ORIGINAL ARTICLE

The Difference of D-Dimer Levels between Chronic Hepatitis and Cirrhotic Hepatic

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ABSTRACT

Background: Chronic hepatitis and cirrhotic hepatic are chronic liver disease that cause liver function abnormalities. One of them is hemostasis. Chronic hepatitis in long term can develop into cirrhotic hepatic. Hyperfibrinolysis, a hypercoagulable process, marked by increasing D-dimer level, enhance bleeding occurence. D-dimer level in chronic hepatitis and cirrhotic hepatic need to be measured and analyzed the difference.
Aim: To determine the difference of D-dimer level between chronic hepatitis and cirrhotic hepatic.
Methods: A cross sectional study was conducted on each 16 chronic hepatitis and cirrhotic hepatic patients in Goverment Hospital of Semarang City, Telogorejo Hospital and Kariadi Hospital during March 2014 to May 2014. D-dimer level was measured by latex enhance turbidimetric method. Mann Whitney test was applied to analyze the difference of D-dimer level between chronic hepatitis and cirrhotic hepatic.
Results: Median of D-dimer in chronic hepatitis was 190±82,30 µg/L and cirrhotic hepatic was 4860±57,17 µg/L. There was significant difference of D-dimer level between chronic hepatitis and cirrhotic hepatic (p=0,00).
Conclusion: There was significant difference of D-dimer level between chronic hepatitis and cirrhotic hepatic.
Key words: D-dimer, chronic hepatitis, cirrhotic hepatic

INTRODUCTION

Chronic liver disease consists of chronic hepatitis and cirrhotic hepatic[1]. The morbidity and mortality of this disease has significantly increased in developing countries primarily due to viral hepatitis, especially hepatitis B and C[2.,3]. Anatomically, cirrhotic hepatic according to Sherlock in Islamuddin (2011) is the state in which fibrosis extends with nodule formation in all parts of the liver, and the occurrence of liver fibrosis is not only on one lobule alone.

Liver failure in chronic liver disease results in hyperfibrinolysis.[4] Tissue plasminogen activator levels in hyperfibrinolysis increase because of the increased release by the endothelium due to lack of clearance from the liver. This condition leads to product degradation of fibrinogen and D-dimer.[5] D-dimer plasma levels are a marker of accurate fibrinolysis activity showing plasmin and thrombin activity.[6,7,8] Islamuddin (2011) states that D-dimer escalation is associated with bleeding in the esophagus in patients with hepatic cirrhosis[9]. Dhanunjaya *et al.* (2013) states that the increased fibrinolysis activity is an important factor responsible for the occurrence of bleeding tendency in liver disease. D-dimers is considered to be an important parameter for assessing fibrinolysis status in chronic liver disease[10].

Measurements of D-dimer levels are mostly performed on patients with cirrhotic hepatic, and are still poorly practiced in patients with chronic hepatitis. The differences in D-dimer levels on both diseases are not widely discussed in most studies. This study measures the differences of D-dimer levels in patients with chronic hepatitis and cirrhotic hepatic.

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METHODS

Cross sectional study was conducted from March to May 2014 in outpatients and inpatients of Telogorejo Hospital and Dr. Kariadi Hospital with consecutive sampling. The sample size was counted and there were 32 respondents consisting of 16 chronic hepatitis and 16 cirrhotic hepatic. Chronic hepatitis was diagnosed with positive HBsAg test for more than 6 months for positive chronic hepatitis B and anti-HCV infection for more than 6 months for positive chronic hepatitis C. Hepatic cirrhosis was diagnosed with clinical features of liver cell failure and portal hypertension; as well as the results of abdominal ultrasound examination with nodules, irregularity, increased ecogenesity, and liver atrophy with HBsAg and/or anti-HCV positive results.

The respondents were ≥ 21 years old and willing to join the study. Respondents who used drugs that cause coagulation abnormalities such as aspirin, heparin or warfarin; used contraceptive drugs; were pregnant; with history of malignancy or other organ malignancies; with history of coronary heart disease; stroke; infection/ sepsis; joint disease; autoimmune disease; lipemic and haemolysis samples were excluded in this study.

Respondent's identity, history related to chronic hepatitis and cirrhotic hepatic, history of other disease and physical examination were collected, afterward respondent's blood was taken for D-Dimer examination. The respondent's blood was taken through median cubital vein for about 3 cc and then was stored in vacuum tube containing sodium citras 3.2%. The blood was homogenized and centrifuged 3000 rpm for 5 minutes. The D-dimer content was checked without delay using tool and reagent Coagulometer Sysmex CA-1500 with latex enhance turbidimetric test method. The reference value of D-Dimer is 0-500 µg/L.

