

# Association Between Red Cell Distribution Width (RDW)/Platelet Ratio and Degree of Fibrosis in Patient with Chronic Hepatitis B

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## ABSTRACT

**Background:** Histological examination of the liver remains the gold standard of assessing liver cirrhosis. However, this examination is an invasive method with many complications. This study aims to determine the relationship between degree of liver fibrosis with red cell distribution width (RDW)/platelet ratio which can then be used as non-invasive diagnostic method of liver fibrosis.

**Method:** This was a retrospective study, the data of hematological profiles including hemoglobin, RDW, and platelet was taken from medical records of all chronic hepatitis B patients undergoing Fibroscan at Sanglah Hospital in January 2016 to February 2017.

**Results:** Of 58 patients, 10 patients was excluded due to chronic kidney disease, malignancy and coincide with hepatitis C and HIV. The analysis using Kruskal-Wallis test, found a significant relationship between RDW/platelet ratio with degree of fibrosis in chronic hepatitis B ( $p < 0.05$ ). Of the 48 patients, 23 patients with mild-moderate fibrosis (metavir F0-2) and 25 patients with severe fibrosis (metavir F3-4) were found. In ROC analysis, the AUC was 0.734, using cut off 0,065 RDW/platelet ratio predict severe fibrosis about 7% sensitivity, specificity 73.9%, positive prediction value 73.1%, and negative prediction value 70.8%.

**Conclusion:** The RDW/platelet ratio can be used as a noninvasive diagnostic test of liver fibrosis in chronic hepatitis B patients.

**Keywords:** fibroscan, RDW/platelet ratio, liver fibrosis, chronic hepatitis B.

## ABSTRAK

**Latar belakang:** Pemeriksaan histologi hati merupakan baku emas diagnosis sirosis hepatis. Akan tetapi pemeriksaan ini merupakan pemeriksaan yang invasif dan memiliki banyak komplikasi. Penelitian ini bertujuan untuk mengetahui adanya hubungan antara derajat fibrosis hati dengan rasio red cell distribution width (RDW)/platelet yang selanjutnya dapat digunakan sebagai petanda fibrosis hati non-invasif.

**Metode:** Penelitian ini merupakan penelitian retrospektif, data diambil dari rekam medis semua penderita hepatitis B kronik yang menjalani Fibroscan di RSUP Sanglah pada bulan Januari 2016 sampai Februari 2017.

**Hasil:** Dari 58 pasien, dieksklusi pasien dengan penyakit ginjal kronik, keganasan, dan koinfeksi dengan hepatitis C maupun HIV, sehingga jumlah subyek yang diteliti sebanyak 48 pasien. Analisa hubungan menggunakan kruskal-wallis, didapatkan adanya hubungan yang signifikan antara RDW, platelet, RDW/platelet rasio dengan derajat fibrosis pada hepatitis B kronik. Dari 48 pasien, didapatkan 23 pasien dengan fibrosis

ringan-sedang (metavir F0-2) dan 25 pasien dengan sirosis (metavir F3-4). Pada analisa ROC didapatkan AUC 73,4%, dan dengan menggunakan cut off 0,065 didapatkan sensitivitas 76%, spesifisitas 73,9%, nilai prediksi positif sebesar 73,1%, nilai prediksi negatif 70,8%.

**Simpulan:** Disimpulkan bahwa rasio RDW/platelet dapat digunakan sebagai petanda non-invasif derajat fibrosis hati pada penderita hepatitis B kronik.

**Kata kunci:** fibroscan, rasio RDW/platelet, fibrosis hati, hepatitis B kronik.

## INTRODUCTION

Chronic Hepatitis B infection is one of the main causes of liver fibrosis and cirrhosis, as well as other known causes such as hepatitis C virus, alcoholic liver disease, and non-alcoholic liver disease. These infections often show no symptoms until eventually the patient falls under conditions of liver cirrhosis with various complications such as; bleeding due to variceal rupture, hepatic encephalopathy, ascites, renal impairment, and so fort.<sup>1</sup> In the world, more than 600,000 people die each year due to hepatitis B, with the highest endemic rate was found in Asia, which is about 45%<sup>1</sup>. The prevalence of chronic hepatitis B in Indonesia varies from moderate to high (2.5-10%) with the most sub-genotype being HBV/B3.<sup>2</sup> In general, chronic hepatitis B results in 45% of HCC (Hepatocellular Carcinoma) cases and 30% of hepatic cirrhosis.<sup>1</sup> Therefore examination of liver fibrosis is important for early detection of liver complications, reduces morbidity and mortality due to hepatitis B.

