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## CORRELATION OF AA INDEX WITH DEGREE OF LIVER FIBROSIS IN CHRONIC HEPATITIS B PATIENTS

**Rika Andriany, Ibrahim Abdul Samad, Mansyur Arif**

Department of Clinical Pathology, Faculty of Medicine, Hasanuddin University, Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia.  
E-mail: riekarieka@rocketmail.com

### ABSTRACT

Chronic Hepatitis B is a global problem, and Indonesia has a high prevalence. A liver biopsy is a good standard for diagnosing and staging liver fibrosis in chronic hepatitis B patients but it has many disadvantages so it is difficult to be used as a routine examination. Research on index-based serum marker is helpful in predicting liver fibrosis. This research aimed to the alpha-fetoprotein (AFP) and activated partial thromboplastin time (APTT) index or AA index in relation to the degree of liver fibrosis in chronic hepatitis B patients. This study was a retrospective cross-sectional study in the Dr. Wahidin Sudirohusodo Hospital Makassar by taking data from the medical records of chronic hepatitis B patients from January 2015 to December 2016. Samples were chronic hepatitis B patients who were tested for AFP, APTT, and Fibroscan. The result showed a total of 79 chronic hepatitis B patients, 23 with severe fibrosis, 9 with moderate fibrosis, 26 with mild fibrosis, and 21 with no fibrosis. The Spearman correlation test showed a significant correlation between the AA index and the degree of fibrosis ( $p < 0.001$ ) and showed a positive correlation between both of them with a powerful correlation ( $r = 0.830$ ). The oneway ANOVA test showed a significant difference between the AA index and the degree of fibrosis ( $p < 0.001$ ). The results of this study indicated that the AA index could be used as a predictor of fibrosis in chronic hepatitis B patients. It is suggested to do another study with a larger sample based on the degree of fibrosis.

**Key words:** AFP, APTT, AA index, the degree of fibrosis, chronic hepatitis B

### INTRODUCTION

Hepatitis B is an inflammation of the liver caused by the hepatitis B virus (HBV). This disease has a high prevalence, about 2 billion people around the world have been infected by HBV and 240 million of which become chronically infected. Data from Indonesia Ministry of Health 2014 stated that about 28 million people have hepatitis B and C, 14 million of them have the potential to be chronically infected and 1.4 million of the chronically infected have the potential to progress to liver cancer.<sup>1-3</sup>

Liver cirrhosis is a complication of liver disease characterized by loss of normal hepatocytes and irreversible scarring of the liver. The World Health Organization (WHO) defined cirrhosis histologically as a diffuse liver abnormality characterized by fibrosis and conversion of normal liver tissue to abnormal nodules.<sup>1,3</sup>

Fibrosis is a result of fibrogenesis which is the process of scarring that occurs due to damage of liver tissue. This damage can be necrosis or hepatocellular apoptosis with a variety of causes, including viral infections, parasites or bacteria, autoimmune processes, alcohol and metabolic

disorder such as fatty liver. The on going liver damage results in fibrotic tissue extending to all parts of the liver. Besides the formation of diffuse fibrotic septa, another essential response is the collapse of the liver lobules and the regrowth of the liver cells that form regenerated nodules which eventually alter the entire liver structure.<sup>2,4-7</sup>

The gold standard examination to assess the degree of fibrosis of the liver is liver biopsy. However, because a biopsy is expensive and invasive, it is difficult to make it a routine examination. Fibroscan is sign of progress in non-invasive imaging of liver fibrosis. The Fibroscan imaging technique has demonstrated its superiority in determining the degree of liver fibrosis with high accuracy and is thought to replace liver biopsy as a gold standard. This approach can be more sensitive to determine the degree of liver fibrosis by measuring the liver flexibility associated with fibrosis degree expressed by kilo Pascals (kPa).<sup>1,3,4</sup> Never the less, the accessibility of health service centers to Fibroscan is still minimal, so a method to determine the degree of fibrosis which can be an alternative to Fibroscan is needed.