The collected data were in the form of interviews, physical examination and laboratory examination. The collected data was edited, coded, and incorporated into computer programs. The data of D-Dimer levels in chronic

hepatitis and cirrhotic hepatic were tested by Mann-Whitney. The significance level was assumed at p <0.05.

All research respondents were requested to give written informed consent and patient's identity was confidential. This research was approved by The Health Research Ethics committee of Faculty of Medicine Diponegoro University/ RSUP Dr. Kariadi Semarang number 070/ EC/FK-RSDK/2014.

RESULTS

The results yielded that there were 16 people with chronic hepatitis and 16 people with cirrhotic hepatic and the detailed information is presented in table 1.

The median age of chronic hepatitis was 40.50 ± 3.30 years with a minimum and maximum value of 22 and 67 years, while the median age of cirrhotic hepatic was 51.50 ± 2.29 years with a minimum and maximum value of 35 and 62 years. Men (68.8%) had more chronic hepatitis than women (31.2%), as did men (62.5%) suffered more from cirrhotic hepatic than women (37.5%).

There were more occurrences of hepatitis B (93.8%) than hepatitis C (6.2%) in both chronic hepatitis and cirrhotic hepatic. There were 18.8% of respondents with chronic hepatitis did not perform treatment, 56.2% of respondents with chronic hepatitis received treatment in hospital, and 25% of respondents with chronic hepatitis consumed supplements. Most cirrhotic hepatic patients (87.5%) received no hepatitis treatment while 12.5% of respondents with cirrhotic hepatic received hepatitis treatment at hospitals.

Four chronic hepatitis respondents and 13 cirrhotic hepatic respondents did not know how long they suffered from chronic hepatitis. The minimum and maximumvalue of suffering duration in chronic hepatitis are 7 months and 252 months respectively (table 1). Mean while, the minimum and maximum value of duration of suffering from hepatitis in cirrhotic hepatic were 108 months and 168 months (table 1).

Not all cirrhotic hepatic respondents knew when they were diagnosed with cirrhotic hepatic. Three cirrhotic hepatic respondents knew when they were diagnosed, while the rest of them did not know. The minimum and maximum duration of suffering from cirrhotic hepatic were 3 months and 72 months (Table 1).

D-dimer levels in chronic hepatitis and cirrhotic hepatic were tested using Mann-Whitney test as shown on Table 2. Based on Table 2, the median of D-dimer levels in the chronic hepatitis group were 190 ± 82.30 µg/L with the minimum value of 190 µg/L and the maximum value of 1211 µg/L. Three respondents in the chronic hepatitis group had D-dimer levels exceeding the cut off value, while 13 respondents had D-dimer level below the cut off value. The three respondents suffered from chronic hepatitis B. There was only one respondent with chronic hepatitis C with D-dimer levels below the cut-off value.

The overall cirrhotic hepatic respondents based on Table 2 have D-dimer levels that exceed the cut-off value. The median of D-dimer level was 4860 ± 57.17µg/L with the minimum value of 3955 µg/L and the maximum value of 4860 µg/L. Cirrhotic hepatic respondents with chronic hepatitis C had D-dimer level that exceeds the cut off value. It was the same case as other respondents with a history of chronic hepatitis B.

Table 1. Distribution of respondents based on individual characteristics

Respondent characteristics	Variable	
	Chronic Hepatitis	**Cirrhotic Hepatic**
Age (years) Median ± SE Min-max value	 40,50± 3,30 22 – 67	 51,50± 2,29 35 – 62
Gender Male (%) Female (%)	 11 (68,8) 5 (31,2)	 10 (62,5) 6 (37,5)
Type of Hepatitis Hepatitis B (%) Hepatitis C (%)	 15 (93,8) 1 (6,2)	 15 (93,8) 1 (6,2)
Hepatitis Treatment Untreated (%) Antiviral Therapy (%) SuplementTherapy (%)	 3 (18,8) 9 (56,2) 4 (25)	 14 (87,5) 2 (12,5) 0 (0)
Duration of suffering from Hepatitis (Months) Min value – max value	 7 - 252	 108 – 168
Duration of suffering from cirrhotic hepatic (Months) Min value – max value	 -	 3 – 72

Table 2. The Differences of D-Dimer levels in chronic hepatitis and cirrhotic hepatic

D-Dimer level (µg/L)	Variable		P
	Chronic Hepatitis	**Cirrhotic Hepatic**	
Median ± SE Min value-max value	190 ± 82,30 190 - 1211	4860 ± 57,17 3955 – 4860	0,00*

* the statistical test was conducted by using Mann-Whitney test and the statistical significance was achieved if p <0.05.

