Correlation Between Tp-Te Interval With the Degree of Disfunction in Liver Cirrhosis Based on Child Pugh Turcotte Score in Dr. Sardjito General Hospital

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Abstract

Background. Hyperdynamic syndrome due to portal hypertension in cirrhosis of the liver leads to failure of contractions and cardiac structures that result in complications of cardiomyopathy cirrhosis. The incidence of arrhythmias was reported in various non- cardiac diseases including liver cirrhosis. We aim to evaluate the *T peak* wave - *T end (Tp-Te)* as a parameter for suspected arrhythmias that occur in liver cirrhosis.
Aims. To determine the correlation between the *Tp-Te* interval with dysfunction in the degree of liver cirrhosis, which was assessed using the *Child Pugh Turcotte* score.
Methods. This research is a cross-sectional study. Data taken from liver cirrhosis patients who has been met the inclusion and exclusion criteria were admitted to the Inpatient and Outpatient Hospital Dr. Sardjito until May 2020, an assessment of the degree of dysfunction of liver cirrhosis with Child Pugh score Turcotte, and electrocardiographic examination to assess *Tp-Te* wave. The independent variable was the Child Pugh Turcotte score, the dependent variable was the *Tp-Te* wavelength. Analysis of correlation data using the *Spearman test.*
Results. Subjects included 51 patients with liver cirrhosis, correlation analysis found a strong correlation, the higher the *Child Pugh Turcotte* score was linearly correlated with the *Tp-Te* wavelength (r = 0.692; p <0.05). Wavelength *Tp-Te* at Child Pugh to any group showed a significant (p <0.001) , the wavelength of Tp-Te *Child Pugh A* group 67.94 ± 7.80 ms, the *Child Pugh* B group 77.26 ± 8.38 ms, whereas in the *Child Pugh* C group 92.31 ± 11.36 ms.
Conclusion. There was a strong positive correlation between the *Tp-Te* interval with the degree of liver cirrhosis dysfunction which was assessed using the *Child Pugh Turcotte* score.

***Keywords**: Tp-Te, Child Pugh Turcotte, liver cirrhosis*

Abstrak

***Latar Belakang.** Sindrom hiperdinamik akibat hipertensi porta pada sirosis hati menyebabkan kegagalan kontraksi dan struktur jantung yang menimbulkan komplikasi kardiomiopati sirosis. Kejadian aritmia dilaporkan dalam beberapa penyakit nonkardiak termasuk sirosis hati. Kami bertujuan untuk mengevaluasi gelombang T peak - T end (Tp-Te) sebagai parameter dugaan aritmia yang terjadi pada sirosis hati.*
***Tujuan.** Mengetahui hubungan interval Tp-Te dengan disfungsi derajat sirosis hati yang dinilai menggunakan skor Child Pugh Turcotte.*
***Metode.** Penelitian ini merupakan penelitian potong lintang. Data diambil pada sirosis hati yang telah melalui kriteria inklusi dan eksklusi yang dirawat di Instalasi Rawat Inap dan Rawat Jalan RSUP Dr.Sardjito sampai*

dengan Mei 2020, dilakukan penilaian derajat disfungsi sirosis hati dengan skor Child Pugh Turcotte, dan dilakukan pemeriksaan elektrokardiografi untuk menilai gelombang Tp-Te. Variabel bebas adalah skor Child Pugh Turcotte, variabel terikat adalah panjang gelombang Tp-Te. Analisis data korelasi menggunakan Spearman test.
Hasil. *Subjek berjumlah 51 pasien sirosis hati, analisis korelasi didapatkan hubungan yang kuat, semakin tinggi skor Child Pugh Turcotte berhubungan linier dengan semakin panjang gelombang Tp-Te (r = 0,692; p< 0,05). Panjang gelombang Tp-Te pada setiap kelompok Child Pugh didapatkan hasil yang signifikan (p< 0,001), panjagn gelombang Tp-Te kelompok Child Pugh A 67,94 ± 7,80 ms, pada kelompok Child Pugh B 77,26 ± 8,38 ms, sedangkan pada kelompok Child Pugh C 92,31 ± 11,36 ms.*
Kesimpulan: *Terdapat hubungan positif kuat antara interval Tp-Te dengan derajat disfungsi sirosis hati yang dinilai menggunakan skor Child Pugh Turcotte.*

Kata Kunci: *Tp-Te, Child Pugh Turcotte, sirosis hati*

Introduction

Liver cirrhosis was a pathological condition that describes the end-stage progressive liver fibrosis characterized by distortion of the architecture of the liver and the formation of regenerative nodules.[1] In Indonesia, the average prevalence of liver cirrhosis is 3.5% of all patients treated in the Internal Medicine ward or an average of 47.4% of all liver diseases treated.[2] The most common complication of cirrhosis was portal hypertension. More than 95% of cases of portal hypertension were the main cause of intrahepatic disorders with cirrhosis.[3]

