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Association between red cell distribution width-to-platelet ratio and hepatic fibrosis in nonalcoholic fatty liver disease

A cross-sectional study

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Abstract

Background: We aimed to assess the association between red cell distribution width-to-platelet ratio (RPR) and hepatic fibrosis in nonalcoholic fatty liver disease.

Methods: The 388 subjects fulfilling the diagnostic criteria of Nonalcoholic fatty liver disease (NAFLD) were enrolled in this cross-sectional study. Red cell distribution, platelet, and other clinical and laboratory parameters were measured.

Results: NAFLD patients with advanced fibrosis had significantly higher RPR than those without fibrosis ($P < .001$). Spearman correlation analysis showed that RPR were significantly correlated with age, sex, creatinine, hemoglobin, white blood cell, and advanced fibrosis (all with $P < .05$). Multivariate logistic regression analysis showed that RPR was an independent factor predicting advanced fibrosis (fibrosis-4 calculator ≥1.3) in NAFLD patients (OR: 5.718, 95%CI: 3.326–9.830, $P < .001$).

Conclusions: Our findings suggested that RPR were significantly associated with advanced fibrosis in nonalcoholic fatty liver disease patients.

Abbreviations: γ-GT = γ-glutamyltransferase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = Body Mass Index, Cr = creatinine, CRP = C-reactive protein, DBP = diastolic blood pressure, DM = diabetic mellitus, FIB-4 = fibrosis-4 calculator, FPG = fasting plasma glucose, HDL-c = high-density lipoprotein cholesterol, Hgb = hemoglobin, LDL-c = low-density lipoprotein cholesterol, NAFLD = nonalcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis, PLT = platelet, RDW = red cell distribution width, RPR = red cell distribution width-to-platelet ratio, SBP = systolic blood pressure, Tch = total cholesterol, TG = triglycerides, WBC = white blood cell.

Keywords: advanced fibrosis, fibrosis-4 calculator, nonalcoholic fatty liver disease, red cell distribution width-to-platelet ratio

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) has recently been recognized as a major public health problem, the prevalence of NAFLD varies from 20% to 51%, depending on the study population in China over the past few decades.[1,2] The broad spectrum of NAFLD diseases ranges from simple liver steatosis to nonalcoholic steatohepatitis (NASH) and advanced fibrosis and cirrhosis.[3,4] Only a minority of individuals, those with NASH, are prone to the risk of fibrosis and cirrhosis.[3,4] Compared with these invasive tests to diagnosis NAFLD, we used the noninvasive ultrasound technique, in our study, which has high sensitivity and specificity in detecting steatosis and fibrosis.[5,6]

Red blood cell distribution width (RDW) is a measure of variability of erythrocyte size in peripheral blood (i.e., anisocytosis).[7] In recent past, RDW has gained substantial attention as a prognostic marker of various medical conditions, such as sepsis, acute myocardial infarction, heart failure, autoimmune diseases, liver diseases, and various malignancies.[8–13] Some studies found elevated RDW was independently associated with advanced fibrosis in NAFLD, RDW was higher in the severe inflammation group in non-alcoholic steatohepatitis and can be used as an indicator in non-alcoholic steatohepatitis patients with high sensitivity and specificity.[14]

Platelet (PLT) count is decreased in liver diseases has long been known. The utility of PLT count stems from the observations in liver cirrhosis patients and pathophysiologic changes which occur including splenomegaly and sequestration of PLT.[15,16] Several studies have found the platelet count to be an independent predictor of liver cirrhosis, fibrosis severity (grade) in NAFLD, and nonalcoholic steatohepatitis (NASH).[16] Moreover, PLT

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count has been included in some NAFLD fibrosis scoring systems for adults, such as APRI, FIB-4, King, Lok, FI, Forns, and Fibro Index score.[17–21]

Therefore, the platelet count and RDW are ideal biomarkers of the severity of fibrosis in NAFLD patients, RDW-to-platelet ratio (PRR) will enhance this function. In recent past, RPR has gained substantial attention as a prognostic marker of various medical conditions such as severe burn injury, primary biliary cholangitis, patent ductus arteriosus, predicting hepatic fibrosis and cirrhosis in chronic hepatitis B, diagnosis of premature ovarian insufficiency; myocardial infarction; acute pancreatitis in pregnancy.[18,19,22–27] Because it is simple, easy to measure and handle, cost-effective, and accurate for predicting the severity of fibrosis, we plan to research the association between PRP and the level of fibrosis in NAFLD.

