CORRELATION BETWEEN CHILD PUGH SCORE AND CYSTATIN C IN LIVER CIRRHOSIS PATIENTS

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ABSTRACT

Background*. Renal dysfunction is a serious problem and it provides a poor prognosis for patients with advanced liver cirrhosis. This condition can progress to kidney failure, which is known as hepatorenal syndrome. Cystatin C utilization as a marker of decreased kidney function in patients with liver cirrhosis has been widely proven. Data on how far the severity of liver cirrhosis can affect the decline in renal function has not been widely known.*

Objective. *This study aimed is to verify correlation between the severity degree of the liver (Child Pugh/CP score) with levels of Cystatin C serum.*

Methods. *This study was a cross sectional study. Population studied were patients with liver cirrhosis who visited the clinic of Gastroentero-hepatology and treated in the Department of Internal Medicine ward Dr. Sardjito Hospital - Yogyakarta during October 2009 - March 2010. Data were analyzed with a computer; the analysis of the CP score correlation with increased levels of Cystatin C using Spearman correlation for data not normally distributed.*

Result. *We found 48 research subjects during the month of October 2009 - March 2010. The subjects were 35 male (72.9%) and 13 female (27.1%) with average age 53.1 ± 11.9 years old. Subjects with CP-A were 9 patients (18.8%), CP-B were 14 patients (29.2%) and CP-C were 25 patients (52.1%). The range value of Cystatin C between CP class shows CP-A 0.7 - 0.97 mg/L, CP-B 0.7 - 0.49 mg/L, and CP-C 0.7 – 2.49 mg/L (statistically significant difference with p <0.05). Liver cirrhosis patients who had Cystatin C levels <0.96 mg/L were 22 patients (45.83%) and 26 patients (54.1%), had higher levels of Cystatin C> 0.96 mg/L. Child score was positively correlated to increased levels of Cystatin C (p= 0.000; r= 0.566) linear regression equation with Cystatin was = 0.37 + 0.08 * Child score (r square 0.32).*

Conclusion. *This study concluded that the Child score had a moderate positive correlation with Cystatin C serum level.*

Key words: *Liver Cirrhosis – Child Pugh score - Cystatin C*

INTRODUCTION

Chronic liver disease and cirrhosis cause 350,000 deaths annually in the United State of America (USA). Cirrhosis is the ninth leading cause of death in the USA and was responsible for 1.2% of all deaths. Patients who have liver cirrhosis aged between fifth and sixth decades. In Indonesia, with a total estimated population of 238,452,952 people, the number of people who suffer from liver cirrhosis is estimated about 350,666 [2]. In Yogyakarta, the number of hospitalized patients with cirrhosis ranges from 4.1% of all patients treated in the Internal Medicine ward by the year 2004 [3].

Cirrhosis is the final process of liver cells injury that turned into a form of fibrosis and nodular regeneration in almost all liver cells. Cirrhosis is a serious disease and generally is irreversible and in the USA, it included 10 largest cause of death. Arising clinical signs are the result of liver cell dysfunction, and portal hypertension portosistemik shortcut [4].

Some of the scoring system used to assess the severity of the disease and determine the prognosis in patients with cirrhosis. Child Pugh (CP) score is based on the severity of disease according to the signs, symptoms and laboratory examination results, this score proved to be able to predict the survival rate [5].

Various kinds of complications can occur in patients with liver cirrhosis. Hepato-renal syndrome (HRS) occurs in approximately 4 of 10,000 patients with heart disease, such as acute liver failure, liver cirrhosis, or alcoholic hepatitis. Reported mortality

rates from an HRS were greater than 95% with an average survival less than two weeks [6].

