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Relationship red distribution width to platelet ratio with fibrosis degrees based on transient elastography in chronic hepatitis B patients

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ABSTRACT

Introduction: Chronic hepatitis B virus infection is a major health problem in developing countries like Indonesia. A chronic HBV infection of approx. 40% leads to liver fibrosis and hepatocellular carcinoma. Furthermore, liver biopsy is the gold standard in diagnosing liver fibrosis, but this examination is invasive and has many complications. Transient elastography has been validated to assess fibrosis in several liver diseases including HBV infection. However, not all hospitals have temporary elastography facilities in such a way that cheaper and more affordable examinations are needed. This study aims to examine the relationship between Red cell distribution width to platelet ratio with the degree of liver fibrosis based on transient elastography in chronic hepatitis B patients.

Method: This study was a cross-sectional examination, which involves 48 chronic hepatitis B patients receiving outpatient care from September to November 2020 at dr. Zainoel Abidin Banda Aceh. The routine blood tests were performed using the Sysmex XT 1800i. The red cell distribution width to platelet ratio value is calculated by dividing the Red Distribution Width value by the platelets, and the degree of liver fibrosis was assessed using TE (Fibroscan® 502 Echosens).

Result: In the 48 patients, the mean value of Red cell Distribution Width to Platelet Ratio for various degrees of liver fibrosis F0-1, F2, F3 and F4 were 0.051; 0.050; 0.077 and 0.108, respectively. It was reported that red cell distribution width to Platelet Ratio levels also increased according to the increase in liver fibrosis degree and was statistically significant with a p-value of 0.002. Analysis of the relationship between red cell distribution width to platelet ratio with the degree of liver fibrosis using ordinal regression method, while the red cell distribution width to platelet ratio level variable has a fairly large estimate value that is 31098 with a p-value of 0.003. The p-value of the test of less than 0.05 proves that the red cell distribution width to platelet ratio level affects and has a relationship with the degree of liver fibrosis.

Conclusion: Red cell distribution width to platelet ratio relates to the degree of liver fibrosis in patients with chronic hepatitis B.

Keywords: Chronic hepatitis B, red cell distribution width to platelet ratio, liver fibrosis, transient elastography.
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INTRODUCTION

Chronic infection with the hepatitis B virus (HBV) is a major health problem worldwide. Furthermore, it is estimated that one-third of the world's population is exposed to this virus and 350 to 400 million are infected with hepatitis B.[1] The highest prevalence of hepatitis B is in the Western Pacific was 6.2% and in Africa 6.1% of the adult population infected. The prevalence in the East Mediterranean, Southeast Asia and Europe is estimated to about 3.3%, 2.0% and 1.6%, respectively. Meanwhile, only 0.7% of the population of the region in America is infected.[2] Hepatitis prevalence is higher in developing countries, including Indonesia. Based on data from the Indonesian Basic Health Research 2018, it was estimated that 0.4% of the population in the country has hepatitis, this condition has doubled compared to 2013, which is about 0.2%. In Aceh the prevalence of hepatitis is estimated to about 0.4% in 2018, this condition has decreased by about 0.3% compared to 2013, which was 0.7%.[3]

Patients with chronic hepatitis B develop liver fibrosis and hepatocellular carcinoma. The prevalence of liver fibrosis in chronic hepatitis B patients is 34% with a higher prevalence in older patients, men and in patients with higher alanine transaminase (ALT) levels. Liver fibrosis is a cause of morbidity and mortality in chronic hepatitis, and therefore early determination of fibrosis is necessary to determine the appropriate treatment.[4,5]

Liver biopsy is the gold standard for diagnosing the degree of liver fibrosis. A biopsy is an invasive procedure with disadvantages, such as pain and bleeding complications. The results of different interpretations between examiners may occur due to sampling errors and difficulty

