

## 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. So that the necessary biomarkers 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. MELD score is the most excellent alternative of the Child-Pugh score. MELD score can be used in patients with liver cirrhosis spacious ranges severity of disease and etiology even in patients whose cirrhosis are not clear why. Currently, there was not any data showed the correlation between the level of plasmatic fibrinogen and MELD score in the patients with liver cirrhosis. This study aimed to find the correlation between the levels of plasmatic fibrinogen and MELD score in the patients with liver cirrhosis.

**Method.** The design of this study was cross-sectional. Samples were obtained by the consecutive sampling. Subjects of the study were the patients with liver cirrhosis who visited as outpatient and inpatient in the Gastroenterohepatology clinic of Dr. Sardjito hospital between November 2011 to October 2012, and who already met the inclusion and exclusion criteria. The correlation between the level of plasmatic fibrinogen and MELD score was assessed statistically using correlation test. The final result of correlation test was stated in the correlation coefficient ( $r$ ).

**Result.** There were 40 subjects that met criteria, 28 male and 12 female, age average was  $53 \pm 12$ , 51. Cause of cirrhosis was viral hepatitis B as much 16 (40, 0%) subject, hepatitis C 11 (27,5%) subject and non viral 13 (32,5%) subject. Subjects with ascites are 19 (47, 5%) and without ascites are 20 (52.5%). Bleeding with 30 (80.0%) subjects, 10 (20, 0%) without bleeding. Mean of plasma

fibrinogen was  $198 \pm 102$ , 89 mg / dl, meanwhile the MELD score was  $17, 05 \pm 8.79$ . Spearman correlation coefficients between fibrinogen and MELD score was  $r = -0,404 (p = 0,010)$ .

**Conclusion.** In conclusion, there was a negative correlation between plasma fibrinogen and MELD score in liver cirrhosis patients.

**Keywords:** liver cirrhosis, fibrinogen, MELD score

### INTRODUCTION

Cirrhosis of the liver is a journey final pathology of various liver diseases, in which the liver is found liver damage 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. (Kusumobroto 2007). In Peru due to liver cirrhosis mortality rate reached 10.45 per 100,000 population.<sup>10</sup> 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. 6 One common complication is bleeding in liver cirrhosis. Severity of bleeding, closely related to hemostasis disorders, hemostasis disorders are usually nothing to do 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.<sup>1</sup> Model for end-stage liver disease (MELD) is the best alternative of the Child-Pugh score. This score was formed as a very serious challenge to replace Child-Pugh score and overcoming its limitations. MELD score is useful in patients with liver cirrhosis wide range of disease severity and etiology even in patients with cirrhosis is not causes clear.<sup>2</sup>

### METHOD

The study design was cross-sectional. A study was conducted in the clinic and hospital ward Medicine Unit Sardjito, Yogyakarta. The study began in November 2011 to October 2012. Subjects were patients with liver cirrhosis treatment in gastroenterology clinic or hospitalized in the Internal Medicine ward Sardjito Hospital who meet inclusion and exclusion criteria. Fibrinogen is a

plasma protein that is synthesized by parenchyma cells fibrinogen tests using serum or plasma samples as much as 3 cc of heparin stored at  $-20^{\circ} \text{C}$ . Reference values for normal fibrinogen level is 200-400 mg / dL. MELD score is calculated according to the formula =  $3.78 [\text{Ln serum bilirubin (mg / dL)}] + 11.2 [\text{Ln INR}] + 9.57 [\text{Ln serum creatinine (mg / dl)}] + 6,45$ . Course of study can be explained in Figure 1.

