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COMPARISONS OF FIBRO Q INDEX AND FIB-4 IN VARIOUS STAGES OF CHRONIC B HEPATITIS

Evy Adrianti, Liong Boy Kurniawan, Ibrahim Abdul Samad

Department of Clinical Pathology, Faculty of Medicine, Hasanuddin University/Wahidin Sudirohusodo Hospital, Makassar, Indonesia.
E-mail: evyadrianti@gmail.com

ABSTRACT

Fibro Q and FIB-4 index are non-invasive biomarkers to evaluate liver fibrosis in chronic hepatitis. This study aimed to evaluate and compare the diagnostic accuracies of Fibro Q and FIB-4 index compared with Fibroscan in chronic B hepatitis. This research was a cross-sectional study including 145 patients with chronic B hepatitis who had a Fibroscan examination at the Dr. Wahidin Sudirohusodo Hospital during July 2014-June 2016. The clinical data included sex, age, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), platelet, Prothrombin Time (PT)/International Normalized Ratio (INR). Fibro Q and FIB-4 index were compared with Fibroscan to predict various fibrotic degrees of chronic B hepatitis patients. There were significant differences compared to Fibroscan, the highest Fibro Q average was found in the medium degree of fibrosis and the lowest in the normal Fibroscan ($p < 0.01$) while the highest FIB-4 average was found in the high degree of fibrosis and the lowest in the normal Fibroscan ($p < 0.001$). Fibro Q sensitivity and specificity test against Fibroscan have AUC value of 0.579 by using a 9.33 cut-off with a sensitivity of 80.5% and specificity of 28.1%, while FIB-4 has AUC value of 0.723 by using cut-off 14.31 with sensitivity 80.5% and specificity 46.9%. These results show that both Fibro Q and FIB-4 index can be used to assess liver cirrhosis as well as Fibroscan. FIB-4 Index has a better diagnostic value compared to Fibro Q, so this marker can be used as a simple screening instrument.

Key words: Chronic B hepatitis, Fibro Q, FIB-4, Fibroscan

INTRODUCTION

Chronic hepatitis B is a health problem especially in Asia where there are at least 75% from 300 million individuals with positive HbsAg throughout the world.¹ According to Riset Kesehatan Dasar (Riskesdas) in 2013, people diagnosed with Hepatitis in Health Service Facilities according to symptoms that show a two fold increase compared to data in 2007 and 2013, this indicates that there is potential for trouble if measures are not taken to control this.^{1,2}

Liver cirrhosis is the last stage of progressive diffuse liver fibrosis that is marked by distortion of the liver architecture and the formation of regenerative nodules. Liver fibrosis is caused by activation of the liver's stellate cells. This activation is triggered by the release from hepatocytes and Kupffer cells. Liver stellate cells are the leading producer of the Extracellular Matrix (MES) after the injury to the liver. The formation of MES is due to fibroblast-like tissue produced by the stellate cell and influenced by a couple of cytokines such as transforming growth factor β (TGF- β) and Tumor Necrosis Factor (TNF α).^{1,3} Serum markers reflect the extracellular matrix components when liver

destruction occurs. Liver cells destruction will be followed by the release of enzymes inside the liver, such as aminotransferases (AST/ALT). AST/ALT enzymes are one of the indicators to find out the extent of damages of the liver, and whether hepatocytes are undergoing inflammation or not, this will decrease the level of thrombopoietin (TPO) that influences thrombopoiesis following the lysis of thrombocytes causing thrombocytopenia. The decrease of thrombocytes is a sign of the increase of fibrosis in patients with chronic Hepatitis B.⁴⁻⁸

This research's purposes was to assess and compare the Fibro Q index and FIB-4 with Fibroscan to predict the level of liver fibrosis in patients with chronic B hepatitis.

METHODS

This research was cross-sectional and done in the Clinical Pathology Installation of the Dr. Wahidin Sudirohusodo Hospital Makassar throughout July 2014 – June 2016. Data were obtained from 145 subjects that were diagnosed with chronic B hepatitis, fulfilled the inclusion and exclusion criteria and were examined with Fibroscan.

Laboratory examinations linked with Fibro Q index, and FIB-4 using AST and ALT measured with kinetic colorimetric method on ABX Pentra 400, (reference range: 6 – 40 IU/L), Prothrombin Time (PT), International Normalized Ratio (INR) was clotting time measured according to the standard value of prothrombin ratio measured with the hemostasis automatic equipment Sysmex XT 2000i, (reference range: (150 – 400) x 10⁹ U/L).

