Diagnostic accuracy of liver fibrosis based on red cell distribution width (RDW) to platelet ratio with fibroscan in chronic hepatitis B

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Abstract. Red cell Distribution Width (RDW) and platelet ratio (RPR) can predict liver fibrosis and cirrhosis in chronic hepatitis B with relatively high accuracy. RPR was superior to other non-invasive methods to predict liver fibrosis, such as AST and ALT ratio, AST and platelet ratio Index and FIB-4. The aim of this study was to assess diagnostic accuracy liver fibrosis by using RDW and platelets ratio in chronic hepatitis B patients based on compared with Fibroscan. This cross-sectional study was conducted at Adam Malik Hospital from January-June 2015. We examine 34 patients hepatitis B chronic, screen RDW, platelet, and fibroscan. Data were statistically analyzed. The result RPR with ROC procedure has an accuracy of 72.3% (95% CI: 84.1% - 97%). In this study, the RPR had a moderate ability to predict fibrosis degree (p = 0.029 with AUC> 70%). The cutoff value RPR was 0.0591, sensitivity and specificity were 71.4% and 60%. Positive Prediction Value (PPV) was 55.6% and Negative Predictions Value (NPV) was 75%, positive likelihood ratio was 1.79 and negative likelihood ratio was 0.48. RPR have the ability to predict the degree of liver fibrosis in chronic hepatitis B patients with moderate accuracy.

1. Introduction
Indonesia is a country with a high prevalence and high endemicity of hepatitis B. There are approximately 9.4% of Indonesia's population or about 23 million people infected with hepatitis B.[1] Liver fibrosis is a cause of morbidity and mortality in chronic hepatitis disease, so the early determination of fibrosis is necessary to determine appropriate treatment.

Liver biopsy is a gold standard to diagnose the degree of liver fibrosis. A biopsy is an invasive method that has disadvantages, such as pain and bleeding complication. Different interpretation results between examiners can happen due to sampling error and difficulty in obtaining samples for each group of fibrosis degree.[2] Weakness of the invasive method makes researchers trying to diagnose the degree of liver fibrosis with non invasive methods. Ultrasound Elastography (Fibroscan) has a high accuracy, almost matching a liver biopsy in diagnosing liver fibrosis.

The advantages of Fibroscan is that the patient does not feel pain during the examination, quickly in diagnosing the degree of liver fibrosis and lower interpretation errors than liver biopsy. However, the fibroscan examination is expensive and not widely available, onlyin the central healthcare center. This limitation makes many studies with non-invasive methods that use the parameters of biochemical examination in the laboratory to diagnose the degree of liver fibrosis.[3]
Red cell Distribution Width (RDW) is a description of size variation or heterogeneity of erythrocyte cell. Increasing Red cell Distribution Width (RDW) has been reported to be associated with the severity and mortality of infectious diseases, heart, and kidney. Red cell Distribution Width (RDW) can be a representation of nutritional deficiencies (such as iron, vitamin B12, and folic acid), bone marrow depression, and chronic inflammation. This condition is often found in people with liver disease. Lou et al. (2012) had conducted a study of Red cell Distribution Width (RDW) in hepatitis B patients, and the increase of Red cell Distribution Width (RDW) was significantly in accordance with the degree of severity of the liver. [4] Another study by Chen et al. (2013) tried to investigate by combining the ratio of Red cell Distribution Width (RDW) and platelet counts compared with liver biopsy. The results were found that the ratio of Red cell Distribution Width (RDW) and platelet counts can predict liver fibrosis and cirrhosis in chronic hepatitis B significantly with relatively high accuracy, and superior to other non-invasive methods ever studied in several studies earlier to predict liver fibrosis, such as AST and ALT ratios, AST and platelet Ratio Index, and FIB-4. [5]

In this study, researchers want to assess the diagnostic accuracy liver fibrosis by using two routine laboratory markers that affordable and can be performed in any healthcare centers to predict liver fibrosis in chronic hepatitis B patients based on RDW ratio to total platelets compared with Fibroscan.

2. Methods

2.1. Patient Selection
This study was a cross-sectional study design on thirty-four consecutive chronic hepatitis B patients that were admitted to General Hospital Haji Adam Malik Medan in January-June 2015. Inclusion criteria was patients aged ≥ 18 years with chronic liver disease caused by hepatitis B virus with HBsAg (+) ≥ 6 months and exclusion criteria were patients with coinfection with HIV and hepatitis C, consumption alcohol > 30 gr/day, liver cirrhosis decompensated stage, hepatoma, heart failure, dengue hemorrhagic fever, purpura idiopathic thrombocytopenia, and history of blood transfusion (≤ 4 months for erythrocyte component; ≤ 2 weeks for platelet component). This study was approved by the local ethics committee.