Portal hypertension caused hyperdynamic syndrome which is characterized by an increase in heart rate and output as well as a decrease in systemic vascular resistance and arterial blood pressure[4] . This will stimulate baroreceptors and volume receptors, thereby activating the reninangiotensin-aldosterone system (RAA) and the sympathetic nervous system. Activation of these two systems will cause contraction failure and electrophysiological abnormalities of the heart, resulting in cirotic cardiomyopathy.[5]

The prevalence of cirotic cardiomyopathy is reported between 40% to 50% in cirrhosis patients. Previous studies show there was a change picture cardiomyopathy patients' electrocardiogram (ECG) was the change in QRS duration, QT interval (QTc) interval and *Tp-Te.*[6]

Tp-Te is associated with the spread of transmural repolarization and was a predictor of ventricular arrhythmia and sudden cardiac death. Their interval *Tp-Te* elongated and interval ratio *Tp-Te* / QT has been studied in patients with chronic hepatitis B infection, showed an increase in the heterogeneity of ventricular repolarization.[7]

At present new indices such as *Tp-Te* and *Tp-Te* / QT ratios have been suggested as a more accurate measure of the spread of ventricular repolarization compared to QTd and cQTd in ecg waves.[8] Other studies suggest that the *Tp-Te* interval has been shown to be a prognostic marker in subjects with cirrhosis, regardless of the severity of the disease.[9] The purpose of this study was to determine the correlation between the *Tp-Te* interval with the degree of liver cirrhosis dysfunction which was assessed using the *Child Pugh Turcotte* score.

Research Methods

The design of this research was observational design cross section conducted

since January 2019 until May 2020. The data were taken from the primary data and secondary data on liver cirrhosis patients treated in Inpatient and Outpatient Hospital Dr Sardjito.

The inclusion criteria of the subjects of this study were patients diagnosed with liver cirrhosis based on clinical, laboratory, and ultrasound criteria of the liver, adults aged ≥18 years and had signed the research agreement. Exclusion criteria are severe infection or sepsis, hepatocellular carcinoma, liver cirrhosis patients using anti-oxidant drugs, along with other diseases such as diabetes mellitus, chronic kidney failure, valvular heart disease, congenital heart disease, ischemic heart disease, conduction abnormalities, electrolyte imbalances such as hyperkalemia and anti-arrhythmic drugs other than beta blockers such as digoxin, verapamil, diltiazem propafenone, lidocaine and amiodarone, antihistamines, antipsychotics, macrolides and quinolones.

The independent variable in this study was the *child pugh turcotte* score. The dependent variable was the wavelength *Tp-Te.* Subject characteristics include age, sex, and *Child Pugh* scores. Information collected by history, physical examination (encephalopathy and ascites), and laboratory examination; *Prothrombin,* INR , Albumin, Bilirubin and *Tp-Te* ECG overview .

After being approved by the Ethics Committee of the Faculty of Medicine, Public Health and Nursing (FKKMK) UGM and obtained a research permit from the Director of RSUP Dr. Sardjito Yogyakarta, began collecting data from medical records.

The results of the study were tested for normality with the *Kolmogorov Smirnov test* because the study sample was above 50. The basic characteristics displayed descriptively included the percentage, median, or mean according to the results of normality data. The correlation between Tp-Te waves and *Child Pugh Turcotte* scores using the *Spearman* test analysis. Statistically determined with a value of p <0.05 and a 95% confidence interval (IK). *Tp-Te* interval waves and *Child Pugh* scores were performed univariate analysis followed by multivariate analysis with multiple linear regression.

Result and Discussion

Research subjects who met the inclusion and exclusion criteria totaled 51. The general basic characteristics of the study subjects consisted of age, sex, etiology of liver cirrhosis, albumin levels, INR, percentage of ascites, hepatic encephalopathy and degree of liver cirrhosis described in table 4.1. The overall study subjects had an average age of 52.53 ± 11,471 years with the youngest age being 35 years and the oldest age 72 years. Results of age are similar to previous studies conducted in the United States that the average age of research subjects in liver cirrhosis patients is 51.15 years and in Indonesia the average age of research subjects is 51.4 years.[10,] The study subjects consisted of 33 men (64.7%) and 18 women (35.3%), these results are almost similar to the results of research in the United States with more male results than women which is 72% compared 27%.[10] The etiology of liver cirrhosis in the study subjects that was found most due to hepatitis virus were 46 people hepatitis B (90.2%) and hepatitis C as many as 5 people (9.8%) , while other causes were not found in the study subjects. Similar to research conducted in Indonesia, liver cirrhosis was mostly caused by hepatitis B virus in 40-50% of cases and hepatitis C in 30-40%. [1] APRI scores in the study subjects had an

average value of 2.20 ± 1.00 results >> 2 had a specificity of 91% in detecting liver cirrhosis, and a value > 1.5 had a positive predictive value for the diagnosis of liver cirrhosis.[11]

