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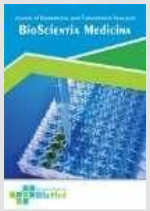

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Correlation of Platelet-Derived Growth Factor-BB Levels as a Biomarker of Liver Fibrosis with the Degree of Fibrosis Based on Fibroscan in Chronic Hepatitis B Patients

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A B S T R A C T

Background: Liver fibrosis is scar tissue that forms due to excessive accumulation of ECM proteins due to chronic liver injury, mediated by cytokines involving complex cellular interactions, such as platelet-derived growth factor-BB (PDGF-BB). In Indonesia, no research has been conducted to determine the correlation between PDGF-BB levels and the degree of liver fibrosis based on fibroscan. The aim of this study is to assess the correlation between PGDF-BB levels and the degree of liver fibrosis based on fibroscan in chronic hepatitis B. **Methods:** A cross-sectional study was conducted on the chronic hepatitis B population at the internal medicine clinic of Dr. Mohammad Hoesin General Hospital Palembang from January to Agustus 2023. The assessment uses fibroscan to determine the degree of liver fibrosis, measured in kilopascals (kPa). PDGF-BB levels measured by ELISA. **Results:** From 40 subjects, the majority of chronic hepatitis B patients were women (57,5%). The lowest PDGF-BB level was found in chronic hepatitis B patients with fibroscan F0, and the highest PDGF-BB level in fibroscan F4. Fibroscan results are directly proportional to PDGF-BB level. **Conclusion:** PDGF-BB has a strong positive correlation with the degree of fibroscan in chronic hepatitis B patients in Dr. Mohammad Hoesin General Hospital. The higher the range of PDGF-BB levels, the higher the degree of fibroscan in chronic hepatitis B patients.

1. Introduction

Chronic liver disease is a liver disease that lasts more than 6 months and is characterized by the process of changing liver cells into fibrotic tissue (fibrosis process). Liver fibrosis is part of the progressive disease of chronic hepatitis, which is a very important health problem. The limited availability of fibroscan by several health facilities encourages the emergence of various non-invasive modalities to assess the degree of liver fibrosis. This non-invasive modality is broadly divided into 2 large parts, namely biomarkers or serum markers, detecting both direct and indirect markers and imaging techniques (USG, CT scan, MRI, and fibroscan).[1-5] Indirect seromarkers reflect changes in liver function caused by liver cell damage. Indirect seromarker examination, among others, the aspartate-platelet ratio index (APRI), fib-4 index, and cirrhosis determines score (CDS). Meanwhile, seromarker examination directly reflects turnover extracellular matrix, and/or describe the fibrogenic or fibrolytic activity of liver cells and provide information about the degree of fibrogenic activity.[4,6]

Non-invasive examinations currently used in several health service centers include fibroscan. The results are obtained in the form of kilopascal (kPa), then matched into a range of values according to the etiology, and the degree of liver fibrosis will be obtained. This examination is recommended as part of the guidelines European Association for the Study of the Liver (EASL) and the Asian Pacific Association for the Study of the Liver (APASL) to monitor the progression of chronic liver disease. This examination is not available at all health care centers and requires expensive costs for examination.[6]

Liver fibrosis is an accumulation of ECM (extracellular matrix) protein scar tissue and is mediated by cytokines that involve complex cellular interactions, one of which is platelet-derived growth factor (PDGF). Platelet-derived growth factor is expressed by platelets, fibroblasts, endothelial cells, mast cells, and macrophages. Different isoforms and ligands will also bind to different receptors. The PDGF-BB ligand plays a role in the activation and transdifferentiation of profibrogenic HSCs (Hepatic stellate cells) to become myofibroblasts in liver fibrosis. Another study showed that PDGF-BB mRNA expression was found to be markedly increased in chronic liver disease. Currently, PDGF-BB, as an important angiogenic factor released by platelets during the inflammatory process, can be developed into a direct biomarker examination that is closely related to liver fibrosis. This seromarker can be used especially in patients in whom liver biopsy is not possible fibroscan.[6,7] Other studies show a relationship between PDGF-BB and the degree of liver fibrosis in hepatitis B patients and can be used as a non-invasive examination to assess the degree of liver fibrosis. Another study involving 465 chronic hepatitis B patients with varying degrees of liver fibrosis showed a positive correlation between the degree of liver fibrosis and PDGF-BB.[7,8] The aim of this study is to assess the correlation between PGDF-BB levels and the degree of liver fibrosis based on fibroscan in chronic hepatitis B.

2. Methods

This study is an analytical observational research with a cross-sectional approach. This study uses primary data obtained from research subjects. A total of 40 research subjects participated in this study, where the research subjects met the inclusion criteria. The inclusion criteria for this study were all chronic hepatitis B patients who received treatment at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia, patients aged 17 years and over and willing to take part in the research by signing an informed consent form. This study has received approval from the research ethics committee of Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia, with the number LB/.02.03/XVII.5.11/ETIK/34/2023.

