Prolonged QTc-Interval in Liver Cirrhotic Patient: Prevalence and It's Relationship with Severity of Liver Dysfunction

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ABSTRACT

Background: The aim of the study was to determine the prevalence of prolonged QTc -interval and it's relationship with the severity of liver dysfunction in liver cirrhotic patient in the outpatient clinic of Hepatology, Dr. Cipto Mangunkusumo General National Hospital

Materials and Methods: cross sectional study. Eighty one subjects was recruited and being followed as a consecutive non random sampling. The patient was divided according to the modified Child-Pugh classification and undergo to the ECG examination (with minimal 2 leads have measured QT-interval; one of these is II, aVL, V_2 or V_3 lead).

Result: The prolonged QTc-interval prevalence in liver cirrhotic patient was found in 55 subjects (67,9%) with the mean 448.6 msec (SD = 28,9; 95% CI = 442.2 - 454.8). Using the Forward Stepwise method in multivariate analysis to the independent variables ($p < 0.05$) was found only the modified Child-Pugh classification had strongly correlation with the prolonged QTc-interval (OR = 11.2; 95% CI = 3.57-35.47; $p = 0.000$)

Conclusion: The prolonged QTc-interval prevalence in liver cirrhotic patient is 67.9%. The prolonged QTc-interval were strongly associated with the severity of liver dysfunction.

***Keywords**: The prolonged QTc-interval, liver dysfunction, liver cirrhosis.*

INTRODUCTION

Prolonged QT-interval is frequently correlated with the increased incidence rate of malignant ventricular arrythmia.[1] Tachycardia episodes can improve spontaneously, but repeated attacks frequently occur that can proceed to ventricular fibrillation, syncope and even ends up with sudden death.[1-3]

Camm et al[4] found a significant linear QT-interval in people who were prone to ventricular tachyarrythmia compared with the healthy control group. Left ventricular hypertrophy and congestive heart failure are conditions correlated with the abnormality of ventricular repolarization and each of them runs a high risk for sudden death.[4] Schwartz et al (1975) reported death of 41 deaf and mute students out of 68 (78%) students in Milan that had prolongation of QT-interval, but did not get any treatment.[5] In other trials, Schwartz and Wolf (1978) obtained prolonged of interval QTc in 16 out of

28 (57%) patients that died suddenly among 55 myocard infarct patients.[6] Whereas Laakso et al (1987) reported prolonged of QTc-interval in 14 out of 21 (66.7%) patients with coronary heart disease that died.[2]

The prolongation QT-interval is categorized into the primary and secondary forms. Etiologically, due to a variety of causes, among others: administration of particular medicines, coronary heart disease as well as non-cardiovascular disease including autonomy disfunction.[1,2,4,7] The prolonged of QT-interval is often found to be secondary due to administration of anti-arrhythmic agents to patients with heart disease. Other drugs, metabolic disorders, electrolyte imbalance, as well as other particular diseases can also lead to prolonged of QT-interval and/or induction of *torsade de pointes* (TdP).[1,2,4,7,8]

Bernardi et al[9] found that prolonged of QTc-interval was significant in patients with liver cirrhosis due to a variety of causes correlated with the hyperactivity of sympatoadrenergic; the prevalence was linearly compared with the degree of liver dysfunction.[9] In the 2 - 33 months follow up. Bernardi et al found death in 21 out of 44 (47.7%) patients with liver cirrhosis with prolonged of QTc-interval (mean QTc-interval: 463.9 $\pm$ 7 msec, $p < 0.001$).[9] Day CP et al reported that 14 out of 69 (20.3%) patients with alcoholic cirrhosis died in the 30-48 months follow-up; 6 out of them (42.90%) died suddenly with the mean QTc-interval > 490 msec ($p < 0.02$).[10] Survival of patients with liver cirrhosis that had prolonged of QTc-interval was also lower than that of patients who had normal QTc-interval.[9] However, the mean of survival did not correlate with the degree of liver dysfunction.[9]

Trevisari et al[11] found prolonged of QTc-interval in 22 out of 32 (68.8%) patients with liver cirrhosis that became normal following liver transplantation.[11] Improvement of QTc-interval post transplantation was also found by Mohammed R et al in patients with endstage liver disease with prolonged of QTc-interval and autonomic dysfunction.[12]

Even though the mechanism of QTc-interval prolonged in chronic liver disease has not been able to be explained, improvement of QTc-interval with resolution of liver dysfunction has advocated the explanation that prolonged of QTc-interval is correlated with liver function and the prevalence is linearly compared with the severity of liver dysfunction.[11,12] It is also said that etiology of liver disease does not influence the prevalence of abnormal QT-interval.