2. Materials and methods

2.1. Patients

This study included 485 participants who underwent individual health examinations that included a physical examination and clinical laboratory tests at the West China Second University Hospital between May and October 2017, and were diagnosed with fatty liver. All participants underwent anthropometric and biochemical parameter analyses. Patients were excluded if they exhibited any of the following conditions: drinkers (alcohol consumption >140 g/week for men and >70 g/week for women were categorized as drinkers, n=46),viral hepatitis (n=35), chronic liver disease (n=5), renal insufficiency (n=3), cancer (n=2), elevated tumor markers (n=3), pregnancy (n=1), and recent infection (n=2). The remaining 388 participants (301 men and 87 women) were enrolled in the study. Informed consent was obtained from all participants and the study was approved by the ethics committee of the West China Second University Hospital, Sichuan University.

2.2. Clinical laboratory and anthropometric parameters

Weight, height, and blood pressure (systolic blood pressure SBP; diastolic blood pressure DBP) were measured, and Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared. RDW to platelet ratio (RPR)=RDW $\times 100/$ PLT (10^9/L). FIB-4 index was calculated according to the following equation[19]:

$$\text{Age(years)} \times \text{aspartate aminotransferase (U/L)}/\text{PLT}(10^9/\text{L}) \times \sqrt{\text{alanine aminotransferase (U/L)}}$$

The clinical examinations were conducted in the morning after an overnight fast. RDW, hemoglobin (Hgb) level, PLT, and white blood cells (WBC) were determined using the XE-2100 automated hematology analyzer (Sysmex Corp, Kobe, Japan). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (γ-GT), triglycerides (TG), total cholesterol (Tch), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), high-sensitivity C-reactive protein (CRP), fasting plasma glucose (FPG), and creatinine (Cr) were assessed using an automatic biochemical analyzer (Hitachi 7600; Hitachi, Tokyo, Japan) with Roche reagents (Roche Diagnostics, GmbH, Mannheim, Germany).

2.3. Diagnostic criteria for NAFLD

Liver ultrasound examinations were performed by experienced radiologists who were unaware of the clinical and laboratory data, using a Toshiba Nemio 20 sonography machine with a 3.5-MHz probe (Toshiba, Tokyo, Japan). Liver ultrasound examinations was used to define NAFLD patients. Hepatic steatosis was diagnosed according to the guidelines established for the diagnosis and treatment of NAFLD issued by the Fatty Liver Disease Study Group of the Chinese Liver Disease Association.[28] Specifically, hepatic steatosis was diagnosed according to characteristic echo patterns, such as diffuse hyperechogenicity of the liver relative to the kidneys, ultrasound beam attenuation, and poor visualization of intrahepatic structures. Liver ultrasound examinations were performed by a single experienced radiologist blinded to the clinical and laboratory data.

We used the fibrosis-4 calculator (FIB-4) index for evaluating advanced fibrosis (FIB-4 ≥1.3) of NAFLD according to the study of Xun et al.[29] Although slightly less accurate than liver biopsy, FIB-4 index can reliably indicate advanced fibrosis in Chinese NAFLD patients.[29]

2.4. Statistical analyses

Statistical analyses were performed using SPSS version 16 (SPSS, Chicago, IL). Data that were normally distributed are reported as mean ± standard deviation and data that had a skewed distribution are reported as median and range. Differences between 2 groups were analyzed using the Student *t* test or the Mann–Whitney *U* test. Differences among multi-groups were analyzed using one-way analysis of variance or the Kruskal–Walls *H* test. Spearman correlation analysis was used to examine correlations between PRP and clinical and laboratory parameters. Univariable and multivariable logistic regression was used to examine associations between PRP and NAFLD participants. All statistical tests were two-tailed and a P value $< .05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics of participants