This study carried out observations of the clinical symptoms and routine laboratories of the research subjects. PDGF-BB levels were examined using the ELISA sandwich (Enzyme-Linked Immunosorbent Assay). Measuring liver stiffness using a tool fibroscan (echosens, Paris, France) is a non-invasive method for assessing liver fibrosis. Data analysis was carried out using SPSS version 25 software. Data analysis was carried out univariately and bivariately. Univariate analysis was carried out to present the frequency distribution of each variable. Bivariate analysis was carried out to assess the relationship between test variables, with a p-value <0.05.

3. Results

In this study, the results showed that there were no differences in fibroscan (kPa) by gender (p = 0.080), age (p = 0.472), and BMI (p = 0.678). However, there are differences in fibroscan (kPa) based viral load (p = 0,020).

Table 1. Comparison of fibroscan based on the characteristics of research variables.

Characteristics	Amount (n =40)	Percentage	Mean± SD	Median (Min-Max)	p
Gender					
Male	17	42,5	14,62 ± 18,16	7,7 (2,9- 75)	0,080[a]
Female	23	57,5	7,54 ± 7,78	4,9 (2,8 – 32,4)	
Age (years)					
18 – 60	37	92,5	10,79 ± 13,99	5,4 (2,8 – 75)	
≥ 60	3	7,5	7,53 ± 2,60	7,6 (4,9 – 10,10)	0,472[a]
BMI (kg/m^2)					
Underweight	3	7,5	28,8 ± 40,02	6,8 (4,6 – 75)	
Normoweight	16	40,0	10,32 ± 10,41	5,1 (3,2 – 34,3)	0,678[b]
Overweight– Obesity	21	52,5	8,11 ± 7,55	5,9 (2,8 – 30,6)	
Viral load					
Low (<10^4)	23	57,5	6,71 ± 6,47	4,6 (2,8 – 34,3)	0,020[a]*
High (≥10^4)	17	42,5	15,74 ± 18,33	7,6 (3,2 – 75)	

[a]Mann Whitney test, *p < 0,05 [b]Kruskal Wallis test, *p < 0,05.

Patients with chronic hepatitis B disease with viral load patients with chronic hepatitis B disease had significantly higher kPa values and low viral load.

In this study, the results showed that there were no differences in PDGF-BB based on gender (p = 0.087), age (p = 0.457), and BMI (p = 0.711). However, there are differences in PDGF-BB-based viral load (p = 0,020). Patients with chronic hepatitis B disease with viral load patients with chronic hepatitis B disease had significantly higher PDGF-BB values viral load low.

Table 2. Comparison of PDGF-BB based on research variable characteristics.

Characteristics	Amount (n = 40)	%	Mean± SD	Median (Min-Max)	p
Gender					
Male	17	42,5	874,2 ± 597,5	924,9 (61.08-1858,54)	
Female	23	57,5	529,6 ± 447,7	345,6 (17,15-1556,25)	0,087[a]
Age (years)					
18 – 60	37	92,5	662,49 ± 545.3	406,3 (17,15-1858,54)	
≥ 60	3	7,5	842,8 ± 493,1	857,1 (342,67-1328,57)	0,457[a]
BMI (kg/m^2)					
Underweight	3	7,5	949,2 ± 805,5	663,7 (325,42-1858,54)	
Normoweight	16	40,0	705,9 ± 591,6	362,5 (96,94-1812,92)	0,711[b]
Overweight– Obesity	21	52,5	614,3 ± 469,9	537,9 (17,15-1477,20)	
Viral Load					
Low (<10^4)	23	57,5	519,2 ± 477,2	330,4 (17,15-1812,92)	0,019[a]*
High (≥10^4)	17	42,5	888,2 ± 555,7	857,1 (96,94-1858,54)	

[a]Mann Whitney test, *p < 0,05.
[b]Kruskal Wallis test, *p < 0,05.

The PDGF-BB value range based on degrees of fibroscan is shown in Table 3. Based on the One Way ANOVA test, there are differences in PDGF-BB values based on degrees of fibroscan (p = 0.000). The lowest PDGF-BB value was found in sufferers of chronic hepatitis B with fibroscan F0, and the highest PDGF-BB value was found in sufferers of chronic hepatitis B with fibroscan F4.

Table 3. Comparison of PDGF-BB values based on fibroscan degrees.

Fibroscan	Amount (n = 40)	Percentage	Mean± SD	Median (Min-Max)	p
F0	17	42,5	208.5 ± 110,2	188,5 (17,15-345,55)	0,000[a]*
F1	7	17,5	486,4 ± 111,2	520,9 (359,59-663,69)	
F2	6	15,0	913,6 ± 138,6	891,0 (737,37-1150,93)	
F3	4	10,0	1278,9±72,2	1274,1 (1214,48-1353,0)	
F4	6	15,0	1582,3±206,6	1516,2 (1364,7-1858,54)	

[a]One Way ANOVA test, *p < 0,05.