DISCUSSION

The results show that D-dimer levels below the cut-off value in most chronic hepatitis respondents are not in line with the results of some other studies. Li *et al.* (2011) stated that chronic hepatitis had elevated D-dimer levels as occurs in acute hepatitis and cirrhotic hepatic.[11] Another researcher, Pan *et al.* (2006) found out that D-dimer levels in chronic hepatitis increase, but their levels were lower when compared with acute hepatitis and cirrhotic hepatic[12].

Respondents in the chronic hepatitis group has D-dimer levels that are mostly below the cut off value. This is probably the results of adequate antiviral therapy, supplement consumption as hepatoprotectors, inactive viruses either because of therapy or not being treated, and a good liver condition that does not progress to liver failure. The opposite happened to all three respondents whose D-dimer levels exceed the cut off value. The increased D-Dimer levels probably happened because of the active virus proven by viral load examination, inadequate treatment,untreated respondents, or the long duration of chronic hepatitis contraction that lead to cirrhotic hepatic because respondents are not biopsied. Those factors are not analyzed in this study, hence, the correlation between those factors with the D-dimer levels exceeding the cut off value in chronic hepatitis cannot be clearly stated.

D-dimer levels that exceeds the cut-off value occurred on cirrhotic hepatic group are in line with other research results. Wesam *et al.* (2011) stated that the D-dimer levels in all respondents of cirrhosis hepatic increased above the

cut off value.[6] Dhanunjaya *et al.* (2013) stated that the rise of the D-dimer levels was in line with the increasing severity of chronic liver disease based on Child Pugh scores with p-value of 0.001, while the same was written by Islamuddin (2011) [9,10] Saray *et al.* (2012) reported that the mean of D-dimer levels increased significantly in patients with cirrhotic hepatic compared with healthy controls with p value of <0.001.[13] Gursoy *et al.*(2005) stated that there was a significant increasing in D-dimer levels in cirrhotic hepatic, and D-dimers were important to reveal the prognosis of cirrhotic hepatic to decompensated cirrhosis[14.]

The analysis of D-dimer level differences in chronic hepatitis and cirrhotic hepatic based on Table 2 shows statistically significant differences with p values of 0.00. The results of this study are in accordance with the research results conducted by Pan *et al.* (2006). They conducted a research with 54 chronic hepatitis B patients and 25 cirrhotic hepatic patients with hepatitis B history. The results showed that the D-dimer levels in cirrhotic hepatic are significantly higher than those of chronic hepatitis[12]. Li *et al.* (2011) stated that the levels of D-dimer in 33 patients with cirrhotic hepatic with hepatitis B history were higher than the D-Dimer levels of 35 patients with chronic hepatitis B and significantly different.[11] Another researcher, Zhu *et al.* (2009) conducted a research on 87 cirrhotic hepatic patients with hepatitis B history and 42 patients with chronic hepatitis B. The result showed that the D-dimer levels of cirrhotic hepatic patients are significantly higher than those of chronic hepatitis[15].

The D-dimer levels difference in chronic hepatitis and cirrhotic hepatic are caused by different liver damage in both situations. Chronic hepatitis is a histological liver disease with necrosis, inflammation, and fibrosis of hepatocytes in various levels, light for more than 6 bulan.[3] Cirrhosis is a condition of fibrosis and scar tissues on the liver are replaced by hard fibrous nodules, both small and large and fibrosis bands that contract and encircle the hepatocytes. The normal architecture and function of liver are disrupted.[16] In chronic hepatitis, there are abnormalities of hepatic function, but its function can still be compensated, in contrast to cirrhotic hepatic, its function cannot be compensated.