The alpha-fetoprotein (AFP) and activated partial

thromboplastin time (APTT) index or AA index is one of the non-invasive indices used as a predictor of liver fibrosis in chronic hepatitis B patients. The AA index is a number obtained from the formula:  $\log \text{ index} = - 9.164 + 0.114 \times \text{AFP} + 0.236 \times \text{APTT}$ . Research by Feng *et al.* showed a positive correlation between AA index and degree of liver fibrosis in chronic hepatitis B patients.<sup>2,8</sup>

The AFP value has long been used as a tumor marker for hepatocellular carcinoma. A study by Liu *et al.* stated that elevated serum AFP levels correlate with the degree of liver fibrosis in chronic hepatitis B patients. Activated partial thromboplastin time or APTT aims to assess intrinsic coagulation factor activity, which APTT values correlate to the severity of coagulation factor disorders associated with the degree of liver damage.<sup>8,9</sup>

Study on the correlation of index AA with the degree of liver fibrosis to our knowledge has never been published in Indonesia, especially in Makassar. Based on the mentioned background, researchers conducted this study to assess the correlation of AA index with a degree of liver fibrosis in chronic hepatitis B patients at the Dr. Wahidin Sudirohusodo Makassar.

**METHODS**

This study was a retrospective study with a cross-sectional approach which was done by taking secondary data of chronic hepatitis B patients in the Medical Record Installation of the Dr. Wahidin Sudirohusodo Makassar from January 2015 to December 2016. The population of this study was the medical record data of chronic hepatitis B patients in the Dr. Wahidin Sudirohusodo Hospital Makassar, the sample was taken from the population undergoing AFP and APTT test at the Laboratory and Fibroscan at Gastroenterohepatology Subdivision of the Dr. Wahidin Sudirohusodo Hospital. Inclusion criteria were patients diagnosed with chronic hepatitis B by an internist based on history, physical examination and supporting test, while exclusion criteria were incomplete medical record data. Correlation of AA index and the degree of liver

fibrosis was analyzed using the Spearman correlation test. Ethical clearance was obtained from the Commission of Medical Research Ethics, Faculty of Medicine, Hasanuddin University Dr. Wahidin Sudirohusodo Hospital Hasanuddin University Hospital, Makassar.

**RESULTS AND DISCUSSION**

From the data collected between January 2015 and, December 2016 we obtained a total of 79 patients diagnosed with chronic hepatitis B with the characteristics of the sample as shown in Table 1. The data showed there were more males which were 52 subjects (65.8%) than females which were 27 subjects (34.2%). The data also showed more subjects diagnosed with chronic hepatitis B in the age group of 41-50 years which was 22 subjects (27.8%). From this study, the highest number of the samples found based on a degree of fibrosis group was the mild group which was 26 subjects (32.9%).

**Table 1.** Subjects characteristics

Variables		n = 79	(%)
Sex	Male	52	65.8
	Female	27	34.2
Age	21 - 30	9	11.4
	31- 40	14	17.7
	41 - 50	22	27.8
	51 - 60	15	19.0
	61 - 70	15	19.0
	71 - 80	4	5.1
Fibroscan (kPa)	< 5 (Normal)	21	26.6
	5 - 9 (Mild)	26	32.9
	9.1-14.5 (Moderate)	9	11.4
	>14.5 (Severe)	23	29.1

The distribution of sex and age in this study was consistent with Hadi *et al.* study that the incidence of chronic liver disease worldwide, including in Indonesia, was more prevalent in males than females (2-4: 1) with an average age in the range of 30-59 years (with the peak around 40-49 years). The national data reported the comparison of males and females was 2.1: 1 with the mean age of 44 years.<sup>1,3</sup>

**Table 2.** Comparison of AFP values based on Fibroscan results

Fibroscan	N	Min	Max	Mean ±SD	p*
< 5 (Normal)	21	0.77	1.94	1.35 ± 0.38	0.001
5-9 (Mild)	26	0.86	6.2	3.05 ± 1.39	
9.1-14.5 (Moderate)	9	4.80	21.72	10.45 ± 5.48	
>14.5 (Severe)	23	16.45	400	304.73 ± 46.54	

\*Oneway ANOVA test

**Table 3.** Comparison of APTT values based on fibroscan results

Fibroscan	N	Min	Max	Mean ±SD	p*
< 5 (Normal)	21	22.5	32.4	27.05 ± 3.19	0.03
5-9 (Mild)	26	21.2	44.9	28.93 ± 4.48	
9.1-14.5 (Moderate)	9	22.4	43.30	31.78 ± 6.6	
>14.5 (Severe)	23	24.9	43.10	30.19 ± 3.79	