Data on the prevalence of QTc-interval prolonged in patients with liver cirrhosis in our hospital have never been reported whereas some literature has shown that mortality of patients with liver cirrhosis with prolonged of QTc-interval is quite high and the mean of survival is low.

METHOD

It was a cross-sectional, observational study conducted from August 2001 to October 2003. The subjects were patients with liver cirrhosis (clinical, laboratory and/or liver USG) at the outpatient clinic of Hepatology, Dr. Cipto Mangunkusumo General National Hospital that were obtained non-randomly and consecutively. They underwent ECG; minimally two leads could be measured to obtain the QT-interval; one of these is II, aVL, V_2, V_3 lead.[13]

The exclusion criteria were: absence of co morbidities: previous history of heart disease, hypertension, diabetes mellitus, hypotiroidism, hypomagnesaemia/hypopotassaemia/hypocalcaemia/ hiponatremia, neurological anomalies or congenital prolonged QT syndrome.[7,8] Alcoholism or drug abuse influences QT-interval and/or loop diuretics and tiazid for the last one week.[9] On the ECG findings, there were traces of brach block, fibrillated atrium, block AV, ventricular extrasystole/supraventricle.[2]

The subjects were then assigned based on the classification modification Child Pugh and each of them underwent measurement of QTc-interval. Measurement of the ECG recorded findings was manually conducted by the investigator and another evaluator by using a digital caliper *(Mitutoyo Digimatic Caliper)* at the accuracy of up to 0.01 mm. In order to determine the point more accurately, a foldable magnifier-No.52,936 was used. The mean value of the measurement results was taken as the outcome of the trial.

All of the outcomes of the QT-interval measurement and RR (mm) were multiplied by 0.04 second. In order to determine the magnitude of interval QTc, all of the outcomes of the multiplication of QT-interval were corrected against the outcome of the multiplication of interval-RR by using the formula Bazett[6,14,15] with the aid of a canon scientific statistical calculator F-720 in milliseconds (msec).

All of the mean QTc-interval findings were then calculated for each trial subject. Prior to the use of the data for statistical analysis, the mean QTc-interval had been concluded prolonged or normal.

Data from the questionnaire and the conclusion of the calculation of each mean QTc-interval were tabulated into the main table by using a computer

program. The data were then processed and analyzed by using SPSS 11.5 for Windows Program. The results of the analysis were considered significant if the $p < 0.05$.

The descriptive data were presented in texts, tables and illustrations for analysis. The outcome of the trial was then presented as the mean score, standard deviation and odds ratio (OR). To find out the trend of correlation between the degrees of lever dysfunction with the prevalence of prolonged QTc-interval in patients with liver cirrhosis, univariate, bivariate and multivariate analysis was performed.

RESULTS

Eighty one subjects at the outpatient clinic of the Hepatological Division, Department of Internal Medicine, Faculty of Medicine University of Indonesia/ Dr. Cipto Mangunkusumo General National Hospital were investigated. The trial subjects were patients with liver cirrhosis whose data were taken from August 2001 until October 2003.