1. Index Fibro Q was obtained from this calculation:^{7,9}

$$\text{Indeks Fibro Q} = (10 \times \text{age (years)} \times \text{AST} \times \text{PT INR}) / (\text{PLT} \times \text{ALT})$$

2. Index FIB-4 was obtained from this calculation:^{7,8}

$$\text{FIB-4} = \text{age (year)} \times \text{AST (U/L)} / \text{PLT (10⁹/L)} \times \text{ALT (U/L)}^{1/2}$$

3. Fibroscan is a technology of Transient Elastography (TE) that can determine the degree

of liver fibrosis, that is as follows: Normal (F0): <5 kPa; Mild (F1): 5-9 kPa; Moderate (F2-F3): 9.1–14.5 kPa; Severe (F4): > 14.5 kPa.¹⁰

Data analysis was done by using Kolmogorov-Smirnov tests to asses the distribution of Fibroscan data, Fibro Q index and FIB-4. Spearman's Correlation test was used to see the correlation between fibroscan variables and Kruskal-Wallis to see the mean of variables according to the results of Fibroscan. Results were significant if $p < 0.05$.

RESULTS AND DISCUSSION

From July 2014 until June 2016 there were 145 subjects of chronic B hepatitis, most of the subjects were male (66.9%) with the mean age of 16-67 years old. Laboratory results show an index Fibro Q in the range of 3.31 until 906.88 with a mean of 65.23. Fibroscan has a range of 0.60 until 30.30 with the mean of 7.88 as shown in Table 1.

Table 1. Biologic and laboratory characteristics (n=145)

Variable		N	%	Range	Mean±SD
Sex	Male	97	66.9		
	Female	48	33.1		
	<30 y.o.	30	20.7		
Age	30 - 39 y.o.	44	30.3		
	40 - 49 y.o.	40	27.6	16 – 67	39.7 ± 11.5
	≥ 50 y.o.	31	21.4		
Fibro Q +index				3.31 - 226.03	21.12 ± 24.08
FIB -4 index				3.16 - 906.88	65.23 ± 114.14
Fibroscan				0.60 - 30.30	7.88 ± 4.56

Source: Secondary data

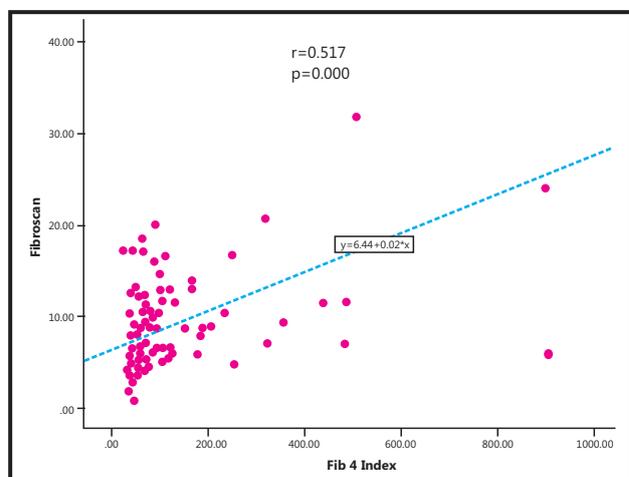
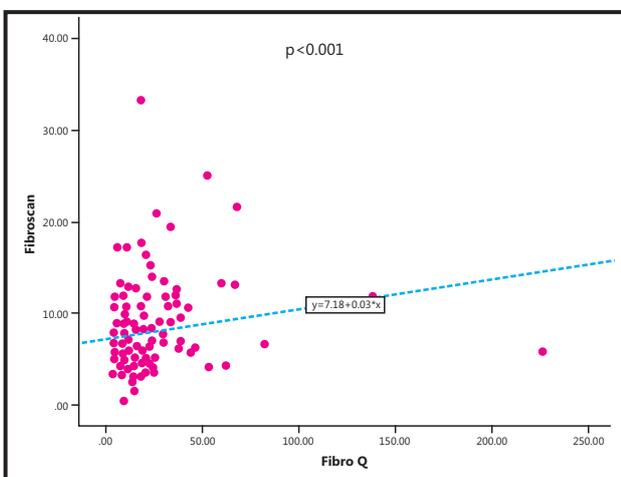


Figure 1 & 2. The Correlation between Fibro Q with Fibroscan and the correlation of Fib4 with Fibroscan

Table 2. Comparison of Fibro Q and FIB-4 index mean with Fibroskan

Variables	Fibroskan	N	Median	Mean	SD	*p
Fibro Q index	Normal	32	14.35	16.54	12.29	0.005
	Mild	75	13.30	19.11	26.88	
	Moderate	28	25.75	29.31	26.40	
	Severe	10	22.17	27.95	18.90	
FIB-4 index	Normal	32	16.30	25.30	38.12	0.000
	Mild	75	26.93	47.38	67.90	
	Moderate	28	52.46	101.65	121.88	
	Severe	10	72.43	224.89	283.18	