Renal dysfunction is a serious problem in patients with advanced liver cirrhosis, where patients with liver cirrhosis accompanied by ascites can cause kidney failure, a condition known as Hepato-renal syndrome [7]. The declined in renal function in patients with liver cirrhosis, showed a poor prognosis. A prospective cohort study prove that in patients with cirrhosis, HRS type I has median survival rates 1.7 weeks and only 10% of patients survive more than 10 weeks, while in HRS type II survival rate reached 50% in first 5 months and 20% in the first [8].

Creatinine, based on calculation of filtration glomerolus showed limitations in predicting GFR in patients with cirrhosis. Creatinine clearance have a higher estimation in estimating true GFR up to 200% [9]. Cystatin C (cys C), is a non-glycosylated 13 kDa protein that is expected to predict the decline in GFR in patients with cirrhosis. Cystatin C is not influenced by age and body mass so that the measurement of Cystatin C is recommended to detect renal insufficiency in patients with liver cirrhosis [9]. Increased Cystatin C proved to have significant correlation to the decline glomerolus filtration rate (r -0.85, p <0.001) than creatinine (r -0.32, p <0.05) in patients with liver cirrhosis. Calculation of Cystatin C in patients with cirrhosis of the liver is not affected by age or body mass index [10]. A liver cirrhosis accompanied by ascites and normal creatinine levels, Cystatin C concentration calculation proved to be as a prognostic marker of future occurrence of HRS [11].

Due to the nature of reversible renal dysfunction in patients with liver cirrhosis, on this occasion we want to know any correlation between Child score with the levels of Cystatin C in patients with liver cirrhosis, and factors that significantly influence to the worsening of kidney function, so hopefully with this knowledge we can prevent the occurrence of an HRS in patients with liver cirrhosis.

METHODS

This study was a cross-sectional study, with the aims of determining whether there was a correlation between Child Pugh score with Cystatin C levels in the blood. This research was conducted in the gastroentero-hepatologist clinic and internal medicine ward of Dr. Sardjito Hospital Yogyakarta during October 2019 - March 2010.

Target populations were those who suffer from liver cirrhosis who visited at Dr. Sardjito Hospital Yogyakarta. Inclusion criteria were: Patients with liver cirrhosis, aged 18 years or older, and signed inform consent. Exclusion criteria were: Patients with heart failure or cardiac cirrhosis, patients with renal failure, sepsis, hepatocellulare carcinoma, long-term steroid use, thyroid dysfunction, hypertension and diabetes mellitus.

Patients who meet inclusion and exclusion criteria underwent anamnesis, physical and laboratory examination (albumin, bilirubin, prothrombin time, creatinine, urea nitrogen, INR, Cystatin C) and liver ultrasound. Patients were divided into two groups: those with normal levels of Cystatin C ≤0.96 and those with higher levels of Cystatin C> 0.96 and then we measured the factors that relate to differences in the levels of Cystatin. Data were analyzed with a computer; we analyze the child score correlation with increased levels of Cystatin C using the Pearson correlation for normally distributed data and Spearman correlation for data not normally distributed.

RESULTS

During six months of research, 48 patients (male 72.9% and female 27.1%) who met the criteria for exclusion or inclusion were enrolled in the study. Based on Child criteria, there were 9 patients (19.8%) with Child A, 14 patients (29.2%) with Child B, and 25 patients (52.1%) with Child C. The average score of Child was 9.56 ± 2.7 and the average of age was 53.1 ± 11.9 years old. Most of the subjects had history of Hepatitis B (23 patients; 47,0%)

Table 1. Baseline characteristics of subjects (total subjects 48)

Variable	n (%) mean±SD
Sex	
Male	35 (72.9%)
Female	13 (27.1%)
Age mean (year)	53.1 ±11.9
Child Pugh (CP)	
CP-A	9 (18.8%)
CP-B	14 (29.2%)
CP-C	25 (52.1%)
HBs Ag positive	23 (47.9%)
Anti-HCV total positive	4 (8.3%)
Alcoholics	8 (16.47%)

In this study, subjects were divided into two groups based on the value of Cystatin C. The first group was those with normal Cystatin C levels (≤ 0.96 m/L) and the second group was those with Cystatin C levels > 0.96 mg/L. As many as 22 patients had Cystatin C ≤ 0.96 mg/L and 26 patients had higher levels of Cystatin C (>0.96 mg/L). There was statistically significant difference between the two group based on gender (male 72.7% vs.73.1%, female 27.3% vs.26.9%; p> 0, 2005).