Table 1. Basic Characteristics

Variable	Degree of Liver Fibrosis (n, %)				p-value
	F0-1	F2	F3	F4	
Gender					
Male	10 (34.5)	4 (13.8)	6 (20.7)	9 (31.0)	0.624*
Female	9 (47.4)	4 (21.1)	2 (10.5)	4 (21.1)	
Age Group					
≤ 30 years	7 (70.0)	1 (10.0)	1 (10.0)	1 (10.0)	
31– 40 years	7 (70.0)	1 (10.0)	1 (10.0)	1 (10.0)	
41 - 50 years	4 (28.6)	4 (28.6)	3 (21.4)	3 (21.4)	0.059*
51 - 60 years	1 (9.1)	2 (18.2)	3 (27.3)	5 (45.4)	
> 60 years	0 (0.0)	0 (0.0)	1 (33.3)	2 (66.7)	
Marital status					
Married	14 (34.1)	7 (17.1)	8 (19.5)	12 (29.3)	0.375*
Not Married	5 (71.4)	1 (14.3)	0 (0.0)	1 (14.3)	
Education					
Elementary school	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Junior high school	1 (20.0)	1 (20.0)	2 (40.0)	1 (20.0)	
High school	8 (47.1)	2 (11.8)	2 (11.8)	5 (29.4)	0.677*
Diploma	3 (42.9)	3 (42.9)	1 (14.3)	0 (0.0)	
Bachelor	5 (33.3)	2 (13.3)	3 (20.0)	5 (33.3)	
Postgraduate	1 (33.3)	0 (0.0)	0 (0.0)	2 (66.7)	
Profession					
Housewife	6 (60.0)	1 (10.0)	1 (10.0)	2 (20.0)	
Civil servants	3 (20.0)	2 (13.3)	4 (26.7)	6 (40.0)	
entrepreneur	3 (33.3)	3 (33.3)	2 (22.2)	1 (11.1)	
Army	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	0.654*
Farmer	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)	
Midwife / nurse	2 (40.0)	2 (40.0)	0 (0.0)	1 (20.0)	
Not yet working	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Others	3 (75.0)	0 (0.0)	0 (0.0)	1 (25.0)	
tribe					
Aceh	19 (41.3)	8 (17.4)	7 (15.2)	12 (26.1)	0.360*
Others	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	
Laboratory results					
RDW	13.14 ± 1.52	12.74 ± 0.92	13.18 ± 1.29	14.31 ± 1.99	0.050†
Platelets	273.58 ± 60.50	262.75 ± 52.25	225.63 ± 114.72	164.15 ± 68.53	0.002†
RPR	0.051 ± 0.014	0.050 ± 0.011	0.077 ± 0.047	0.108 ± 0.063	0.002†

*Fisher Exact Test, †Kruskal-Wallis test

in obtaining samples for each group of fibrosis degrees. The drawback of the invasive method led the researchers to diagnose the fibrosis degrees using a non-invasive method. Furthermore, the non-invasive methods currently developed include laboratory examinations of serum markers (indirect and direct markers) and imaging modalities.[6,7] Transient elastography (TE) is one of the imaging modalities with high accuracy in diagnosing liver fibrosis.[8] The advantage of TE is quick and lower misinterpretation. However, TE testing is expensive and not widely available. This limitation led to non-invasive methods that use laboratory serum markers to diagnose fibrosis degrees in many studies.[7]

Red cell distribution width (RDW) to platelet ratio (RPR) is one of the routine laboratory tests and an indirect marker to determine the degree of liver fibrosis. RDW is a description of the variation in the size or heterogeneity of erythrocyte cells. Furthermore, high levels of RDW slowed death by severity and mortality of heart and kidney disease. The RDW levels represent nutritional deficiencies (such as iron, vitamin B12 and folic acid), bone marrow depression and chronic inflammation. This condition is also often reported in people with liver disease. Lou Y and colleagues explained a significant increase in RDW levels according to the severity of the liver fibrosis.[8] Chen et al.[9] also reported that RPR could significantly predict liver fibrosis and cirrhosis compared with aspartate transaminase (AST) / ALT ratio (AAR), AST/platelet ratio index (APRI) and fibrosis-4 (FIB-4).[1,2] This study aims to examine the relationship between RPR with the degree

Table 2. RPR Levels at Various Degrees of Liver Fibrosis

Degree of Liver Fibrosis	Mean	CI 95%		p-value
		Lower limit	Upper limit	
F0-1	0.051	0.044	0.057	0.002#
F2	0.050	0.041	0.060	
F3	0.077	0.038	0.116	
F4	0.108	0.070	0.146	