Etiology of liver cirrhosis most encountered was patients with positive anti-HCV virus marker (55.6%). The most frequent liver disorder found was classification-modification *Child-Pugh* B (44.4%) (table 1)

Tabel 1. Characteristic Distribution of Demography and Clinic (n=81)

Characteristic	*Number*	*Percentage*
Gender		
Male	50	61.7
Female	31	38.3
Age Group		
< 50 years	18	22.2
50- 59 years	32	39.5
≥ 60 years	31	38.3
Etiology of Liver Cirrhotic		
Alcohol	8	9.9
HbsAg (+)	38	46.9
Anti-HCV (+)	45	55.6
Child-Pugh Classification		
Degree A	30	37.04
Degree B	36	44.44
Degree C	15	18.52
Portal Hypertension (USG)		
Present	47	58.0
Absent	34	42.0
Ascites		
(++)	4	4.9
(+)	35	43.2
Absent	42	51.9
Ensephalopathy		
Present	13	16.0
Absent	68	84.0

Mean distribution of laboratory test variable scores and confidence interval of all trial subjects is presented in table 2 as follows:

Table 2. Mean of Laboratory Test Variable Scores and Standard Deviation (n=81)

Laboratory Test Variable	Mean	SD	95% CI	
			L	H
Albumin	3.3	0.7	3.1	3.4
Bilirubin	1.8	1.5	1.5	2.1
Prothrombin	15.5	5.1	14.4	16.6
Sodium	139.5	4.0	138.6	140.4
Potassium	4.1	0.5	4.0	4.2
Calcium	9.7	0.4	9.6	9.8
Magnesium	2.4	0.5	2.3	2.5

After calculation was conducted by using the Bazzet pattern, the means were calculated and conclusions were taken. The prevalence of prolonged QTc-interval was obtained to be 55 people (67.9%) whereas the remaining 26 people (32.1%) were within the normal limits (table 3).

Table 3. QTC-Interval in 81 Patient with Liver Cirrhosis

Interval-QTc	Number	Percentage
Prolonged	55	67.9
Normal	26	32.1

The mean QTc-interval in this trial was 448.6 msec cross section: 28.9; 95% CI= 442.2 - 454.8) (table 4).

Tabel 4. Mean Value of QTc-Interval dan SD (n=81)

Variable	n	Mean QTc-Interval	SD	95% CI	
				L	H
Child-Pugh A	30	431.7	30.5	420.8	441.6
Child-Pugh B	36	453.3	22.2	446.0	460.6
Child-Pugh C	15	471.0	20.0	460.9	481.1
Total	81	448.6	28.9	442.2	454.8

Distribution of the prevalence of prolonged QTc-interval was in accordance with: *Child-Pugh* modification (figure 1):
Child-Pugh A: 10 out of 30 people (33.33%)
Child-Pugh B: 30 out of 36 people (83.33%)
Child-Pugh C: 15 (100%) subject had prolonged QTc-interval.

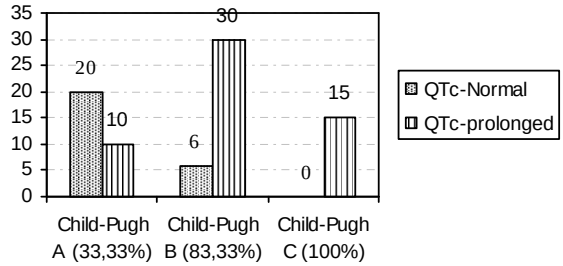

Figure 1. Distribution of Prevalence of Prolonged QTc-interval according to *Child-Pugh* Classification Modification (n=81)

With the confidence interval (CI) = 95%, the prevalence of prolonged QTc-interval in patients with liver cirrhosis in population II was 67.9% + 6.4%

To find out the correlation between the free variable determinant factors with the prevalence of prolonged QTc-interval, bivariate analysis was conducted with student t-test and chi-square test except for the alcohol variable, Fisher was used. Mann Whitney ranking test was used for the bilirubin variable as shown in tables 5 and 6:

Tabel 5. Correlation Between The Free Variable Determinant Factors with The Prevalence of Prolonged QTc-interval (n=81)

Determinan Factor	QTc-Interval		OR	95% CI		*p*
	↑	N		L	H	
Gender						
Male	34	17	1.17	0.44	3.09	0.810
Female	21	9				
Child-Pugh Classification						
Child C	15	0				
Child B	30	6	60.52	9.09	402.8	0.000
Child A	10	20	10.00	2.76	38.39	0.000
Alcohol						
Yes	6	2	1.47	0.28	7.83	1.000
No	49	24				
HbsAg						
Positive	22	16	0.42	0.16	1.09	0.096
Negative	33	10				
Anti HCV						
Positive	34	11	2.21	0.85	5.71	0.158
Negative	21	15				