Table 2. The Comparison of clinical and laboratory between groups Cystatin C

Characteristic	Cystatin ≤ 0.96 mg/L (n=22)	Cystatin > 0.96 mg/L (n=26)	p	95% CI
Child Pugh			0.000	
CP-A (n,%)	8 (36.4)	1 (3,8)		
CP-B (n,%)	8 (36,4)	6 (23,1)		
CP-C (n,%)	6 (37,3)	19 (73,1)		
CP-score median	8	11	0.000	0.00 – 0.61
Gender			0.978	
Male (n,%)	16 (72.7)	19 (73.1)		
Female (n,%)	6 (27.3)	7 (26.9)		
Age (mean±SD)(year)	51.41±0.82	54.5±12.7	0.37	-10.08;3.82
BMI(median)(kg/m^2)	20.92	20.72	0.89	0.78;1
Clinical				
Hematemesis (n,%)	14 (29.8)	14 (29.8)	0.595	
Melena (n,%)	17 (35.4)	15	0.152	
Ascites (n,%)	11 (22.9)	(31.31)	0.281	
		17 (35.4)		
Encephalopathy (EH)			0.000	
(n,%)	10 (20.8)	2 (4.2)		
nonEH	4 (8.3)	6 (12.5)		
EH grade I	4 (8,3)	4 (8.3)		
EH grade II	2 (4.2)	10 (20.8)		
EH grade III	2 (4.2)	4 (8.3)		
EH grade IV				
NCT (median)(sec)	52.5	100	0.000	0.000; 0.061
Laboratory				
BUN (median)(mg/dl)	14.4	12.5	0.479	0.34 – 0.62
CCT (mean)(ml/min)	69.03	58.06	0.119	-2.91;-24.86
Creatinine (median)	1.09	0.04	0.354	0.219 – 0.49
(mg/dl)	0.81±2.8	2.5±0.69	0.104	-0.078;-0,79
Albumin	1.49	2.3	0.000	0 – 0.061
(mean±SD)(mg/dl)	1.28	1.51	0.000	0 – 0.061
Bilirubin tot (median)(mg/dl)				
INR (median)				
Ascites(liver ultrasound)			0.813	
No (n,%)	11 (50)	10 (38.5)		
Mild-moderate (n,%)	7 (31.8)	10 (38.5)		
Severe (n,%)	4 (18.2)	6 (23.1)		

Average age in the first group was 51.41 ±10.82 years and in the second group 54.5 ±12.7 years (p> 0.05). There were statistically significant difference between the two groups based on CP class (p <0.005) and median of CP score (p <0.05). Between both groups there were no statistically significant differences in body mass index and clinical complaints variables between the two groups. Subjects without encephalopathy were more prevalent in the group of Cystatin C ≤ 0.96 mg/L. Encephalopathy grade II was found comparable in both groups, whereas encephalopathy grade III and IV degrees were more prevalent in groups with Cystatin C > 0.96 mg/L, statistically significant difference (p <0.05). There were no statistically significant differences against the value of BUN, creatinine, and albumin between the two groups. Even, statistically significant difference was found for total bilirubin and INR (bilirubin 1.49 vs.2.3 mg/dl ; INR 1.28 vs.1,51 ; p < 0.05). The degree of encephalopathy based on numeric connection test (NCT), there were significant different (52.5 vs. 100 seconds; p<0.05). (Table 2)