The demographic and biochemical characteristics of study participants were shown in Table 1. There were 388 NAFLD participants included in the study and 74 (19.1%) NAFLD participants with advanced fibrosis. NAFLD with and without advanced fibrosis had significant differences in SBP, ALT, PLT, FPG, WBC, RDW, and prevalence of diabetic mellitus (DM). We referred to the study of Chen et al that devised the RDW to platelet ratio (RPR) to amplify the difference in the RDW and platelets among patients with different fibrosis stages. In Table 1, NAFLD with advanced fibrosis had significant higher RPR than NAFLD without advanced fibrosis [7.03 (3.58–12.86) vs 5.48 (3.23–11.22), $P < .001$].

3.2. Association between RPR and various parameters in NAFLD participants

Our results show that RPR were significantly correlated with age ($r = .157$, $P = .002$), sex ($r = -.132$, $P = .009$), Cr ($r = .136$, $P = .007$), Hgb ($r = .155$, $P = .002$), WBC ($r = -.250$, $P < .001$), and advanced fibrosis ($r = .440$, $P < .001$) (shown in Table 2). The study of Chen et al[17] observed that RPR can predict significant

Table 1

Characteristics of the NAFLD patients with and without advanced fibrosis.

Variable	Without advanced fibrosis (314)	with advanced fibrosis (74)	*P* value
Age (yr)	42.2 ± 9.6	58.9 ± 10.5	<.001
Sex (F/M)	68/246	19/55	.456
Body mass index (kg/m^2)	25.2 ± 2.7	26.0 ± 2.3	.659
Systolic blood pressure (mmHg)	130 ± 16	138 ± 19	<.001
Diastolic blood pressure (mmHg)	80 ± 11	83 ± 11	.085
Alanine aminotransferase (U/L)	29 (11–1184)	26 (7–164)	.034
Aspertate aminotransferase (U/L)	23 (14–87)	26 (13–101)	.006
Glutamyltransferase (U/L)	34 (7–97)	33 (11–98)	.333
Triglyceride (mmol/L)	1.66 (0.34–21.05)	1.55 (0.53–10.91)	.647
Creatinine (mmol/L)	72.5 ± 13.7	71.9 ± 14.0	.734
Total cholesterol (mmol/L)	4.95 ± 1.00	5.11 ± 0.93	.213
High-density lipoprotein cholesterol (mmol/L)	1.12 ± 0.26	1.17 ± 0.26	.145
Low-density lipoprotein cholesterol (mmol/L)	2.67 ± 0.58	2.76 ± 0.68	.286
Fasting plasma glucose (mmol/L)	5.23 (3.95–12.42)	6.07 (4.27–16.46)	.003
Uric acid (umol/L)	372 (146–570)	345 (231–536)	.057
High-sensitivity C-reactive protein (mg/L)	1.5 (0.3–11.7)	1.5 (0.4–10.9)	.386
Hemoglobin (g/L)	155 ± 12	152 ± 12	.524
Platelet (10^9/L)	240 ± 47	186 ± 44	<.001
White blood cells (10^9/L)	6.6 (3.7–11.4)	6.3 (3.9–9.1)	.014
Red blood cell distribution width	13.04 ± 0.71	13.24 ± 0.73	.036
RDW × 100/PLT	5.48 (3.23–11.22)	7.03 (3.58–12.86)	<.001
DM prevalence (%)	29.3	47.3	<.001

DM = diabetic mellitus, NAFLD = nonalcoholic fatty liver disease, RDW = red cell distribution width.

fibrosis in chronic hepatitis B patients with relatively high accuracy, to get a further research of the association between RPR and advanced fibrosis in NAFLD *participants*, we used univariate logistic regression and multivariate logistic regression with forward selection to analyze the odds and *P* values. The results of Univariate and multivariate logistic regression models were shown in Table 3. We put age, sex, SBP, DBP, BMI, ALT, AST, γ- GT, TG, Cr, Tch, HDL-C, FPG, CRP, Hgb, PLT, RDW, RPR, and DM prevalence into the univariate logistic regression analysis, and we found age, SBP, AST, FPG, RPR, and DM prevalence were significantly correlated with advanced fibrosis (all $P < .05$). Then, we put age, SBP, AST, FPG, RPR, and DM prevalence into multivariate logistic regression with forward selection, and found age, AST, and RPR were significantly associated with advanced fibrosis (all $P < .05$). This result suggested that RPR (OR: 5.718, 95%CI: 3.326–9.830, $P < .001$) was an independent factor for advanced fibrosis prediction in NAFLD *participants*.