OR = odds ratio, CI = confidence interval, *p* = significant value, ↑ = prolonged, N = normal, L = lower limit, H = upper limit

Table 6. The Mean Values of Laboratory Variables According to Interval-QTc

Variable	QTc-↑ (n=55)		QTc-Normal (n=26)		*p*
	Mean	SD	Mean	SD	
Age	56.3	11.4	54.9	9.3	0.570
Albumin	3.1	0.7	3.8	0.5	0.000
Bilirubin	2.2	1.6	1.0	0.6	0.000
Prothrombin mass	16.2	5.7	14.2	2.8	0.106
Sodium	138.8	3.5	141.1	4.4	0.013
Potassium	4.1	0.4	4.3	0.5	0.055
Calcium	9.7	0.4	9.7	0.5	0.695
Magnesium	2.5	0.4	2.3	0.6	0.101

The analysis results, ANOVA, toward the mean value of QTc-interval in each classification-modification *Child-Pugh* to find out the trend of correlation between the severity degree of liver dysfunction with the prevalence of prolonged QTc-interval yielded a significant correlation ($p = 0.000$).

To determine which variable that most influenced the prolonged QTc-interval, multivariate analysis was performed against free variables with $p < 0.05$, this context, *Child-Pugh* classification modification, albumin, bilirubin and sodium-level serum. By using forward stepwise method, the most influential *Child-Pugh* classification modification on the prolonged QTc-interval was as follows (table 7):

Table 7. The Results of Analysis of Multivariate Determinant Factors That Correlated with The Prevalence of Prolonged Interval-QTc

Variable	OR	95% CI		*p*
		L	H	
Child-Pugh Classification	11.25	3.57	35.47	0.000

DISCUSSION

In this trial, the prevalence of prolonged QTc-interval in patients with liver cirrhosis was 67.9%. If compared with the results of the trial conducted by Trevisani et al[11] in Italy (1997) that obtained the prevalence of prolonged QTc-interval in liver cirrhotic patients 68.8% with the mean 449 msec (95% CI = 440 - 458), the results of this trial were not much different 67.9% + 6.4% with the mean QTc-interval 448.6 msec (95% CI = 442.2 - 454.8).

The distribution of etiology in this trial was more or less similar to that by Puthumana et al,[16] Bernardi et al,[9] Mohamed R et al[12] and Trevisani et al[11] in which the

number of non-alcoholic cirrhosis was much higher than that of alcoholic cirrhosis so that the results cannot be used to compare the prevalence of prolonged QTc-interval among patients with alcoholic cirrhosis and non-alcoholic cirrhosis. However, this trial supports the results of the previous trials that the etiology of liver cirrhosis is not correlated with the prevalence of prolonged QTc-interval.

This trial also supports the conclusion of the results of a trial conducted by Puthumana et al[16] and Bernardi et al[9] that explains that the degree of liver dysfunction is significantly correlated with the prevalence of prolonged QTc-interval. A variety of conditions could underlie this conclusion in addition to criteria, and the similar methods, mean age, etiologic distribution of liver cirrhosis as well as similar *Child-Pugh* classification modification even though the numbers of samples were different: 130 subjects in Puthumana's trial, 94 and 81 samples in Bernardi's and the investigator's respectively.[9,16] Mohammed R et al[12] found 8 out of 9 liver cirrhotic patients with the degree *Child-Pugh* A, compared just 82% Child-Pugh B and Child Pugh C had prolonged QTc-interval. This difference was probably attributed to the number of samples in Mohamed R's trial, only 53 people.