Figure 1. Comparison of Cystatin C between groups Child Pugh

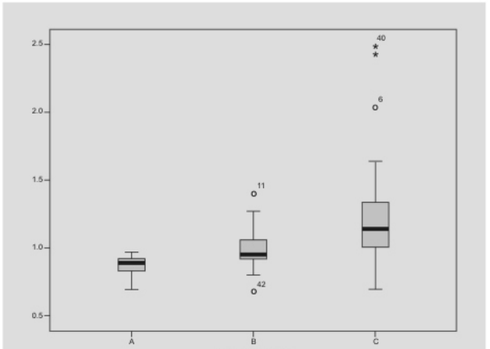
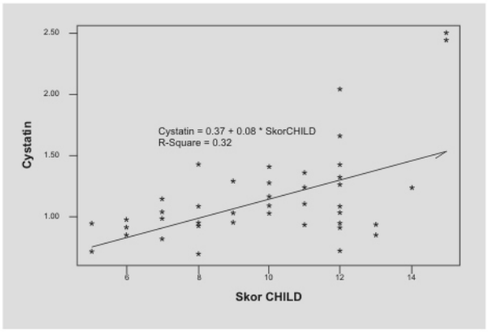


Figure 2. Scatter plot diagram of Child Pugh score and Cystatin C level



* p < 0,05, r = 0,566

The range value of Cystatin C between CP class shows CP-A 0.7 - 0.97 mg/L, CP-B 0.7 - 0.49 mg/L, and CP-C 0.7 – 2.49 mg/L (statistically significant difference with p <0.05) (Figure 1). To know the correlation between the degrees of severity of the liver to the decline of renal function we performed regression analysis as seen in scatter diagram on figure 2.

Table 3. Child score component relationships and Cystatin C levels

Variable	P	R
Albumin	0.032	- 0.310 *
Total bilirubin	0.000	0.501 **
INR	0.000	0.622 ***
NCT	0.259	0.166
Encephalopathy[5]	0, 001	0.474 *
Degree of ascites (USG) [5]	0.281	0.158

In table 3, shows correlation between factors (components) in CP criteria to the level of Cystatin C (p: 0.000; r: 0.566). Albumin, total bilirubin and INR have a correlation of the levels of Cystatin C with the p value was significant (p <0.05). Levels of albumin with higher levels of Cystatin C had a weak negative correlation. Total bilirubin levels with higher levels of Cystatin C had a positive correlation (r: 0.501). INR levels with levels of Cystatin C had a strong positive correlation (r: 0.622).

Table 4. Multivariate analysis of liner-related factors

No	Variable	β	p
1	Constant	0.544	0.053
	Albumin	0.053	0.437
	Total Bilirubin	0.036	0.002
	INR	0.080	0.000
	Ascites	0.040	0.500
	encephalopathy	0.045	0.200
2	Constant	0.653	0.005
	Albumin	0.036	0.565
	Total Bilirubin	0.037	0.002
	INR	0.079	0.000
	Encephalopathy	0.049	0.153
3	Constant	0.775	0.000
	Total Bilirubin	0.035	0.002
	INR	0.079	0.000
	encephalopathy	0.040	0.184
4	Constant	0.822	0.000
	Total Bilirubin	0.039	0.000
	INR	0.084	0.000

From the scatter plot diagram, we obtained linear equations of Cystatin = 0.37 + 0.08 * Child Score with R-Square 0.32. After using multivariate analysis on serum albumin, bilirubin total INR and the degree of encephalopathy (table 4), note that the total bilirubin level and INR were the two factors most associated with elevated levels of Cystatin C, with linear equation = 0.82 + 0.04 * + 0.08 * total bilirubin INR (adjusted r square 51.8%).

DISCUSSION

In this study, we found the prevalence of child C liver cirrhosis to be more frequent than other groups 25 (52.1%) people. This is possible because the sampling was done at the hospital. Previous research conducted at the hospital about the mortality of patients based on the degree of severity of liver found the number of patients with Child C liver cirrhosis who were treated as much as 54% [11].