#Kruskal-Wallis test

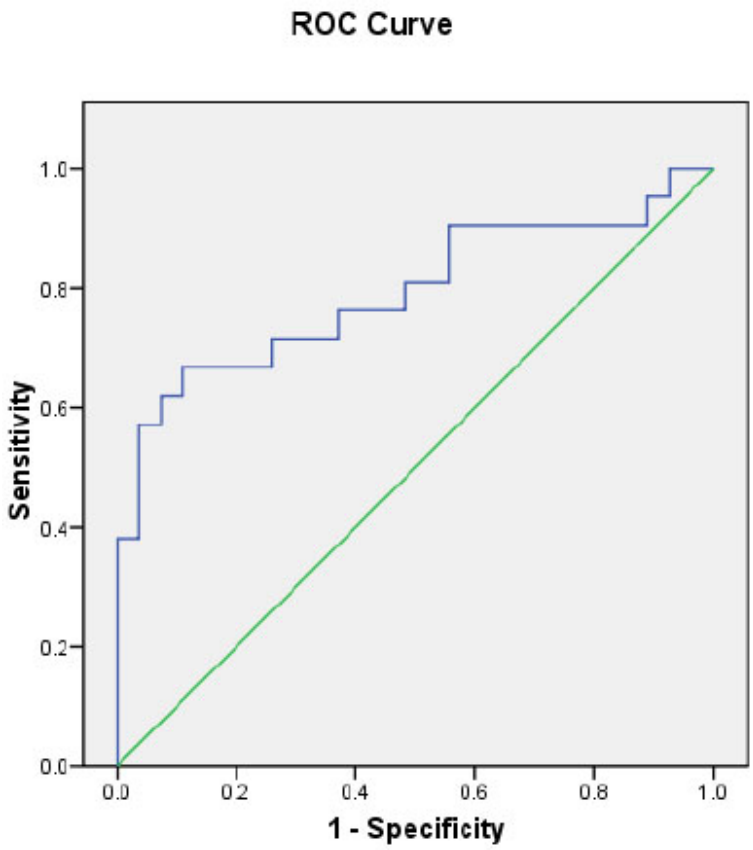

Figure 1. ROC Curve RPR for Degrees of Liver Fibrosis

of liver fibrosis based on TE in chronic hepatitis B patients.

METHOD

Study design

This research was a cross-sectional study, which involves 48 chronic hepatitis B patients that were receiving outpatient care from September to November 2020 at dr. Zainoel Abidin Banda Aceh. The inclusion criteria are age over 18 years. Patients with chronic hepatitis B are characterized by seropositive HbsAg >6 months and have received an overview of the research flow and are willing to follow predetermined procedures (have signed the consent form to follow the research). The patients coinfected with hepatitis C virus and/or HIV, autoimmune diseases, malignant diseases (solid tumors and hematological malignancies) including hepatocellular carcinoma, decompensated liver cirrhosis, chronic renal failure, chronic heart failure, diabetes mellitus, sepsis in the last 2 weeks and history of blood transfusion (erythrocyte component in the last 4 months) and (platelet component in the last 2 weeks) were excluded.

Fibrosis analysis

Routine blood tests were performed using the Sysmex XT 1800i. The RPR value was calculated by dividing the RDW value by the platelets. The degree of liver fibrosis was assessed using TE (Fibroscan® 502 Echosens) with F0-1 = 0-7,1 kPa, F2 = >7,1-9,3 kPa, F3 = >9,3-14,5 kPa and F4 = >14,5 kPa. The success in measuring liver stiffness was obtained after obtaining 10 valid measurements with a success rate of ≥70% and the interquartile range should be less than 30% of the median value.[11,12]

Statistical analysis

Statistical analysis was performed on IBM SPSS Statistics for Windows, Version 23 (Armonk Corporation, NY, USA). Furthermore, bivariate analysis was used to determine the basic characteristics and an overview of the RPR value at various liver fibrosis degrees using Fisher Exact Test and the Kruskal-Wallis test. The spearman rank correlation method was used to assess the relationship between RPR and the degree of liver fibrosis. The data analysis was processed using a computer with a p-value <0.05, which was considered statistically significant and with a confidence interval of 95%.

RESULT

Younger patients had F0-1 or F2 liver fibrosis, while older patients had F3 or F4. The highest RDW levels were reported in the group F4. Furthermore, the highest average platelet level was in the F0-1 group (Table 1).

Although descriptively the fourth degrees of liver fibrosis have adjacent mean RPR values, further test with the Kruskal-Wallis test method showed that the RPR levels at the four degrees of liver fibrosis differed significantly (p=0.002) (Table 2).

RPR had a strong correlation (Correlation coefficient 0.527) with the degree of liver fibrosis and was statistically significant (p<0.001). RPR levels can be used to predict the degree of liver fibrosis.

Meanwhile the area under the curve for the RPR level is 0.792 (79.2%) and is significant (p-value is smaller than 0.05). This suggests that RPR levels can be used to predict the degree of liver fibrosis. Furthermore, the area under the RPR level curve can be categorized in the moderate group, which is between 70% to 80%. The cut-off-point for RPR levels to predict the

degree of liver fibrosis between mild to moderate fibrosis and severe fibrosis was 0.0538 with a sensitivity of 76% and a specificity of 63% (Figure 1).