QTc-interval > 440 msec indicates that the cardiac muscle cells that work in response to electric signals cannot cause normal pulsation anymore,[17] but prolonged QTc-interval is not always correlated with the appearance of clinical symptoms.[7] The mean QTc-interval reported developing to be Torsade de pointes was 470 - 510 msec.[18] Some literature explains that prolonged QTc-interval ≥ 600 msec often triggers Torsades de pointes that can further proceed to be ventricular fibrillation, and even end in sudden death.[18] Based on this, even though the longest QTc-interval in this trial was 517.26 msec with the mean 448.6 msec, the high prevalence of prolonged QTc-interval in some trials was found in patients with liver cirrhosis and there was a bad prognosis for liver cirrhotic patients with prolonged QTc-interval. It is expected that caution should be exercised to do preventive measures such as avoiding drugs that can cause prolonged of QTc-interval and/or trigger Torsade de points. In reality, the tendency of correlation of the severity degree of liver dysfunction with prolonged QTc-interval in this trial revealed significance. The more severe liver dysfunction is, the higher the tendency to trigger cardiac emergency due to such an prolonged QTc-interval.

Besides *Child-Pugh* classification modification other variables such as albumin, bilirubin and sodium serum levels in the bivariate analysis in this trial revealed significant correlation with the prevalence of prolonged QTc-interval. There were similarities with the results of the trial by Bernardi et al[9] in which all of the above variables also showed a significant correlation. In the multivariate analysis, only *Child-Pugh* classification that revealed significant correlation with the prevalence of prolonged QTc-interval. The difference was the nor-epinephrine plasma level was also examined in Bernardi's et al trial that showed significant correlation with the prevalence of prolonged QTc-interval, both in bivariate and multivariate analysis.[9]

Based on the number of ECG lead that was measured, 2 groups of samples were obtained: a group with 2 leads consisted of 36 people (44.44%) collected by the investigator prior to the trial and the other group with 6 leads consisted of 45 people (55.56%). The group with 6 leads had undergone the significance test by using chi-square to compare the validity of measurement between these two groups:

- Ho: there was no significant difference between the measurements of QTc-interval with 2 leads of ECG compared with 6 leads.
- Ha: there was significant difference between the measurements of QTc-interval with 2 leads of ECG compared with 6 leads.

The outcome was $X^2 = 0.25$. If the degree of freedom (df) was 1 and the percentage of error was 5%, the chi-square figure obtained in the table was 3.481, so the results was $0.25 < 3.481$. This means Ho was accepted a Ha was denied with the relative sensitivity 92.31% and relative specificity 89.5%.

QTc-interval is the time required from the beginning of ventricular myocard activity up to the end of repolarization so that the QTc-interval could prolonged due to slowing ventricular activation or elongating repolarization. One of the causes of electrodynamics process at repolarization becoming longer is electrolyte imbalance.[16] The clinical symptoms such as decline in consciousness/disorientation occur in severe hyponatremia (< 120 mEq/L).[19] The change in ECG in hypopotassaemia is characterized by depression of ST segment, decline in wave amplitude T or sometimes by inversion, but it must be accompanied by significant change in QT-interval, except for the potassium concentration < 2.5 mEq/L.[19,20] Hypocalcaemia causes prolonged of phase 2 (plateau phase) that is shown by prolonged of ST segment and interval QT. Anomalities and serious clinical findings will appear at free calcium

concentration < 4.8 mg/dL.[21,22] In many severe cases of high hypomagnesaemia (Mg< 1.0 mg/dl), it is frequently followed with severe high hypocalcaemia.[22] Administration of magnesium can cause shortening of QT-interval, but the explanation for the correlation between hypomagnesaemia with the change of QT-interval has not been elucidated yet.[20]

In this trial, there were seven subjects that had electrolyte disturbance, 3 people each (3.37%) had hyponatremia and mild hypocalcaemia whereas another person had mild hypomagnesaemia, but none had prolonged QTc-interval.

Interobserver errors or discrepancy of the measurement result of QTc-interval by the investigator and other investigator was 3.95%. The error was more or less similar if compared with that by Mohamed R et al[12] 3.17% as well as Bernardi et al[9] 4.4%. This could be attributed to the method used that was more or less similar in each trial. The intraobserver error in this trial was 1.52%.

CONCLUSION

The prevalence of prolonged QTc-interval in patients with liver cirrhosis in our study was 67.9%. There was a tendency of correlation between the severity degree liver cirrhosis and the prevalence of prolonged QTc-interval in patients with liver cirrhosis.

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