Table 2

The correlation between RPR and various parameters.

Variables	*r*	*P* value
Age (yr)	0.157	.002
Sex (F/M)	−0.132	.009
Body mass index (kg/m2)	0.015	.763
Systolic blood pressure (mmHg)	0.050	.329
Diastolic blood pressure (mmHg)	0.029	.565
Alanine aminotransferase (U/L)	0.021	.678
Aspertate aminotransferase (U/L)	0.099	.050
Glutamyltransferase (U/L)	0.025	.625
Triglyceride (mmol/L)	−0.003	.949
Creatinine (mmol/L)	0.136	.007
Total cholesterol (mmol/L)	0.024	.642
High-density lipoprotein cholesterol (mmol/L)	−0.015	.765
Low-density lipoprotein cholesterol (mmol/L)	0.028	.997
Fasting plasma glucose (mmol/L)	0.028	.585
Uric acid (μmol/L)	−0.006	.909
High-sensitivity C-reactive protein (mg/L)	−0.087	.086
Hemoglobin (g/L)	0.155	.002
White blood cells (10^9/L)	−0.250	<.001
DM prevalence (%)	0.025	.628
Advanced fibrosis	0.440	<.001

DM = diabetic mellitus, RPR = red cell distribution width-to-platelet ratio.

3.3. Optimizing the predictive model for advanced fibrosis

To form a more practical model for predicting NAFLD advanced fibrosis, we put age, AST, and RPR screened by the multivariate logistic regression into the new model. The new model is presented as logit (N index) = $0.307 \times \text{age} + 0.149 \times \text{AST} + 1.685 \times \text{RPR} - 32.124$. Furthermore, we applied a ROC curve to test the sensitivity and specificity of this new predictive model (Fig. 1). The area under curve (AUC) of new model was 0.976 with the 95% confidence interval from 0.964 to 0.988, the sensitivity and the specificity of which were 98.7% and 87.3%. The AUC of RPR was 0.816 with the 95% confidence interval from 0.765 to 0.868, the cutoff value was 6.39, the sensitivity and the specificity were 74.3% and 79.3%. The AUC of new model was significantly larger than AUC of RPR, z statistic was 6.193, $P < .001$.

4. Discussion

In the current study from NAFLD population, we provided evidence that NAFLD with advanced fibrosis had a higher RPR. The results also indicated that RPR ratio was an independent risk factor for advanced fibrosis. Finally, we established a predictive model for NAFLD by utilizing age, AST, and RPR with a larger AUC, high sensitivity and specificity. Our study is the first to demonstrate a significant association between RPR and NAFLD

Table 3

The odds values (95%CI) of regression analysis of dependent variables for predicting advanced fibrosis in NAFLD participants.