Until now, histological examination of the liver tissue remains the gold standard of liver fibrosis assessment. In addition, liver biopsy examination is also useful for diagnosing various pathologic abnormalities of the liver such as; autoimmune hepatitis, alcoholic liver disease, non-alcoholic liver disease, determine prognosis, and as a guide in determining therapy. However, this procedure is also associated with the incidence of many complications such as bleeding, pain, and infection. Bleeding after a biopsy procedure can be mild to severe and cause death. Mild hemorrhage is bleeding that results in pain, tachycardia, or decreased blood pressure, but does not require transfusions. This condition may occur in 1 per 500 biopsies. While severe hemorrhage is hemorrhage that require hospitalization and blood transfusion, is estimated to occur in 1 per 2,500-10,000 biopsies. Other complications that rarely occur are pneumothorax, hemothorax, and hollow organ perforations.<sup>3</sup>

Non-invasive examination began to be widely developed to replace the role of liver biopsy in order

to avoid the complications of it. Transient elastography (TE, Fibroscan) is one of non-invasive examination using an ultrasound probe to assess the degree of liver fibrosis through liver stiffness.<sup>4,5</sup> Shear waves with low amplitude and frequency are transmitted from the probe and evaluated for speed. The more rigid the liver tissue the waves will be delivered faster.<sup>6</sup> This procedure is easy, fast, and has a good performance (AUC > 0.9), but low sensitivity in conditions of obesity and ascites.<sup>4,6</sup> WHO 2016 recommends TE as a non-invasive examination to assess liver fibrosis in areas with no limitation in cost and resources.<sup>7</sup>

Various laboratory examinations are also widely developed as a model prediction of liver fibrosis, such as aspartate aminotransferase to platelet ratio index (APRI), gamma-glutamyltranspeptidase to platelet ratio (GPR), and FIB-4.<sup>8</sup> Some have been validated and even APRI scores have also been recommended as an early screening of chronic liver disease in areas with limited resources.<sup>7</sup> The red-cell distribution width (RDW)/platelet ratio is also suspected to be associated with degree of liver fibrosis.<sup>9</sup> RDW is a variability of red blood cells volume in the circulation, and is often used to assess anemia type. RDW is routinely reported on complete blood count tests. An increase of RDW is known to be associated with inflammatory conditions, particularly chronic inflammation.<sup>2</sup> While chronic hepatitis B patients is known to have dynamic condition related to the inflammation and fibrosis of the liver. Several previous studies have suggested that the RDW/platelet ratio is associated with liver fibrosis in patients with chronic hepatitis B.<sup>9,10,11,12</sup> Study in primary biliary cirrhosis patients, the RDW/platelet ratio can predict liver fibrosis with 46.7% sensitivity and 96.4% specificity.<sup>13</sup> Another study also showed an increase in RDW was associated with the incidence of cardiovascular complications and increased mortality.<sup>14</sup>

## METHOD

This is an analytic retrospective study. The data were taken from medical record and *Fibroscan* register of Sanglah Hospital Bali in January 2016

until February 2017. Inclusion criteria were all chronic hepatitis B infected patients aged >12 years with positive HBsAg test results for 6 months or more, who came to Sanglah Hospital Denpasar and performed Fibroscan examination. Exclusion criteria were patients with coinfection HIV and hepatitis C, liver malignancy, iron deficiency anemia, chronic renal disease, idiopathic thrombocytopenia purpura and dengue hemorrhagic fever.

In the subjects of the study conducted medical record tracking of routine laboratory blood tests, liver physiology, HBsAg, diagnosis, and Fibroscan examination. The RDW/platelet ratio is calculated using the formula = RDW (%) / Plt ( $10^9$  L-1). RDW data was taken within 1 month period of Fibroscan examination. If the patient has more than 1 data, the closest data period to the time of Fibroscan examination was chosen to minimize the bias. Fibroscan examination results were classified according to metavir, and groupings were made into 2 groups; mild-moderate fibrosis (metavir F0-2) and severe fibrosis (metavir F3-4). Analysis of the relationship between the RDW /platelet ratio to Fibroscan was performed using Kruskal-wallis. If the results are significant, the data will continue to analyse using receiver operating characteristic (ROC) curve to determine the area under curve (AUC), cut-off point, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

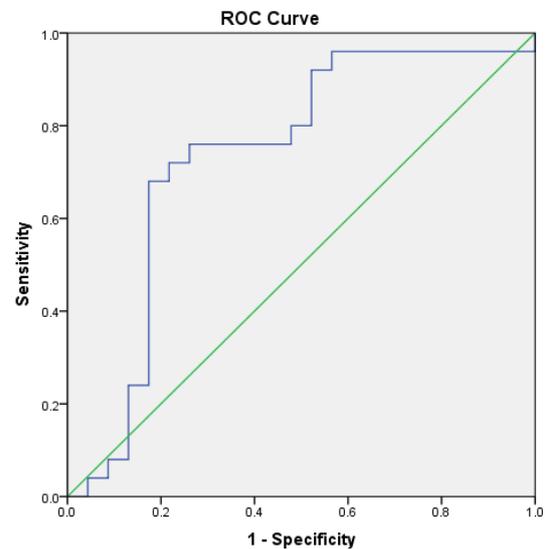
## RESULTS

Of the 58 patients with chronic Hepatitis B, Fibroscan examined, excluded patients with chronic kidney disease, malignancy, and co-infection with hepatitis C or HIV, so that the number of subjects studied was 48 patients. The subjects consisted of 33 men and 15 women, aged 15-71 years with an average of 41 years. Fibroscan examination results obtained 23 people with mild-moderate fibrosis (metavir F0-2) and 25 people severe fibrosis (metavir F3-4). The median RDW value of the study subjects was 13,03 %. The median platelet count was 170,55/mm<sup>3</sup>. The ratio of RDW/platelet obtained a median value of 0,0698. Descriptive statistical data are presented in Table 1.