\*Oneway ANOVA test

**Table 4.** Comparison of the AA Index based on fibroscan results

Fibroscan	N	Min	Max	Mean ±SD	p*
< 5 (Normal)	21	0.001	0.007	0.003 ± 0.001	<0.001
5-9 (Mild)	26	0.009	0.144	0.127 ± 0.004	
9.1-14.5 (Moderate)	9	0.13	1.201	0.675 ± 0.009	
>14.5 (Severe)	23	1.157	2.77	1.786 ± 0.128	

\*Oneway ANOVA test

The study results in Table 2 showed that there was a significant correlation between AFP and the fibroscan group which was grouped into mild, moderate, and severe. The results of this study were consistent with the study by Liu *et al.*, who found that high AFP correlated to the degree of liver fibrosis. A marked increase in AFP values indicated an increasingly widespread inflammation, necrosis and hepatocellular injury.<sup>8,9</sup>

The study results in Table 3 using one-way ANOVA test showed a significant difference in APTT values between the four groups of fibrosis degree in chronic hepatitis B patients (p=0.03). Siddiqui's study found that APTT in patients with severe fibrosis had a significant prolongation. This result was due to the reduced synthesis of coagulation factors, which played a role in hemostasis, as a result of diffuse liver damage. The results of this study showed that the maximum value of APTT was higher in the mild group. This condition might be due to the sampling method which was taking secondary data from the medical records, so more samples were obtained in mild degree compared to a moderate and severe degree. Besides that, the limitation of this study was that it was difficult to exclude patients with bleeding, anticoagulant therapy, and others due to some incomplete medical records.<sup>8,10</sup>

The study results in Table 4 using one-way ANOVA test showed a significant difference in the value of AA index between the four groups of fibrosis degree (p<0.001). This result was consistent with the previous study by Feng *et al.*, which showed that the AA index <0.007 indicated no significant fibrosis and AA index >0.127 indicated significant fibrosis. Results of this study found that the higher the AA

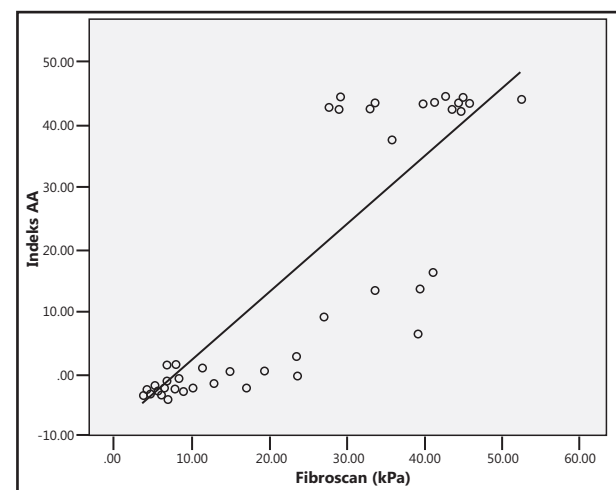
**Table 5.** Correlation between AA index with the degree of liver fibrosis

AA Index	Fibrosis degree
	r = 0.830
	p < 0.001
	n = 79

\*Spearman correlation

index, the higher degree of fibrosis was in chronic hepatitis B patients.<sup>8</sup>

The Spearman correlation in Table 5 test showed a significant relationship between AA Index and degree of fibrosis in chronic hepatitis B patients (p<0.001) and the correlation between the two showed a positive direction with a robust correlation (r=0.830). This result was consistent with a previous study conducted by Feng *et al.*, in which the AA index was positively correlated with liver fibrosis in chronic hepatitis B patients.<sup>8</sup>



**Figure 1.** Scatterplot of AA index and fibroscan results

Scatterplot in Figure 1 also showed a strong correlation between AA index and fibroscan result. This study had limitations that it was solely based on secondary data from the medical records so it was difficult to avoid bias as well as it did not take into account other risk factors of chronic hepatitis B.

### CONCLUSION AND SUGGESTION

Based on this study, it can be concluded that AA index can be used as a degree of liver fibrosis predictor in chronic hepatitis B patients so that it is expected to be one of the references in diagnosis and treatment follow up. The researchers suggest further studies with larger samples based on a degree of fibrosis.

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