2.2. Red cell Distribution Width to Platelet Ratio (RPR)
Assessment Red cell Distribution Width (RDW) and platelet were performed automatically using Sysmex XT-2000i / XT-4000i, required a sample of EDTA blood of 3-5 cc. RDW and platelet normal level was 11.6-14.8% and 150.000-450.000/mm3. Formula for RPR is RDW (%) / Platelet count (10³/mm³)

2.3. Fibroscan
Fibroscan examination using Echosens. The right lobe of the liver is assessed through the intercostal plane, while the patient lies in the supine position with the right arm of the maximal abduction position. The operator places the transducer onto the skin and places a liver position at a depth measurement is between 25-65 mm. This result can only be trusted after 10 successful examinations and more than 65% success rate of measurement is obtained.

2.4. Degree of Liver fibrosis
The degree of liver fibrosis is divided into F0 (No fibrosis) - F1 (mild fibrosis): 0-7.1 kPa, F2 (Fibrosis medium): >7.1-9.3 kPa, F3 (severe fibrosis): >9.3-14.5 kPa, F4 (Cirrhosis): >14.5 kPa. In this study, liver fibrosis was divided into 2 groups: F ≤ 2 is called a mild-moderate group, and F > 2 is called a severe group.

2.5. Statistical Methods
Data analysis was performed using the SPSS 22nd version (SPSS Inc., Chicago). Analysis of Area Under the Curve (AUC) after obtaining cut off the value of the ratio of RDW to platelet ratio (RPR) by
using Receiver Operating Characteristic (ROC) curve. Other diagnostic tests are sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) determined by the Receiver Operating Characteristic (ROC) curve procedure.

3. Result
This study was followed by 34 patients who met the inclusion criteria, divided into 2 groups according to the degree of fibrosis; mild to moderate group \( F \leq 2 \) (n=20) and severe fibrosis group \( F > 2 \) (n=14). Mean of RDW examination was \( 14.43 \pm 2.68 \% \) while mean of platelet count was \( 208.68 \pm 76.66 \times 10^3/\text{mm}^3 \). The mean ratio of RDW to platelets (RPR) is \( 0.09 \pm 0.1 \). Based on fibroscan examination, the mean was \( 12.72 \pm 13.38 \) kPa. (Table 1)

**Table 1. Basic characteristics patients.**

| Characteristics |       |
|-----------------|-------|
| Sex             |       |
| Men             | 23 (67.6) |
| Women           | 11 (32.4) |
| Age\(^b\)       | 37.94 ±12.44 |
| RDW\(^b\) (%)   | 14.43 ±2.68 |
| Platelet count\(^b\) (10\(^3\)/mm\(^3\)) | 208.68 ±76.66 |
| RPR\(^b\)       | 0.09±0.1 |
| Fibroscan\(^b\) (kPa) | 12.72 ±13.38 |
| Degree of liver fibrosis |     |
| Mild to Moderate Group (\( F \leq 2 \)) | 20 (58.8) |
| Severe Group(\( F > 2 \)) | 14 (41.2) |

\(^a\)categorical data : n (%)  
\(^b\)numeric data, mean ± SD

Analysis result using ROC curve obtained that area under the curve (AUC) ROC is 72.3% (95% CI: 84.1% - 97%). The ratio RDW / platelets count (RPR) in this study had a moderate ability to predict liver fibrosis degree (\( p = 0.029 \) with AUC> 70%).

**Figure 1.** ROC curve ratio of RDW / platelets (RPR) to predict the degree of liver fibrosis.
Based on the sensitivity and specificity curve of Figure 2, the cut off value for RDW / Platelet ratio (RPR) is 0.0591. Sensitivity and specificity value Ratio of RDW / Platelet (RPR) is 71.4% and 60%. Positive Prediction Value (PPV) RDW / platelet ratio is 55.6%, and the Negative Predictions Value (NPV) is 75%. The positive likelihood ratio is 1.79, and the negative likelihood ratio is 0.48.

![Sensitivity and specificity curve ratio of RDW/platelet (RPR) to the degree of liver fibrosis.](image)

**Figure 2.** Sensitivity and specificity curve ratio of RDW/platelet (RPR) to the degree of liver fibrosis.

### 4. Discussion

Many studies are looking for a diagnostic model of non-invasive liver fibrosis in a chronic liver disease that has been published within a decade. Some of these diagnostic models include AST / ALT Ratio (AAR), APRI score, Fibro test, and FIB-4. These models have been applied by clinicians to predict liver fibrosis. But the problem is that the model still difficult to be practiced by clinicians.