Variables	Univariate OR (95CI)	*P* value	Multivariate OR (95CI)	*P* value
Age (yr)	1.171 (1.128–1.214)	<.001	1.378 (1.259–1.509)	<.001
Sex (F/M)	0.800 (0.445–1.439)	.456		
Body mass index (kg/m^2)	0.978 (0.887–1.078)	.658		
Systolic blood pressure (mmHg)	1.028 (1.012–1.044)	<.001	0.998 (0.971–1.026)	.890
Diastolic blood pressure (mmHg)	1.020 (0.997–1.044)	.086		
Alanine aminotransferase (U/L)	0.990 (0.977–1.005)	.183		
Aspertate aminotransferase (U/L)	1.036 (1.009–1.063)	.007	1.170 (1.103–1.241)	<.001
Glutamyltransferase (U/L)	0.991 (0.978–1.005)	.218		
Triglyceride (mmol/L)	1.016 (0.882–1.170)	.825		
Creatinine (mmol/L)	0.997 (0.979–1.015)	.733		
Total cholesterol (mmol/L)	1.164 (0.915–1.481)	.216		
High-density lipoprotein cholesterol (mmol/L)	1.981 (0.787–4.986)	.147		
Low-density lipoprotein cholesterol (mmol/L)	1.255 (0.827–1.904)	.286		
Fasting plasma glucose (mmol/L)	1.352 (1.120–1.631)	.002	1.253 (0.906–1.733)	.173
Uric acid (μmol/L)	0.997 (0.993–1.000)	.058		
High-sensitivity C-reactive protein (mg/L)	0.970 (0.843–1.115)	.666		
Hemoglobin (g/L)	0.982 (0.962–1.003)	.086		
Platelet (10^9/L)	0.972 (0.965–0.980)	<.001		
White blood cells (10^9/L)	0.781 (0.642–0.949)	.013		
Red blood cell distribution width	1.400 (1.004–1.952)	.047		
RDW×100/PLT	2.194 (1.791–2.699)	<.001	5.718 (3.326–9.830)	<.001
DM prevalence (%)	2.166 (1.291–3.632)	.003	0.454 (0.136–1.507)	.197

DM = diabetic mellitus, NAFLD = nonalcoholic fatty liver disease, PLT = platelet, RDW = red cell distribution width.

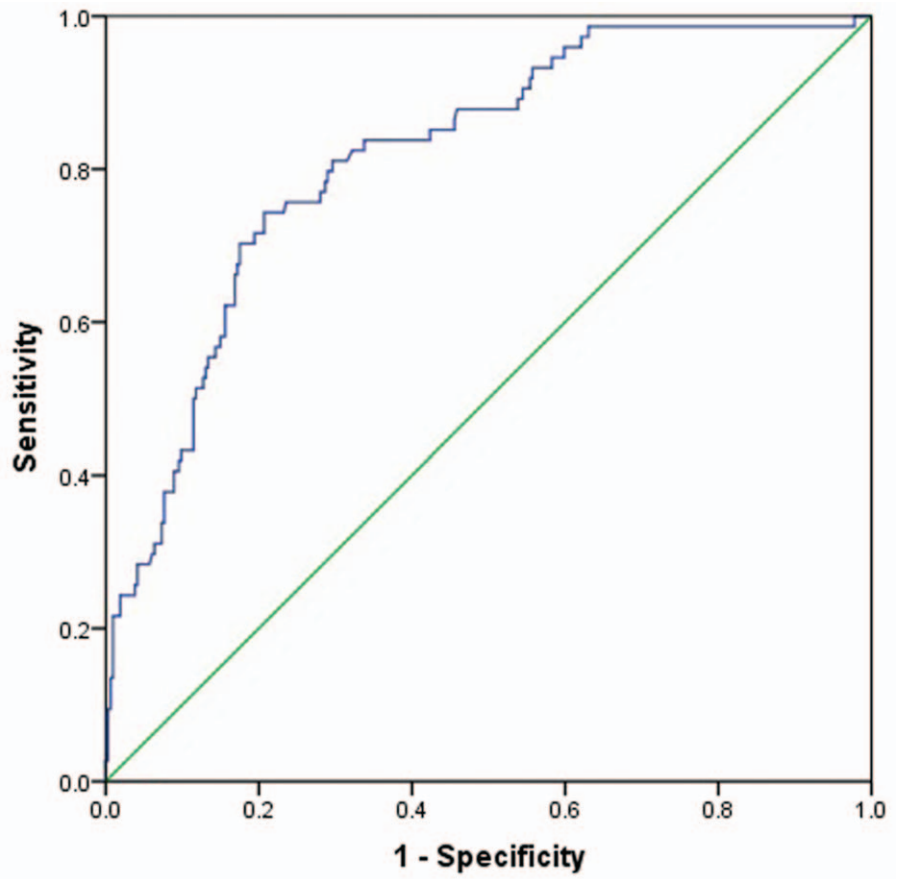

Figure 1. The ROC curve of this new predictive model.

with advanced fibrosis. NAFLD is reported to be associated with genetic, environmental, and metabolic factors. The underlying mechanism by which RPR interacts with NAFLD remained unclear.