Laboratory profiles on the subjects of this study were generally obtained for an average albumin level of 2.91 ± 0.72 g / dl, mean total bilirubin of 1 , 1 mg / dl with a range of 0.4-19.37 mg / dl , and an average INR level of 1.5 with a range of 1.1 - 5.9 . In the research subjects, there were 29 ascites (56.9%) and encephalopathy as many as 9 people (17.64%).

Table 1. General characteristics of research subjects

Variable	N total 51 (%)	Mean ± SD / Median (min-max)*
Age (years)		52.53 ± 11.471
Gender		
Male	33 (64.7)	
Girl	18 (35.3)	
Etiology		
Hepatitis B	46 (90.2)	
Hepatitis C	5 (9.8)	
Etc	-	
Albumin (g / dL)		2.91 ± 0.72
Bilirubin (mg / dL)		2.55 (0.4 - 19.37)
INR		1.72 (1.05 - 5.9)
Ascites	29 (56.9)	
Encephalopathy	9 (17.6)	
Child Pugh A	16 (31.4)	
Child Pugh B	19 (37.3)	
Child Pugh C	16 (31.4)	
APRI score		2.1961 ± 1.00

Based on analysis of test Spearman showed that a strong correlation between the elongation *Tp-Te* with an increased score *Child Pugh* where the higher the score *Child Pugh* linearly related to the higher value of *Tp-Te* (r = 0.692; p <0.05). Specific research on *Tp-Te* waves in liver cirrhosis was still limited. Several electrophysiological abnormalities have been described in liver cirrhosis, prolongation of QT intervals, increased QT dispersion, cardiac chronotropic incompetence, and electromechanical disturbances, for example a study conducted in Brazil assessed the correlation between *Child Pugh* scores prolongation of the QT interval. From these results it was found that the higher *Child Pugh* score had a linear correlation with the longer QT interval (r = 0.5; p <0.05).[12]

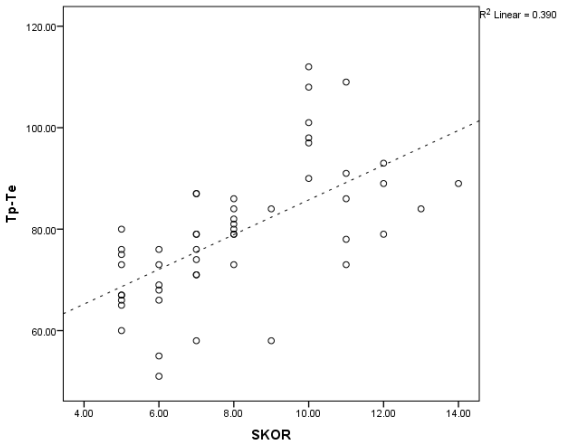

Figure 1. Graph of *Tp-Te* correlation to *Child Pugh Turcotte's* Score level

Tp-Te wave *counts* in the *Child Pugh* A group were obtained 67 , 94 ± 7.80 ms, in the *Child Pugh* B group 77.26 ± 8.38 ms, while in the *Child Pugh* C group 92.31 ± 11.36 ms The results of the analysis the statistics found in the *Child Pugh* C group had the longest *Tp-Te* then followed by *Child Pugh* B and the lowest values were found in the *Child Pugh* A group with a significant difference (p <0.001).

The results of the *Tp-Te* wave analysis on the degree of Child Pugh dysfunction, yielded significant results with a value of p <0.001, continued with the Post Hoc test with the Bonferroni test the following results were obtained:

Table 2. Subject characteristics are based on *Child Pugh Turcotte* scores

Variable	***Child Pugh* A** n = 16	***Child Pugh* B** n = 19	***Child Pugh* C** n = 16	p
Age (years)	48.69 ± 9.43	50.26 ± 12.19	59.06 ± 10.18	0.018 **
Gender				
Girl	7 (43.8%)	5 (26.3%)	6 (37.5%)	0.547 *
Male	9 (56.3%)	14 (73.7%)	10 (62.5%)	
Etiology				
Hepatitis B Virus	14 (87.5%)	18 (94.7%)	14 (87.5%)	.703 *
Hepatitis C Virus	2 (12.5%)	1 (5.3%)	2 (12.5%)	
Etc	0	0	0	
Beta blocker (month)	4 (1 - 18)	4 (1 - 24)	4.5 (0.5 - 12)	0.867 ***
Spironolactone (month)	4 (0.5-16)	6 (1 - 26)	6 (1 - 16)	.601 ***
Tp-te	67.94 ± 7.80	77.26 ± 8.38	92.31 ± 11.36	<0.001 **