With Spearman's Rho correlation test, the results showed that there was a very strong and significant positive correlation between PDGF-BB values and degrees fibroscan (r = 0.954; p = 0.000). The higher the PDGF-BB value, the higher the degree fibroscan on sufferers of chronic hepatitis B, and vice versa.

Table 4. Correlation of PDGF-BB values with degrees fibroscan.

Variable		Fibroscan
PDGF-BB	r	0,954*
	p	0,000**
	n	40

*Spearman's Rho test; **P< 0,05; value r = 0.0 to <0.2: very weak, r=0.2 to <0.4: weak, r=0.4 to <0.6: moderate, r=0.6 to <0, 8: strong, r=0.8 to 1=very strong.

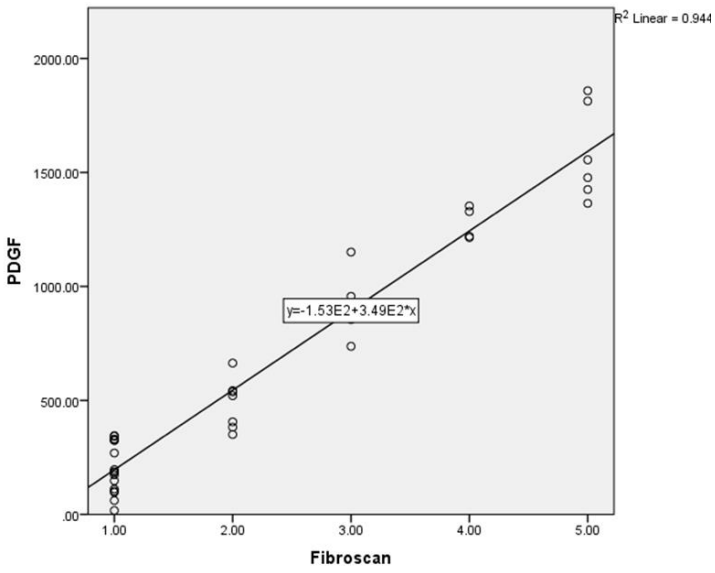

Figure 1. Correlation graph of PDGF-BB with fibroscan.

4. Discussion

With Spearman's Rho correlation test, the results showed that there was a very strong and significant positive correlation between PDGF-BB values and degrees fibroscan (r = 0.954; p = 0.000). The higher the PDGF-BB value, the higher the degree of fibroscan on sufferers of chronic hepatitis B, and vice versa. Based on the results of this study, it can be concluded that the PDFG-BB seromarker can be used as an alternative non-invasive examination that is useful if

other diagnostic support tools cannot be used. Studies others stated that PDGF-BB is more potent than PDGF-AA and PDGF-AB in assessing liver fibrosis activity.[9-12]

The inflammatory response increases with the release of pro-inflammatory cytokines and growth factors, such as PDGF. These growth factors then activate hepatic stellate cells and induce them to undergo transdifferentiation into fibrogenic myofibroblasts. Hepatocytes undergoing apoptosis also stimulate the fibrogenic action of hepatic stellate cells. Activated hepatic stellate cells release cytokines, which further increase the number of activated hepatic stellate cells. Platelet-derived growth factor induces myofibroblast proliferation through mechanisms that are extracellular signal-regulated kinase (ERK) dependent and ERK-independent and through changes in intracellular pH. In the early phase, liver stellate cells and macrophages are able to secrete matrix metalloproteinase (MMP) and its activators but not express tissue inhibitors of metalloproteinase (TIMP), so that the formation of fibrillar collagen will be followed by degradation of the ECM by MMP. However, when liver stellate cells are activated repeatedly and continuously, MMP expression decreases, and they begin to express TIMP so that MMP activity in the degrading matrix is inhibited. These changes cause disruption of the balance of secretion and matrix degradation, which results in matrix accumulation.[13-16]

Other research links the examination scores fibroscan, percutaneous liver biopsy, and serum PDGF-BB results showed that 26.2% of 122 patients with normal SGPT levels had fibrosis values that correlated significantly with the fibrosis stage ($p = 0.007$). Several studies have been conducted in the last 2 decades to assess the relationship between PDGF-BB and liver fibrosis. Platelet-derived growth factor BB is a powerful mitogen that activates HSCs. Several studies show that PDGF-BB values can predict the level of liver fibrosis and have a positive correlation. The limitations of this research are the relatively small number of samples, the fact that it was conducted in a single centre, and the patients who entered this study mostly included mild degrees of fibrosis. The number of samples from each liver fibrosis group was uneven based on fibroscan.[17-20]

5. Conclusion

There is a significant positive correlation with the strength of very strong correlation between serum PDGF-BB levels and the degree of liver fibrosis based on fibroscans in patients with chronic hepatitis B.

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