Relationship between plasma fibrinogen levels with model of end stage liver disease score in patients with liver cirrhosis

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ABSTRACT

Introduction. *One of the complications which often occur in the liver cirrhosis is bleeding. Closely associated with weighing of bleeding were disturbance haemostatic homeostasis disorders that commonly associated with impaired liver function. Therefore certain biomarkers are needed to objectively measure the severity of liver cirrhosis. Fibrinogen is one of the clotting factors that can be used to determine the severity of liver cirrhosis. The model of end-stage liver disease (MELD) score is most excellent alternative of the Child-Pugh score. It can be used in patients with liver cirrhosis spacious ranges severity of disease and etiology even in patients whose cirrhosis etiology are not clear. Currently, there was not any data showing the correlation between the level of plasmatic fibrinogen and MELD score in patients with liver cirrhosis.*

Aims. *This study aimed to determine the correlation between level of plasmatic fibrinogen and MELD score in patients with liver cirrhosis.*

Method. *This study was cross-sectionally conducted used consecutive sampling. Study population were eligible patients with liver cirrhosis who visited outpatient and inpatient clinic in the Division of Gastroentero-hepatology, Dr. Sardjito general hospital, between November 2011 to October 2012. Correlation between the level of plasmatic fibrinogen and MELD score was statistically assessed using correlation test with final result stated as correlation coefficient (r).*

Result. *There were 40 subjects that met criteria, 28 male and 12 female, with average age of 53 ± 12,51 years. Etiology of cirrhosis was viral hepatitis B in 16 (40,0%) subjects, hepatitis C in 11 (27,5%) subjects and non viral in 13 (32,5%) subjects. Subjects with ascites were 19 (47, 5%) and without ascites were 20 (52.5%). Bleeding was experienced by 30 (80.0%) subjects while 10 (20,0%) subjects did not present with bleeding. Mean of plasma fibrinogen was 198 ± 102, 89 mg/dl, and mean of the MELD score was 17,05 ± 8.79. Spearman correlation coefficients between fibrinogen and MELD score was r = -0,404 (p = 0,010).*

Conclusion. *There was a negative correlation between plasma fibrinogen and the MELD score in liver cirrhosis patients visiting our local setting.*

Keywords: *liver cirrhosis, fibrinogen, MELD score*

INTRODUCTION

Cirrhosis of the liver is a final journey pathology of various liver diseases, in which the liver is characterized by fibrosis. Cirrhosis of the liver can lead to around 35,000 deaths per year in the United States (U.S.), which is the ninth leading cause of death in the U.S.[1] In Peru due to liver cirrhosis mortality rate reached 10.45 per 100,000 population.[2] Mortality due to liver cirrhosis has increased from 6 per 100,000 populations in 1993 to 12.7 per 100,000 populations in the year 2000.[3] One common complication in liver cirrhosis is bleeding. Severity of bleeding, closely related to hemostasis disorders. However, hemostasis disorders are usually did not relate with impaired liver function. Levels of blood clotting factors, including fibrinogen, is one of the parameters that can be used to determine the severity of liver cirrhosis.[4] Model for end-stage liver disease (MELD) is the best alternative of the Child-Pugh score. This score was considered as a very serious challenge to replace Child-Pugh score and overcome its limitations. MELD score is useful in patients with wide range of disease severity and even in patients whose etiology of cirrhosis not clear.[5]

METHOD

The study design was cross-sectional. It was conducted in the clinic and hospital ward of Dr. Sardjito general hospital, Yogyakarta. The study began in November 2011 to October 2012. Subjects were patients with liver cirrhosis treated in gastroenterology clinic or hospitalized in the Internal Medicine ward who met the eligibility. Fibrinogen was a plasma protein that synthesized by parenchymal cells fibrinogen tests using serum or plasma samples as much as 3 cc of heparin stored at -20º C. Reference values for fibrinogen level was 200-400 mg/dL. MELD score calculated according to the following formula: 3.78 [Ln serum bilirubin (mg/dL)] + 11.2 [Ln INR] + 9.57 [Ln serum creatinine (mg/dL)] + 6,45. Course of study displayed in Figure 1.