In liver fibrosis, we often found the condition of thrombocytopenia. Various possible causes of thrombocytopenia, such as sequestration and destruction of platelets in the spleen and the consequences of liver damage will affect the formation of thrombopoietin to be reduced. Several studies have shown an association between thrombocytopenia and liver fibrosis, including a study conducted by Sembiring J (2010) who found that there was a correlation of degree of liver fibrosis in chronic hepatitis with decreased thrombopoietin and platelet count. A study by Nwokediuko (2009) found that there was a correlation between the severity of liver disease with decreasing platelet count, especially in patients with liver cirrhosis.[6,7]

In liver disease, we obtained an increase of Red cell Distribution Width (RDW). A study by Lou (2012) found that there was a significant correlation increasing Red cell Distribution Width (RDW) in hepatitis B patients with the severity of liver disease.[4] It is found that Red cell Distribution Width (RDW) can be used to predict liver fibrosis and inflammatory necrosis in patients with hepatitis B when combined with other biochemical markers. Other stated that Red cell Distribution Width (RDW) is elevated in chronic hepatitis B and potentially as one of the examination indexes to assess the severity of chronic hepatitis B disease.[8,9]

To create a new prediction model with the platelet component and Red cell Distribution Width (RDW), Chen (2013) conducted a study with a simple blood laboratory examination component and using a simple formula also, called RDW to Platelet Ratio (RPR formula).[5]
RDW to Platelet Ratio (RPR formula) = \frac{\text{Red cell Distribution Width (RDW) (\%)}}{\text{Platelet count (10^9/mm}^3)}

The results of the study that compares the RDW to Platelet Ratio (RPR formula) with liver biopsy examination in chronic hepatitis B disease are RDW to platelet ratio can significantly predict liver fibrosis in chronic hepatitis B patients with relatively high accuracy. Level of accuracy in liver fibrosis is 82.5% and in liver cirrhosis is 88.4% with Sensitivity 63.1%, Specificity 85.5%, PPV 77.4%, and NPV 74.7%. for liver fibrosis and 73.7% Sensitivity, 93.0% Specificity, 60.8% PPV, and 96.0% NPV. for liver cirrhosis. RPR formulas have greater accuracy than AST / ALT Ratio (AAR), APRI score, and FIB-4. In this study, researchers used the same formula by Chen (2013) and performed statistical analysis to determine the level of accuracy compared with fibroscan.[5]

Fibroscan is a diagnostic tool that capable to compensate liver biopsy in the diagnosis of liver fibrosis. Abdelmaksoud (2015) conducted a study of fibrosis in chronic hepatitis C with fibroscan examination and liver biopsy in the same patient. Similar results were obtained in these patients, most notably the similarities obtained in the degree of F3 liver fibrosis.[10]

In this study, 34 chronic hepatitis B patients were included in inclusion criteria and examined Red cell Distribution Width (RDW) and platelets. The calculation using the RPR formula and compared with fibroscan. The result with ROC procedure was an accuracy of 72.3% (95% CI: 84.1% - 97%). In this study, the RDW / platelet ratio (RPR) had a moderate ability to predict fibrosis degree (p = 0.029 with AUC > 70%). Statistically, the interpretation of the value of Area Under the Curve (AUC) is divided into 5 : AUC> 50 - 60%: Very weak, AUC> 60 - 70%: Weak, AUC> 70 - 80%: Medium, AUC> 80 - 90%: Good and AUC> 90 - 100%: Very good.[8]

This study has a lower accuracy level than the previous study by Chen (2013), where the accuracy level in this study is moderate (AUC > 70 - 80%), while the accuracy of Chen's research is good (AUC > 80 - 90%).[5] The samples size is a weakness of this study, so that future research is needed further on a larger scale. Although we obtained a moderate level of accuracy (72.3%), RPR expected to be one of the clinician's reference in remote areas where there was no advanced liver diagnosis tool in chronic hepatitis B patients and can be an alternative in monitoring and handling chronic hepatitis B disease.

5. Conclusion
The Red cell Distribution Width (RDW) ratio to platelet count (RPR) is a simple mathematical model consisting of routine laboratory markers that can be performed in many health facilities. RPR have the ability to predict the degree of liver fibrosis in chronic hepatitis B patients with moderate accuracy and making it possible to serve as an alternative diagnostic of the liver especially in areas far from sophisticated diagnostic facilities.

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