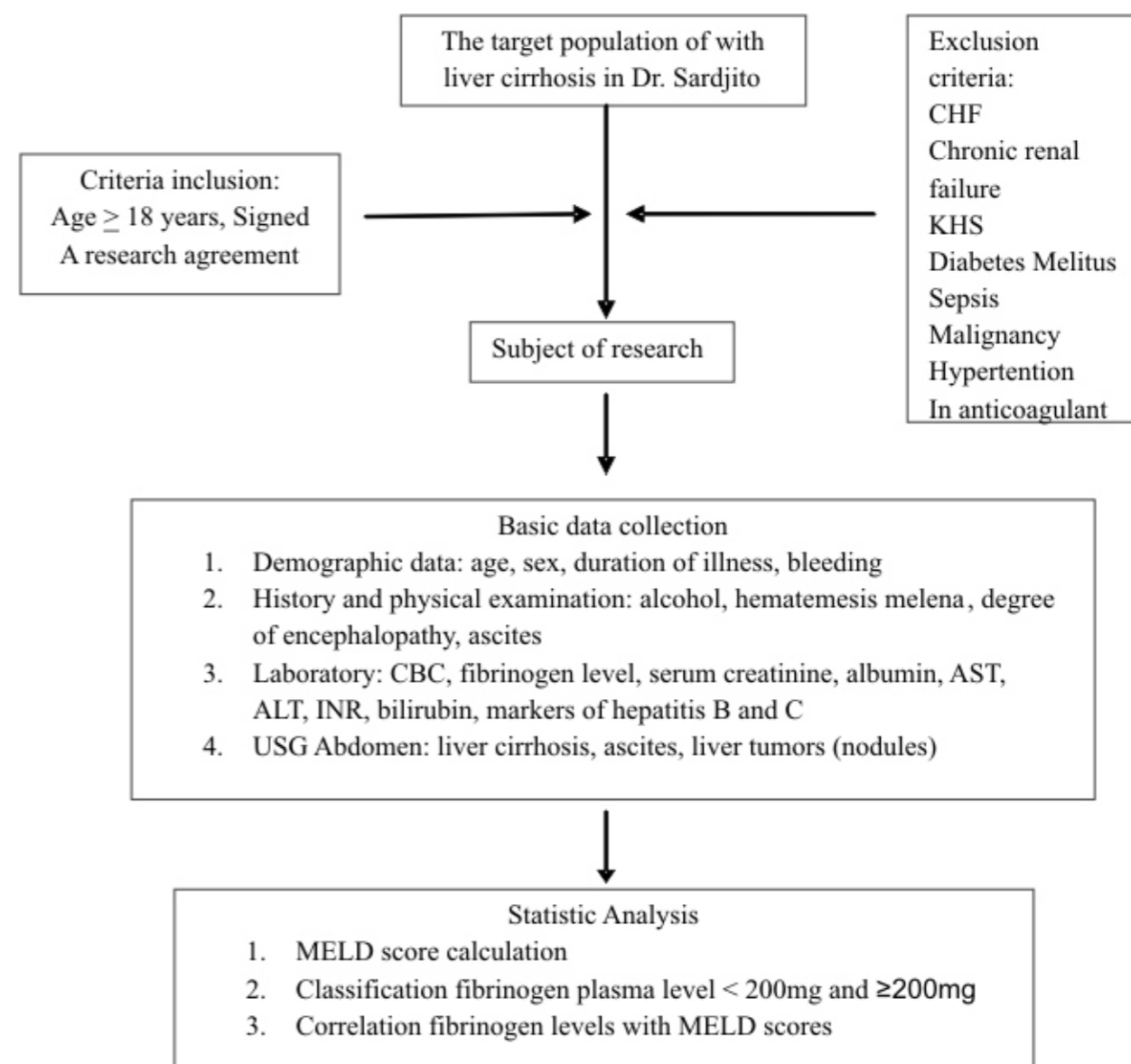


Figure 1. Course of the study

**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 ≥ 200 mg/dl mean±SB (n=17)	P	95%IK
Sex				
Man (n%)	15 (65,2)	13 (76,5)	0,443 <sup>#</sup>	0,14-2,36
Women (n%)	8 (34,8)	4 (23,5)		
Age	54,74 ±10,32	51,24 ± 15,68	0,388 <sup>*</sup>	-4,62-11,63
Bleeding				
Yes (n%)	21 (91,3)	11 (64,7)	0,053 <sup>\$</sup>	-,98-33,24
No (n%)	2 (8,7)	6 (35,5)		

MELD = Model of End Stage Liver Disease; RP = rasio prevalensi; IK = confiden interval; \* = uji t test unpaired ; # = uji Chi square; \$ = Uji Fisher