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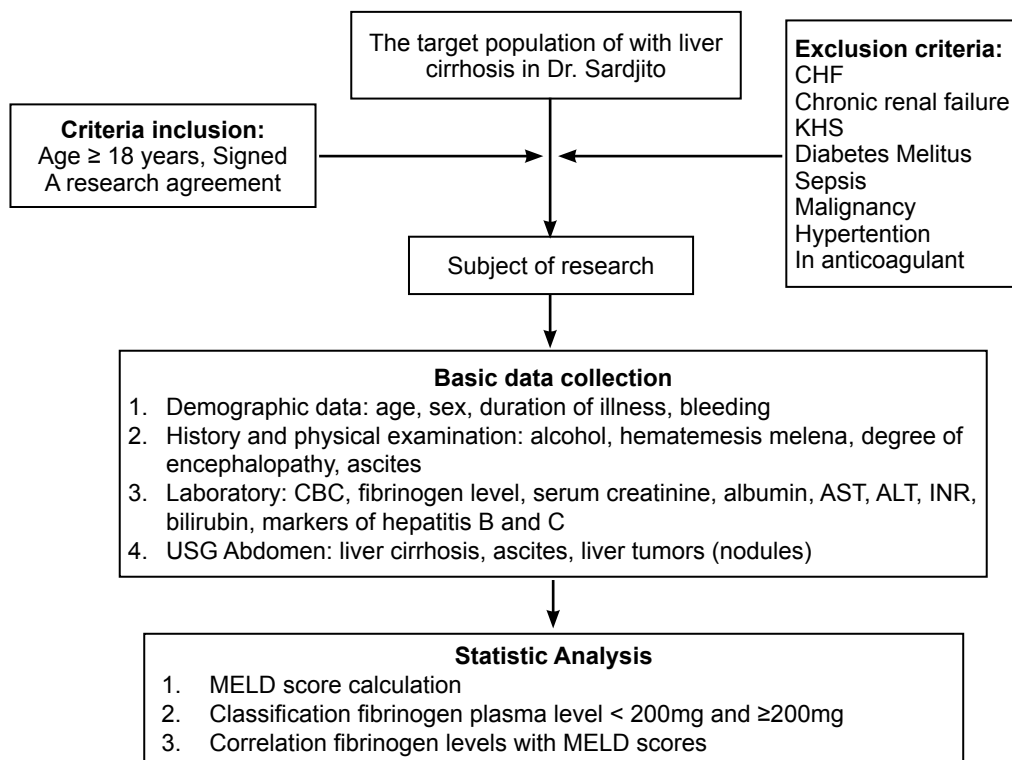
Figure 1. Course of the study

Table 1. Characteristic Subject

Variable	n (%)	Mean ± SD
Sex		
Man	28 (70,0)	
Woman	12 (30,0)	
Age		53±12,51
Cause cirrhosis		
Hepatitis B	16 (40,0)	
Hepatitis C	11 (27,5)	
Non viral	13 (32,5)	
Ascites		
Yes	19 (47,5)	
No	20 (52,5)	
Bleeding		
Yes	30 (80,0)	
No	10 (20,0)	
Plasma fibrinogen level (mg/dl)		198 ± 102,89
MELD score		17,05 ± 8,79

N = total subject of research ; SD = *standard deviation*; INR = *International Normalized Ratio*; MELD = *Model of End Stage liver disease*

Table 2. Comparison clinical between fibrinogen level < 200 mg/dL and fibrinogen level > 200 mg/dL

Variable	Fibrinogen level < 200 mg/dL Mean ± SB (n = 23)	Fibrinogen level ≥ 200mg/dL mean ± SB (n = 17)	P	95%IK
Sex				
Man (n%)	15 (65,2)	13 (76,5)	0.443[#]	0.14-2,36
Women (n%)	8 (34,8)	4 (23,5)		
Age	54,74 ±10,32	51,24±15,68	0,388[*]	-4,62-11,63
Bleeding				
Yes (n%)	21 (91,3)	11 (64,7)	0,053[$]	-,98-33,24
No (n%)	2 (8,7)	6 (35,5)		

MELD = *Model of End Stage Liver Disease*; RP = Prevalence Ratio; IK = confidence interval; *= t test unpaired ; # = *Chi square test*; $ = *Fisher Test*

Table 3. Mean difference fibrinogen levels based on severity of MELD score

MELD score	Fibrinogen level		95% IK
	Mean±SD	P	
<10	339,00 ± 207,0	0,180*	-175,28-853,28
10-19	200,35 ± 85,8		165,65-235,04
20-29	190,26 ± 78,5		92,69-287,82
30-39	111,60 ± 96,0		-7,66-230,86
>40	200,00		

* = *Kruskal Walis test*

Table 4. Correlation of test results with fibrinogen levels MELD score

	Correlation coefficient Spearman (r)	P
Fibrinogen level MELD score	-0,404	0,010

DISCUSSION

Study subjects who met the inclusion criteria were 40 patients, consisting of 28 (70.0%) males and 12 (30.0%) females. This is similar to previous study found that male subjects are more than the female subjects. Previous research conducted to get male cirrhotic patients as much as 64%. The mean age of participants was 53 ± 12.51 years. Based on epidemiological data, cirrhosis of the liver usually inflicted on those who were entering the age of five or six decades.[3] Cause of the liver cirrhosis in this study was hepatitis B virus infection in 16 (40.0%), hepatitis C infection in 11 (27.5%) and not hepatitis B virus infection and C in 13 (32.5%). Previous research conducted by Nurdjanah (2006) showed liver cirrhosis etiologies included hepatitis B virus (40-50%), hepatitis C virus (30-40%) and unknown or not including B and C viruses (10-20%). The present study found 30 subjects with bleeding (80.0%) and 10 (20.0%) subjects without bleeding. Sulaiman (1990) found bleeding manifestations as melena (56.2%), hematemesis (50.6%), bleeding gums (27%), and epistaxis (13.2%).[6] Tambunan (2006) reported that from 121 patients with liver cirrhosis 75 cases (61.9%) experienced bleeding.[7]