Analysis of the relationship between RDW/platelet ratio with degree of liver fibrosis using Kruskal-wallis test showed significant results ( $p = 0.006$ ). In the analysis using the ROC curve obtained, AUC at 73.4%, and using a cut-off point of 0.065, the RDW/platelet ratio can predict the presence of severe fibrosis with a sensitivity of 76%, specificity 73.9%, PPV 73.1%, and NPV 70.8 %.

**Table 1. Characteristics of the subjects**

	Median	Minimum	Maximum
Age (years)	41	15	71
Liver stiffness (kPa)	10,9	4,10	72
Score metavir	3	0	4
Platelet count (/mm <sup>3</sup> )	170,55	6,1	362,90
RDW (%)	13,03	11,22	24,92
RDW/platelet ratio	0,0698	0,04	4,09



**Figure 1. ROC curve**

Area Under the Curve				
Test Result Variable(s): rdw to platelet ratio				
Area	Std. Error <sup>a</sup>	Asymptotic Sig. <sup>b</sup>	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.734	.078	.006	.580	.887

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

**Figure 2. Area under the curve (AUC)**

## DISCUSSION

Chronic hepatitis B leads to fibrosis in the liver resulting from inflammatory processes and chronic liver injury. Severe liver fibrosis will result in decreased liver function and portal hypertension. However, this condition remains no symptoms until the patient is in a condition of decompensated state. Under these conditions, the majority of patients present with many complications such as variceal bleeding, spontaneous bacterial peritonitis, or hepatic encephalopathy.<sup>15</sup> Therefore, histological examination of the liver becomes important in relation to the determination of therapy and prognosis. In 2016, WHO recommends assessing the degree of fibrosis in chronic hepatitis B patients to determine anti-viral therapy.<sup>7</sup> The recommendation to checks are APRI and TE. In addition, this examination is recommended to be done at the first time and repeated at least once a year to assess the disease progression and evaluation of the treatment. When APRI obtained a value greater than

2 or a TE result indicates  $\geq 2$  correlates with a significant fibrosis condition in the liver.<sup>7</sup>

Recently, RDW has been mentioned to be associated with some chronic pathological conditions, also as a prognostic factor in some diseases. Increased RDW was found in chronic liver disease, chronic renal disease, systemic lupus erythematosus (LES), and acute myocardial infarction.<sup>11</sup> In addition, RDW was found to be positively correlated with degree of cirrhosis based on Child-Pugh score and increased mortality of patients with coronary heart disease.<sup>14,16</sup> The mechanisms that can explain the condition until now is still unclear. Some elevation of pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-1 $\beta$  (Interleukin-1 $\beta$ ), and IL-6 (Interleukin-6), was suspected to be the cause of decreased levels of erythropoietin.<sup>17</sup> This condition results in release of the immature red blood cell into the circulation and make an increase of RDW.<sup>18</sup>

Chen et al in 2013 found a significant association between RDW and platelet levels to the degree of liver fibrosis, which then made a prediction model of RDW/platelet ratio. Based on the results of the analysis, this ratio is better than APRI with AUC 0.825 in predicting significant fibrosis.<sup>10</sup> In this study, there was a significant relationship between RDW/platelet ratio and degree of liver fibrosis. In our study ROC analysis, obtained AUC of 0.706, lower than previous studies by Chen et al. This may be due to the small number of samples in this study and the characteristics of the sample also differed between the studies. The limitations of this study include the study was conducted as a retrospective design, which is allowing for a large amount of data that could not be taken, and no direct interviews with patients. In addition, this study was not evaluated for HBV DNA and HBeAg in patients, and no liver biopsy was performed as a golden standard of liver fibrosis.

In general, this RDW/platelet ratio has moderate accuracy in predicting severe fibrosis, and still could not replace the role of TE and liver biopsy in the diagnosis of liver fibrosis. However, this ratio can be used as an initial screening for severe fibrosis in chronic hepatitis B patients, especially in areas with limited resources, in addition to being relatively cheaper than other non-invasive methods such as APRI, FIB-4, and GPR.

## CONCLUSION

There is a relationship between the ratio of RDW/platelet to the degree of liver fibrosis in people with chronic hepatitis B. This RDW/platelet ratio can

then serve as an alternative non-invasive method for predicting severe liver fibrosis in chronic hepatitis B patients, especially in areas with limited resources.

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