**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		

φ = uji Kruskal Wallis

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

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

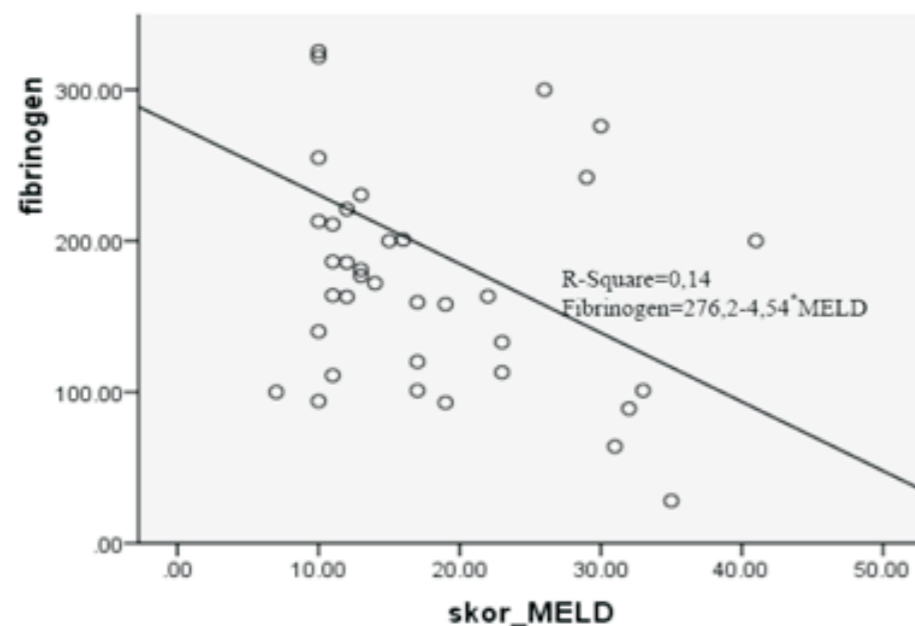
## DISCUSSION

Study subjects who met the inclusion criteria obtained from 40 patients. Consisted of 28 (70.0%) by the subjects of male and 12 (30.0%) female. This is similar to a previous study that found male subjects are more than the female subjects. Previous research conducted to get male cirrhotic patients as much as 64%. The mean age of study subjects was 53 ± 12.51 years. Based on epidemiological data, cirrhosis of the liver usually inflicted on those who are entering the age of five decades or six.<sup>3</sup> Cause cirrhosis of the liver in the study of hepatitis B virus infection by 16 (40.0%), hepatitis C infection were 11 (27.5%) and not hepatitis B virus infection and C were 13 (32.5%). Previous research conducted Nurdjanah, (2006) Indonesian data showed the cause of cirrhosis of the liver are hepatitis B virus (40-50%), hepatitis C virus (30-40%) and 10-20% the cause is unknown and not including group B and C viruses. It was found bleeding subjects with 30 (80.0%) and 10 (20.0%) without bleeding. Sulaiman, (1990) found bleeding manifestations of liver cirrhosis, 56.2% melena, hematemesis 50.6%, 27% bleeding gums and epistaxis 13.2%. Tambunan, (2006) reported on 121 patients with liver cirrhosis 75 cases (61.9%) experienced bleeding. Average fibrinogen levels in this study were 198 ± 102.89 mg / dL. The reference value in this study was 200-400 mg / dL, so we can conclude that the mean of fibrinogen levels below the normal range, although some subjects showed normal or increased values above normal values. The mean MELD score of study subjects was 17.05 ± 8.79. This result is higher than the previous studies that found a mean MELD score 9.7 ± 9, 2 and median MELD Score 9 (4-14).<sup>4</sup> This research study subjects were grouped into two groups based on the value of fibrinogen levels. The first group is those with fibrinogen levels less than normal value is < 200 mg / dl and the second group are those with a normal fibrinogen level is = 200 mg / dl. Conducted

clinical and laboratory data comparisons between the two groups as shown in Table 2. Obtained 23 subjects in the first group comprised 15 men (65.2%) and 8 women (34.8%), the second group comprised 13 men (76.5%) and 4 women (23.5%). The average age of the first group was 54.74 ± 10.32 years in the second group 51.24 ± 15.08. There was no difference in the two groups according to age. The first group of 23 subjects obtained with clinical bleeding were 21 (91.3%) subjects and not bleeding 2 (8.7%) subjects, clinical bleeding, which is much more than the second group of 17 subjects with bleeding 11 (64, 7%) and no bleeding 6 (35.3%) but this did not reach statistical significance (p = 0.053). Table 3 shows the mean fibrinogen levels based on the severity of the value of MELD score. The mean MELD group fibrinogen levels <10 = 339.00 ± 207.0 mg / dl; MELD 10-19 = 200.35 ± 85.8 mg / dl; MELD 20-29 = 190.26 ± 78.5 mg / dl; MELD 30-39 = 116.60 ± 96.0 mg / dl, and MELD > 40 = 200.00 mg / dl. In this study, the mean fibrinogen levels were found non-significant (p = 0.180). In each group according to the severity of which is rated as MELD score <40 obtained mean difference decreased levels of fibrinogen followed in accordance with the increase in the value of MELD score. The group with MELD scores > 40 decreased levels of fibrinogen are not in accordance with their respective groups based on the severity of the MELD score, in this study obtained a sample with a mean value of fibrinogen levels equal to 200 mg / dl. There are several possible causes for this difference. The first possibility, the presence of co morbidities that accompany the research subject is an infection. Co morbidities in these patients obtained a urinary tract infection. Fibrinogen is an acute phase reactant, the level will rises several-fold in the presence of infection. The second possibility is age. The mean age in this study was 53 ± 12.51. Patient age was 56 years approaching old age. Old age affects levels of fibrinogen. The third possibility is

hemolysis in samples that can affect test results. Table 4 shows the *Spearman correlation test* plasma fibrinogen levels on MELD score, which there is a negative correlation decreased levels of fibrinogen and an increase in MELD score ( $r = -0.404$ ,  $p = 0.010$ ), (weak force). This means that the plasma fibrinogen level correlated with MELD scores. This relationship illustrates that most of the subjects in this study 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) In a study on 82 patients with liver cirrhosis compared with 40 normal patients as controls found a decrease in fibrinogen levels compared to mean controls, mild decline found in early liver cirrhosis and a higher reduction in advanced stage liver cirrhosis.



**Figure 2.** MELD scores linear regression with plasma fibrinogen levels

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

## CONCLUSION

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

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