No	
20-30 years	10	04 (40.0%)	06 (60.0%)	<b>0.399</b>
31-40 years	20	10 (50.0%)	10 (50.0%)	
41-50 years	30	20 (66.67%)	10 (33.33%)	
51-60 years	37	19 (51.35%)	18 (48.65%)	

**Table 3:** Stratification for duration of disease

Duration of disease	Frequency	Prolonged QTc interval		P-value
		Yes	No	
>6 months - 1 year	44	16 (36.36%)	28 (63.64%)	<b>0.520</b>
>1 year	53	16 (30.19%)	37 (69.81%)	

**Table 4:** Stratification for severity of cirrhosis

Severity	Frequency	Prolonged QTc interval		P-value
		Yes	No	
Moderate	65	25 (38.46%)	40 (61.54%)	<b>&lt;0.001</b>
Severe	32	28 (87.5%)	04 (12.5%)	

**DISCUSSION**

The purpose of this study was to determine the frequency of prolonged QTc interval in liver cirrhosis patients with moderate to severe disease. The mean age of patients in our study was 47.55 ± 10.88years which was very much larger than study of Zuberi BF et al<sup>10</sup> who had a mean age of 35 years. On the other hand, TariqueS et al<sup>11</sup> and Nasr GMA et al<sup>7</sup> had found mean age of 53 and 50 years in their studies respectively which is much larger compared to our study. In this study, 54.6% were male and 45.4% were females with male to female ratio of 1.2:1. Many previous studies have also found higher incidence of type II diabetes in male than female patients.<sup>12-13</sup>

In our study, most of the patients with liver cirrhosis had non-viral cause i.e. 52.6% and 47.4% had viral (hepatitis B or C) cause. But Firmansyah I et al<sup>12</sup> and Puthumana L et al<sup>14</sup>

had found the viral etiology as the common cause of liver cirrhosis in their studies. Majority of patients 67.01% were presented with moderate disease according to MELD score in our study. The same findings were also observed by TariqueS et al<sup>13</sup> and Firmansyah I et al<sup>12</sup> in their studies.

This study has shown prolonged QTc interval (>450 msec) in 54.64% while 45.36% patients had shown normal QTc interval which is very much comparable to the results observed by Bal JS et al.<sup>15</sup> In a study by Nasr GMA et al<sup>7</sup> had found the prevalence of prolonged QTc interval as 45% in liver cirrhosis patients which is a little lower than our study but Zuberi BF et al<sup>16</sup> had found much lower prevalence i.e. 19%, compared to our study.

On the other hand, some previous trials had found much higher prevalence of prolonged QTc interval in liver cirrhosis patients if compared with our study. The prevalence of

prolonged QTc interval in patients with liver cirrhosis was 67.9% in the study of Firmansyah I et al.<sup>12</sup>

The specific mechanisms responsible for QT prolongation in cirrhotics are controversial. Bernardi et al. reported a direct correlation between the QTc and plasma noradrenalin levels. This shows that enhanced adrenergic stimulation of myocardial cells plays a role in pathologic electrophysiology defined as a prolonged QTc.<sup>17</sup>

A study by Cazzaniga et al<sup>5</sup> showed direct relationship between MELD score and diastolic dysfunction in patients undergoing TIPS. Diastolic dysfunction is manifestation of cirrhotic cardiomyopathy, as is QTc prolongation. Genovesi et al<sup>9</sup> have established significant correlation of increased hepatic venous pressure gradient and prolonged QT interval. These studies provide evidence that cardiac dysfunction in cirrhosis and portal pressure changes can be correlated.

On the whole, it was concluded that frequency of prolonged QTc interval in liver cirrhosis patients is high with male predominance and directly correlated with disease severity. This may be due to lack of awareness and detailed examination at the time of diagnosis of cirrhosis.

## CONCLUSION

This study concludes that the frequency of prolonged QTc interval in liver cirrhosis patients is relatively high (54.6%) and significantly associated with severity of the disease. To develop a proper strategy to reduce the morbidity and mortality in these patients, it is recommended that the patients should be subjected to careful cardiac assessment prior to any procedure.

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