*) Chi- square, **) One Way ANOVA, ***) Kruskal Wallis

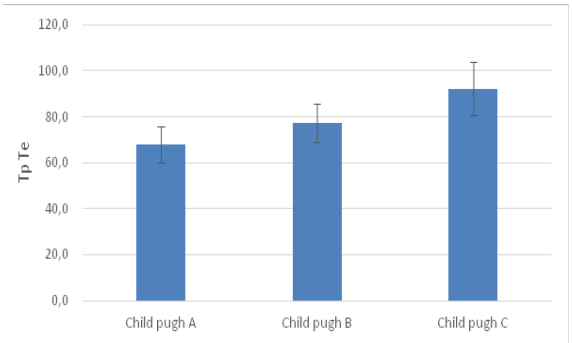

Figure 2. Comparison graph of the *Tp-Te* interval against the degree of *Child Pugh*

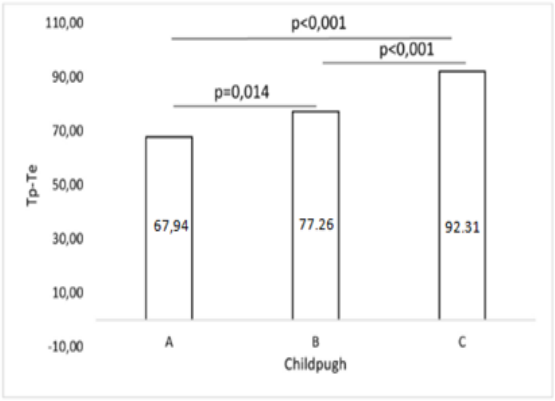

Figure 3. Graph of *post-hoc Tp-Te* interval test for *Child Pugh* degree

The results of the *post hoc* comparison of the multiple *Tp-Te* waves to the Child Pugh degree above show that the comparison of the *Tp-Te* waves in each Child Pugh group has significant results. Child Pugh A group compared to Child Pugh B results obtained p = 0.014, in Child Pugh B group compared to Child Pugh C results obtained p <0.001, and group A Child Pugh A compared to Child Pugh C results obtained p <0.001. These results are different from previous studies with a total of 67 subjects. It was mentioned that the *Tp-Te* interval proved to be a prognostic marker in cirrhosis patients regardless of the degree of liver cirrhosis dysfunction. However, from these results there were no significant differences in the *Tp-Te* interval in each *Child Pugh* score group. In that study the research subjects of the *Child Pugh* C group were far less than the *Child Pugh* A and *Child Pugh* B groups. [12]

From the analysis using One Way ANOVA, showed age variable p <0 , 25 (p 0.018). then performed multivariate analysis with multiple linear regression with the results:

The results of multivariate analysis revealed that only *Child Pugh* had a dominant effect on *Tp-Te* (p <0.001), whereas age was not significant p = 0.374

Table 3. Multivariate analysis of the *Tp-Te* interval

	Regression coefficient	p *Lower Bound*	*95.0% Confidence Interval for B* *Upper Bound*		R^2
(Constant)	50.0	0000	37.435	62.638	0.538
Age	.11	.374	-0.137	.357	
Child Pugh	11.62	<0.001	8.075	15.157	

(p> 0.05). The positive *Child Pugh* regression coefficient 11,62 the higher the degree of Child Pugh also the greater the *Tp-Te* interval.

Beta blockers were one of the main therapies and were almost always used in liver cirrhosis. The subjects of this study mostly used propanolol preparations. Previous research has stated that the use of beta blockers has no effect on the *Tp-Te* interval. This study was conducted on 24 patients with *Long QT syndrome* who were given beta-blocking drugs with the types of Propanolol, Atenolol and Bisoprolol to evaluate the ECG for the first 24 hours.[13] In contrast to other studies of 54 patients with *peripartum cardiomyopathy* (PPCM) given beta bisoprolol blockers at a dose of 2.5 mg to 5 mg for 6 months, a *Tp-Te* interval was calculated before administration and after administration, a significant difference was found.

Conclusion

There was a strong positive correlation between the *Tp-Te* interval with the degree of liver cirrhosis dysfunction which was assessed using the *Child Pugh Turcotte* score. Clinical implications in this study if there was a *Tp- Te* wave lengthening, the clinician can predict cardiomyopathy markers and predictors of arrhythmia events that cause death in patients with liver cirrhosis. Further examination with a better modality can be done to see the structure and function of the heart. Doctors and medical personnel can reduce the risk of arrhythmias with treatment and can be selective in giving arrhythmogenic drugs.

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