*Kruskal Wallis

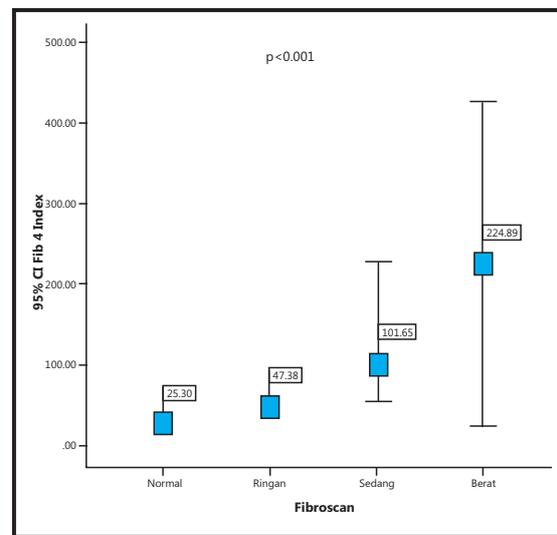
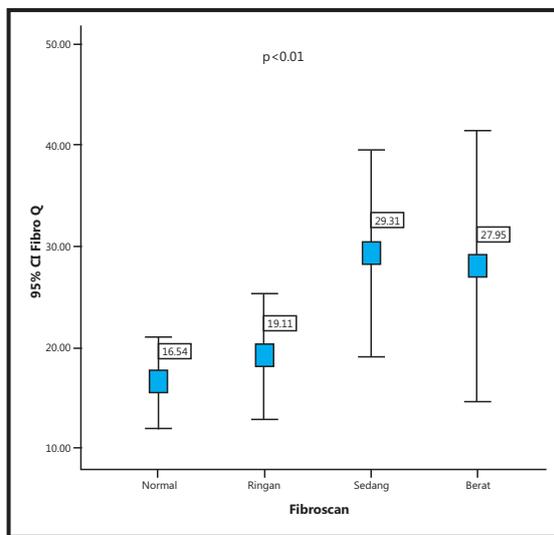


Figure 3 & 4. The Comparison of Fibro Q index mean and comparison of FIB-4 index mean

The relationship of Fibro Q and FIB-4 index with Fibroskan had a significant positive correlation between Fibro Q index with Fibroskan, the higher the Fibro Q index ($p < 0.01$) (Figure 1). There was a significant positive correlation between the FIB-4 index with Fibroskan, the higher the FIB-4 index, the higher Fibroskan ($p < 0.001$) (Figure 2). According to the correlation coefficient score, it can be concluded that the FIB-4 index had a bigger correlation with Fibroskan ($r = 0.517$) while the Fibro Q index had a smaller correlation ($r = 0.255$).

The Kruskal-Wallis test was done to see the mean comparison Fibro Q and FIB-4 index according to Fibroskan results (Table 2).

There was a significant difference of the mean of Fibro Q index according to Fibroskan, where the Fibro Q index was the highest in moderate stage (29.31) and the lowest in the normal stage (16.54) ($p < 0.01$) (Figure 3).

There was a significant difference of the FIB-4 index mean according to Fibroskan, mean index of FIB-4 according to Fibroskan, the highest mean for

the FIB-4 index was in the severe stage (224.89) and lowest in the normal stage (25.30) ($p < 0.001$). It could be concluded that FIB-4 index mean raised according to the damage of the liver (Figure 4).

The subject of this research were 145 patients, mostly male (66.9%) with the highest age group of 30-39 years old (30.3%) and 40-49 years old (27.6%). These results are in correlation with Riskesdas 2013 where the prevalence of hepatitis was higher in males than females (2-4:1) and higher in the age group of 45-54 years old.^{2,12}

The relationship of Fibro Q and FIB-4 index with Fibroskan had a significant positive correlation between the Fibro Q and FIB-4 index with Fibroskan ($p < 0.01$). These results were in concordance with research by Mallet *et al.* in 372 chronic hepatitis patients, with an FIB-4 index that had a diagnostic accuracy that was 86% better to estimate liver fibrosis, Area Under Curve (AUC) 0.81 ($p < 0.001$) with a cut-off of 1.45 sensitivity of 71.1% and specificity 73.1%. Zeng *et al.* retrospective study stated 308 patients with liver cirrhosis had a significant