Some studies suggested that serum RDW and PLT were associated with liver fibrosis and cirrhosis.[14,15] The RDW is an indicator of the variability of the circulating RBC size and often used to diagnose different types of anemia.[7] Recent studies indicated that a higher RDW was associated with a poor survival in gastric cancer,[30] lung disease,[31] ovarian cancers,[32] hepatocellular carcinoma,[33] and fatty liver disease,[14] then RDW may represent an easily obtainable and inexpensive prognostic marker in various patient populations. Chen et al[19] found that hemoglobin, RDW, and platelets were independent predictors of the liver fibrosis stage in patients with chronic hepatic B. Another study by Lou et al[34] found that higher RDW values were associated with disease severity in patients with hepatitis B. PLT count was decreased in liver diseases has long been known, and some studies reported a significant linear decrease in PLT count accompanied with the histological severity of fibrosis in NAFLD worsened.[2,16,20,35] The platelet count has been used in the most predictive models for liver fibrosis and cirrhosis, such as NAFLD fibrosis score, Fibrosis-4 calculator (FIB-4), AST/ALT ratio, and diabetes score, and AST-to-platelet ratio index, These scores have been used to detect fibrosis and cirrhosis in adult patients with hepatitis B and C, alcoholic liver disease and nonalcoholic fatty liver disease with platelet count decreased.[21,36]

Liver fibrosis is the result of excessive accumulation of extracellular matrix components, which consist of collagens and other components.[37] The development of liver fibrosis is considered to be a complex trait. The role of platelets in the progression of fibrosis is not well understood. Lin et al[37] and Iwasaki et al[38] designed to investigate whether platelets could reduce liver fibrosis and promote liver regeneration in fibrotic liver and found that platelets degraded extracellular matrix and reduced liver fibrosis by decreasing expression of TGF-b, and increasing expression of MMP-9, in addition to promoting liver regeneration. Additionally, the mechanism underlying the association between the RDW and the progression of fibrosis is also not well understood. Lippi et al[39] speculated that the association between RDW and inflammatory states was simply an epiphenomenon of underlying abnormal iron metabolism and/or anemia. Lan et al[40] found RDW values were increased and were related with various biomarkers and MELD grades in liver disease, and RDW could be used as an inflammatory marker for predicting chronic hepatitis B, liver cirrhosis, and hepatocellular carcinoma when combined with Hgb, AST, γ-GT, alkaline phosphatase, and globulin. Fujita et al[41] indicated iron overload was considered a putative element that interacts with oxygen radicals in inducing liver fibrosis and insulin resistance, and may have a role in the pathogenesis of NASH. However, some studies suggest that the use of Waist Circumference as a parameter of Metabolic Syndrome,[5] there were few evidences to prove it in Chinese population so far.

This study has some limitations. First, because this is a retrospectively cross-sectional study, the present analysis is limited in its ability to establish causal or temporal relationships between RPR and liver fibrosis. Due to the lack of data, we did not investigate the possible causes that may affect RDW values, such as iron or vitamin B12 deficiency. Second, the diagnosis of NAFLD was based on ultrasonography examination. Although ultrasonography is widely used in epidemiological studies of NAFLD, ultrasonography is not sensitive enough to detect mild steatosis, Third, we used the FIB-4 index for evaluating advanced fibrosis of NAFLD according to the studies of Xun et al.[29] FIB-4 index was not sensitive enough to identify patients with a mild degree of fibrosis who are at risk of progression. Finally, this study involved a single center and have posed a selection bias. Therefore, the performance of the RPR should be further confirmed in multi-center designed studies.

5. Conclusions

In conclusion, our results demonstrate a significant correlation between RPR and advanced fibrosis in NAFLD population. Because RDW and platelet values are easily available at no additional cost and are highly reproducible, RPR may serve as an important marker and potentially reduce the need for liver biopsy in NAFLD population. Further research on the involvement of PRR in NAFLD will enhance our understanding of the development of fibrosis, and benefit in the eventual development of new prevention and treatment strategies for NAFLD.

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