Average fibrinogen levels in this study were 198 ± 102.89 mg/dL. With reference value of 200-400 mg/dL, the mean of fibrinogen levels was below the normal range. The mean MELD score found in this study was 17.05 ± 8.79, higher than reports from previous studies demonstrating a mean of 9.7 ± 9.2 and a median of 9 (4-14).[4] Study subjects were further divided into two groups based on the value of fibrinogen levels. First group included those with fibrinogen levels less than normal value (<200 mg/dL) and the second group included those with a normal fibrinogen level (=200

mg/dL). Clinical and laboratory data comparisons between the two groups was shown in Table 2. First group consisted of 23 subjects (15 men, 65.2% and 8 women, 34.8%). Second group consisted of 17 subjects (13 men, 76.5% and 4 women, 23.5%). The mean of age in the first group was 54.74 ± 10.32 years, similar to the second group where mean of age was 51.24 ± 15.08. The first group of 23 subjects obtained with clinical bleeding were 21 (91.3%) subjects and without bleeding were 2 (8.7%) subjects. These proportions were higher than the second group in which 11 (64,7%) subjects presented with bleeding and 6 (35.3%) subjects presented without bleeding (p = 0.053).

Table 3 showed the mean fibrinogen levels based on the severity of the value of MELD score. The mean fibrinogen levels in MELD score of <10 = 339.00 ± 207.0 mg/dL; MELD score of 10-9 = 200.35 ± 85.8 mg/dL; MELD score of 20-29 = 190.26 ± 78.5 mg/dL; MELD score of 30-39 = 116.60 ± 96.0 mg/dL, and MELD score of > 40 = 200.00 mg/dL. The mean fibrinogen levels were found non-significant (p = 0.180). In subgroups with MELD score of <40 decreased levels of fibrinogen was followed by the increased value of MELD score. The group with MELD scores of >40 decreased levels of fibrinogen did not associate with their respective groups based on the severity of the MELD score. There were several possible caused for this difference. First, the presence of co-morbidities that accompany the research subject was infection; in this study was an urinary tract infection. Fibrinogen was an acute phase reactant where its level will rise several-fold in the presence of infection. Second possibility was age. The mean age in this study was 53 ± 12.51, approaching old age. Old age was known to affect levels of fibrinogen. Third possibility was hemolysis in samples that might affect test results.

Table 4 showed the *Spearman correlation test* plasma fibrinogen levels on MELD score, which showed a negative correlation decreased levels of fibrinogen and an increase score of MELD (r = -0.404, p = 0.010). This means that the plasma fibrinogen level significantly correlated with MELD scores. This relationship illustrates that most of the subjects were patients who had advanced liver cirrhosis. Fibrinogen levels decreased in patients with liver cirrhosis according to the severity of the disease where it can determine the prognosis of patients with liver cirrhosis. The results of this study are also consistent with research on fibrinogen by Arif *et al.,* (2002)[9] on 82 patients with liver cirrhosis who were compared with 40 normal patients. This report found a decrease of fibrinogen levels compared to mean controls, mild decrease in
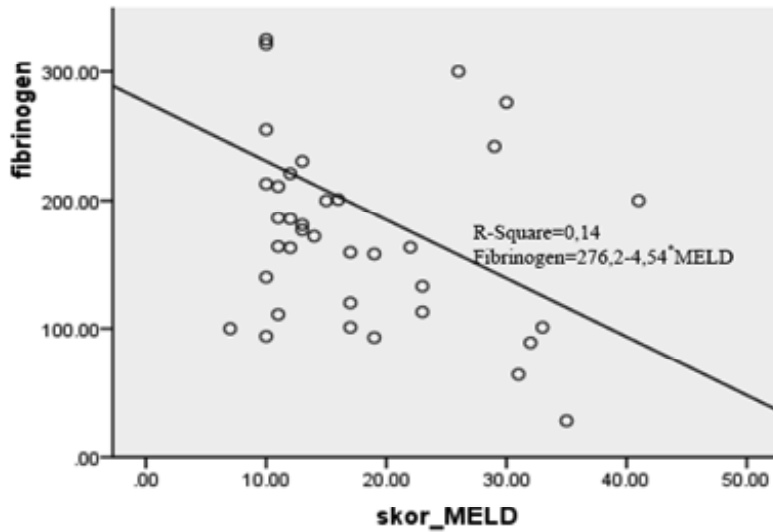
Figure 2. MELD scores linear regression with plasma fibrinogen levels

early liver cirrhosis and a higher reduction in advanced stage liver cirrhosis.

Performed linear regression was to see the effect of the MELD score on levels of fibrinogen. Equation fibrinogen = 276.2 to 4.54 * MELD score, the R-square was 0.14, which means the equation can only predict as much as 14% decrease in fibrinogen levels were associated with the increased MELD score.

CONCLUSION

There was a negative correlation between plasma fibrinogen levels in patients with MELD scores of liver cirrhosis. Obtained decreased levels of fibrinogen was followed by an increased in MELD score.

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