The number gender shows males more than females (72.9% vs.27.1%). This was almost similar to a study conducted in Mexico, where the number of patients who underwent liver cirrhosis reached 25% of the total patients admitted in internal medicine, with the proportion of male - female 3: 1[12]. The role of gender on the incidence of liver cirrhosis has some differences based on the etiology and age. Liver cirrhosis caused by alcohol makes a comparison male – female range from 1.5 to 3:1, whereas in primary billiary cirrhosis in women has a higher incidence. In liver cirrhosis caused by viral infection, a comparison of men and women at age less than 35 years and more than 65 years had no significant difference, but at age 35-65 years the number of men who suffer from cirrhosis of the liver caused by previous hepatitis virus infection is higher than women 3 to 4 : 1. This is apparently due to the influence of estrogen in women who have a protective effect against the occurrence of liver cirrhosis [13]. The average of age with cirrhosis in this study were 53.1±11.9 years. Based on epidemiological data, cirrhosis of the liver is usually suffered by those who entered the age of five or six decade.

Patients with a history of liver cirrhosis with hepatitis B, the most widely encountered in this study were as many as 47.9%. This result is similar to a study conducted in Ghana on the prevalence of viral hepatitis among patients with liver cirrhosis. In their study, they found the prevalence of positive HBsAg was 42.9%, where OR for the occurrence of cirrhosis 8.07 (p: 0.000). HCV is responsible for 7.1% of cases with liver cirrhosis but not proved the

existence of a significant relationship between the incidence of cirrhosis itself [14].

Cystatin C levels increased above normal values, obtained in liver cirrhosis Child B. In previous studies, elevated levels of Cystatin C already observed in Child A, although the increment was not significant. Elevated levels of Cystatin C were more common in those with Child B and C, where the increasing in Child C was significantly higher [15].

Seo *et al*. (2009) found that Cystatin C concentration is a predictive factor for the incidence of HRS. In this study, the patients with liver cirrhosis with ascites and normal creatinine where all cirrhotic patients with Child B and C. In our research, elevated levels of Cystatin C were related with degrees of severity. Increased Cystatin C in our study started in Child B liver cirrhosis. After multivariate analysis with backward method, the levels of bilirubin and INR were factors that influence the increase in Cystatin C. Evidence that the degree of severity of the liver associated with elevated levels of Cystatin C can be seen in previous studies, which showed an average concentration levels of Cystatin C was higher in patients with hepatocellular carcinoma patients (1.16±0.1 mg/L) compared to patients with liver cirrhosis and patients with chronic hepatitis (1.13±0.09 mg/L and 0.68±0.03 mg/L). Cystatin C concentration was also shown to have a correlation with histological degree of liver fibrosis stage and levels of total bilirubin, albumin, and platelets [16]. Increased bilirubin and INR showed increasing degrees of severity of liver. A previous study in patients with primary biliary cirrhosis found that levels of bilirubin and hyaluronic acid are the two independent variables associated with the degree of fibrosis in liver cirrhosis. Increased serum bilirubin of 10 mg/dl led to increased probability of the widespread degree of cirrhosis by 3.4-fold (p: 0.05, CI 1.0 to 11.2) [17].

An elongated period of bleeding in patients with liver cirrhosis is a reflection of the severity of cirrhosis. Elevated levels of bilirubin as a marker of the severity of liver shows strong correlation with the length of bleeding (ß coefficient 0.19, p = 0.007) [18].

CONCLUSIONS

Based on the results of this study there were positive relationships between Child score with elevated levels of Cystatin C. Additional samples were collected from similar studies in the future are expected to increase the strength of the relationship between the severity score of cirrhosis (Child score) with decreased renal function (elevated levels of Cystatin C). Cystatin C is superior to the detection of kidney function than other tools.

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