DISCUSSION

The mechanism underlying the increase in the RDW in the degree of liver fibrosis is not well understood. However, there are several hypotheses, the first and the most widely accepted that inflammation is a hallmark of liver disease, and an association between the inflammatory response and elevated RDW has been identified. Furthermore, inflammatory cytokines can suppress erythrocyte maturation and accelerate the formation of new and larger reticulocytes to enter the peripheral circulation causing an increase in RDW. Second, an increase in RDW has been reported to be associated with kidney failure. The prevalence of impaired renal function is higher in patients with liver disease than in the general population. Therefore, an increase in RDW in liver disease can also be caused by impaired kidney function. Third, nutritional deficiencies are common in patients with liver disease and have lower folic acid levels than healthy controls. A decrease in folic acid can affect the hematopoietic and strengthen the heterogeneity of red blood cells. Fourth, portal hypertension can cause hypersplenism and thereby accelerate the destruction of red blood cells. The shorter lifespan of red blood cells can promote immature red blood cells from the bone marrow into a larger circulation than mature red blood cells, leading to an increase in RDW. However, all of these hypotheses deserve further investigation.[13]

Thrombocytopenia is one of the most common hematological disorders in patients with chronic liver disease. The pathogenesis mechanism is not fully understood, and the mechanism of hypersplenism in patients with chronic liver disease is secondary to portal hypertension. However, in some cirrhotic patients, thrombocytopenia can persist even after splenectomy or after portal decompression. Furthermore, other possible mechanisms such as reduced hepatic release of thrombopoietin, autoimmune thrombocytopenia, antiretroviral therapy or bone marrow suppression may be involved in the development of thrombocytopenia in chronic liver disease.[14]

A positive correlation value indicates that an increase follows an increase in the RPR level in liver fibrosis degree. Inflammation is a hallmark of liver disease, and inflammatory cytokines can suppress erythrocyte maturation and accelerate new and larger reticulocytes to enter peripheral circulation, leading to increased RDW.[13] Thrombocytopenia is one of the most common hematological disorders in patients with chronic liver disease. This occurs due to the inflammatory response of the hepatitis B virus, which inhibits the growth and differentiation of bone marrow progenitor cells and reduces the release of thrombopoietin by the liver.[14,15]

A study conducted by Chen et al.[9] in China, investigated the relationship of hemoglobin, RDW and platelets with liver histology results in chronic hepatitis B patients. There were several significant independent predictors, RDW had a positive correlation with the degree of liver fibrosis, while platelets and hemoglobin had a negative correlation with the degree of liver fibrosis. Furthermore, Chen et al.[9] tried to investigate RPR compared to liver biopsy. The results reported that RPR could predict significant liver fibrosis with AUC ROC: 0.825 and cirrhosis with AUROC: 0.884 in chronic hepatitis B patients with high accuracy compared to AAR, APRI and FIB-4.[13] In addition, Ding and colleagues in 2019 in China that investigated the accuracy of RPR examination on several other causes of liver fibrosis including, chronic hepatitis B, chronic hepatitis C and non-alcoholic fatty liver and other causes, compared to the APRI examination, FIB-4, Forns and S index, reported that the RPR examination had the best accuracy in determining significant liver fibrosis with an AUC ROC of 0.750, a sensitivity of 58% and a specificity of 96%. While APRI with AUROC 0.670, sensitivity 54% and specificity 70% and FIB-4 with AUROC 0.690, sensitivity 59% and specificity 80%.[16] Similarly, the results of the research conducted in Indonesia by Jemi and colleagues in 2018 collected data from 81 chronic hepatitis B patients to compare AUC, sensitivity, specificity, positive predictive value and negative predictive value between RPR and APRI in predicting fibrosis degree. It was reported that in the ROC analysis, the AUC was obtained for the RPR of 0.816 and the APRI for 0.797. If the RPR is used with a cut-off of 0.066, the sensitivity is 76.9% and the specificity is 78.6%. While the APRI score with a cut-off of 0.85 obtained a sensitivity of 69.2% and a specificity of 76.2%. RPR is not inferior to the APRI score and can be used as a diagnostic marker with suitability of 65.3%.[17]

CONCLUSION

The highest RPR level was reported at the degree of liver fibrosis F4. There is a significant relationship between RPR levels and the degree of liver fibrosis based on TE in chronic hepatitis B patients. Furthermore, RPR can be used as a non-invasive diagnostic marker to predict severe fibrosis in chronic hepatitis B patients, with a cut-off point of 0.0538 with a sensitivity of 76% and a specificity of 63%.

CONFLICT OF INTEREST

No conflict of interest.

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This study did not receive any third-party support or funding.

AUTHOR CONTRIBUTION

All authors contributed equally to the study.

ETHICAL CLEARANCE

Ethical Clearance was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Syiah Kuala/Dr. Zainoel Abidin Regional General Hospital Banda Aceh with ethical clearance references number 026/EA/FK-RSUDZA/2020.

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