The increased D-dimer levels in cirrhotic hepatic and a small proportion of chronic hepatitis are caused by tissue plasminogen activator (tPA) levels produced by endothelium. This situation begins with liver clearance ability of tPA is reduced due to the decreased liver function[17]. It will increase the plasmin activity that releases the fibrin which will be converted into D-dimer. Plasminogen activator inhibitor-1 produced by the endothelium fails to balance this state. This condition is called as hyperfibrinolysis. The D-dimer levels will rise later on[8,18,19,20]

This study shows that mostly D-dimer levels in the chronic hepatitis group exceed the cut-off value, while the D-dimer levels in the cirrhotic hepatic group entirely exceed the cut-off value. The D-dimer levels clearly differed significantly between the two groups indicating poor development of hepatic disease from chronic hepatitis to cirrhotic hepatic. This study is limited to investigate the differences in D-dimer levels in chronic hepatitis and cirrhotic hepatic only. The results which show that there is significant differences can be used as a basis for further research on D-Dimer levels as either a parameter or a prognostic factor for the development of chronic hepatitis to cirrhotic hepatic. D-dimer monitoring on chronic hepatitis patients is required in order to monitor the increased levels that may indicate poor liver development. The limitation of this study is the difficulty of getting respondents for both populations, requiring more multi-center research.

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REFERENCES

1. Ivanova L, Russev V. Chronic liver disease and parenterally transmitted hepatitis viruses. Eur J. Inflamm 2007; 5(1):1-6.
2. Ricardo R, Rui TM, Miguel S. Classification and staging of chronic liver disease from multimodal data. IEEE Trans Biomed Eng. 2012;60(5):1336-44.
3. Guntur H. Perspektif masa depan imunologi infeksi. Surakarta: Sebelas Maret University Press; 2006. p. 25-30.
4. Senzolo M, Burra P, Cholongitas E, Burroughs AK. New insights into the coagulopathy of liver disease and liver transplantation. World J Gastroenterol. 2006;12(48):7725-36.
5. Ayesha B, Shahida M. Haemostatic abnormalities in chronic liver disease. Haematology Updates 2010. 2010:143-7.
6. Wesam AI, Sara A, Ameer H, Hatem AEL, Khalid AEW, Mahmoud OA, Doaa GE. Evaluation of plasma D-dimer level in patients with chronic liver disease. Researcher. 2011;3(10):13-8.
7. Hernomo K. Hipertensi portal. Ilmu Penyakit Dalam. Jakarta: Balai Penerbit FKUI; 2007. p. 280-7.
8. Jody LK. Hemostatic defects in end stage liver disease. Crit Care Clin. 2005;21:563-87.
9. Islamuddin. Hubungan peningkatan kadar D-Dimer dengan perdarahan varises esofagus pada sirosis hati stadium dekompensata. Padang: Universitas Andalas; 2011. p. 1-60.
10. Dhanunjaya Y, Usha A, Anand CV. Study of plasma D-Dimer levels in various stages of liver disease. J Liver. 2013;2(2):1.
11. Li XF. The clinical significance of plasma fibrin degradation products and D-dimer in patients with type B hepatitis and liver cirrhosis. International Journal of Laboratory Medicine. 2011;08:1-4.
12. Pan YH, Huang X, Zhang F. Clinical significance of the determinations of plasma fibrinogen and D-dimer to hepatitis B. Journal of Chinese Microcirculation. 2006;05:1-4.
13. Saray A, Mesihovic R, Gornjakovic S, Vanis N, Mehmedovic A, Nahodovic K, Glavas S Association between high D-dimer plasma levels and ascites in patients with liver cirrhosis. Medicinski Arhiv 2012;66(6):372-4.
14. Gürsoy S, Başkol M, Torun E, Yurci A, Soyuer I, Eser B, Güven K. Importance of anticoagulant proteins in chronic liver diseases. Turk J Gastroenterol. 2005;16(3):129-33.
15. Zhu D, Zhu Q, Zhong ZQ. Evaluation of plasma D-dimer and fibrinogen in liver cirrhosis. Chinese Journal of Health Laboratory Technology. 2009;01:1-4.
16. Elizabeth JC. Buku saku patofisiologi. Jakarta: EGC; 2009. 660.
17. Armando T, Pier MM. The coagulopathy of chronic liver disease. New England Journal Medicine. 2011;365(2):147-56.
18. Domenico F, Andrea C, Francesco V. Hyperfibrinolysis in liver disease. Clin Liver Dis. 2009;13:21-31.
19. Yolanda LA, Jose AP. Endothelial cell and hemostatic activation in relation to cytokines in patients with sepsis. Thrombosis Reasearch. 1999;94:95-101.
20. Marcel L, Tymen TK Eric G,Hugo TC. Infection and inflammation and the coagulation system. Cardiovascular Research. 2003;60(1):36-9.