correlation between liver fibrosis and FIB-4 and Fibro Q index.^{12,13}

The comparison of Fibro Q and FIB-4 index towards Fibroscan mean in this research showed a significant correlation ($p < 0.05$), this indicated that an increase in Fibro Q and FIB-4 index value was proportional with Fibroscan results. The higher each marker the more severe the degree of liver fibrosis. This result was in accordance with the previous hypothesis, that each marker that increases was proportional to the degree of the liver fibrosis. Fibro Q and FIB-4 index use the AST and platelet as an indicator in its formula, so the increase of AST and decrease of platelets are in concordance with the degree of liver fibrosis. Serum Alanine Transferase (ALT) that is released from the liver tissue into the circulation is in proportion with the degree of hepatocellular destruction, and its levels are supposed to be one of the most sensitive signs of liver destruction.³ The increase in AST serum levels is correlated to the liver cells destruction that triggers the release of AST from the mitochondria and the decrease in AST clearance due to liver fibrosis. The decrease in platelets due to the decline of thrombopoietin production by damaged hepatocytes. ALT is an intracellular enzyme that is in the cytoplasm of liver cells, so ALT is released when there is mild liver damage, in contrast with AST that is released in further hepatocyte destruction.¹³⁻¹⁵

Sensitivity and specificity results of Fibro Q towards Fibroscan, in mild, moderate and severe fibrosis condition had an AUC of 0.579 with a cut-off of 9.33 with a sensitivity of 80.5% and specificity 28.1%. It conclude that, this stadium Fibro Q index was not good enough to predict the degree of chronic hepatitis.

Research conducted by Hsieh *et al.* in 140 patients with chronic B hepatitis reported that Fibro Q index could predict significant fibrosis with an AUC of 0.783, 77.1% which is substantial for fibrosis.⁹ Mild and moderate fibrosis have a fluctuating increase of AST due to the resolution phase from the necroinflammation activity of hepatocytes and usually without acute flare and stabile transaminase levels.^{3,12-14}

Sensitivity and specificity of FIB-4 index towards Fibroscan, in mild, moderate and severe fibrosis has an AUC of 0.723, indicating that FIB-4 index is not good enough to predict the degree of liver fibrosis in that stadium using a cut-off of 14.31 with a sensitivity of 80.5 % and specificity of 46.9%. The research conducted by Lin *et al.* in chronic hepatitis C patients had an AUC in cirrhosis of 83% with a cut-off of 1.0 with a sensitivity of 76% and specificity of 72%.

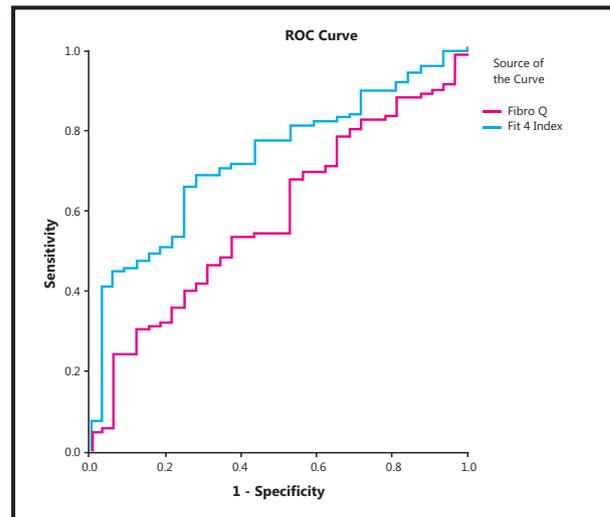


Figure 5. ROC curve of Fibro Q and FIB-4 index

Yuanyuan *et al.* research with an AUC of 0.78 and cut-off of 1.45 sensitivity 78% and specificity of 65% to evaluate severe fibrosis. Almost in concordance with a study by Kai *et al.* in 2372 chronic hepatitis B patients, with an AUC of 0.723, AST/platelet/ GGT/AFP (APGA) index: 0.708 and AST/platelet ratio index (APRI): 0.757.¹¹⁻¹⁶

An analysis of Fibro Q and FIB-4 index on research subjects with mild and moderate fibrosis consecutively have an Area Under The Receiver Operating Characteristics (AUROC) 0.579 dan 0.723 that shows a poor AUC (Figure 5). Eventhough the FIB-4 index had a higher AUC than Fibro Q index, the positive predictive value was 84.3% and negative predictive value 40.5%, and also Fibro-Q has a positive predictive value of 79.8% and a negative predictive value of 29.0%. This results showed that the Fibro-Q and FIB-4 index could be used to evaluate liver cirrhosis like Fibroscan. Both markers had high sensitivity (80.0%-91.3%) to assess liver cirrhosis, so both markers could be used as an ingenuous screening tool to help clinicians in health facilities that did not have Fibroscan.

CONCLUSION AND SUGGESTIONS

There is a significant correlation between Fibro Q and FIB-4 index towards Fibroscan results in patients with chronic hepatitis B. FIB-4 index has a higher diagnostic value towards Fibroscan compared to Fibro Q index.

Each marker has high sensitivity in evaluating the degree of liver fibrosis but low specificity, so the markers can be used as a straight forward screening tool in health facilities that do not have Fibroscan.

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