Red cell distribution width to platelet ratio (RPR) predicts liver fibrosis in patients with autoimmune hepatitis

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Abstract

Background Accurately evaluate the stages of liver fibrosis are critical for the management of patients with autoimmune hepatitis (AIH). We evaluated the accuracy of red cell distribution width (RDW) to platelet (PLT) ratio (RPR) in predicting liver fibrosis in AIH patients.

Methods One hundred and nineteen AIH patients with liver biopsy was retrospectively enrolled. Scheuer scoring system was used to stage liver fibrosis. Receiver operating characteristic curve (AUROC) was performed to evaluate the diagnostic accuracy of RPR.

Results The median RPR values were 0.10, 0.10 and 0.14 for AIH patients with S2-S4, S3-S4 and S4, which were significantly higher than patients with S0-S1 (0.07, P<0.001), S0-S2 (0.08, P=0.025) and S0-S3 (0.09, P=0.014), respectively. The RPR levels were positively associated with the fibrosis stages (r=0.412, P<0.001), whereas there were no associations between liver fibrosis stages and aspartate transaminase to platelet ratio index (APRI) and fibrosis-4 score (FIB-4). The AUROCs of RPR were 0.780 (95%CI 0.696 to 0.865), 0.639 (95%CI 0.530 to 0.748) and 0.724 (95%CI 0.570 to 0.878) in diagnosing significant fibrosis (S2-S4), advanced fibrosis (S3-S4) and cirrhosis (S4) for AIH patients, respectively. The AUROCs of RPR were significantly higher than those of APRI and FIB-4 in staging liver fibrosis for AIH patients.

Conclusion RPR is a simple predictor of liver fibrosis and is superior to APRI and FIB-4 in identifying liver fibrosis in AIH patients.

Background

Autoimmune hepatitis (AIH) is an immune-mediated chronic liver disease with typically clinical characteristics including elevated immunoglobulin G (IgG), hypergammaglobulinemia, specific autoantibodies production and liver interface hepatitis on pathological examination [1, 2]. Chronic liver inflammation is a significant reason of liver fibrosis, cirrhosis and hepatic carcinoma (HCC) in AIH [3]. Given the lack of specific diagnostic markers for AIH, many patients already have significant fibrosis or even cirrhosis when they are firstly diagnosed [3]. Therefore, timely and accurately evaluating the severity of liver fibrosis is essential for the management of AIH patients [4].

Liver biopsy (LB) has always been considered as a gold standard to assess liver inflammation and fibrosis in AIH patients [4, 5]. However, several shortcomings such as serious complications, high cost and observer discrepancy may limit the application of LB in clinical practice [6, 7]. Therefore, non-invasive tests (NITs) for assessing liver fibrosis are highly needed. Numerous studies have demonstrated that transient elastography (TE) is an accurate measurement of liver fibrosis in chronic viral hepatitis [8–10]. However, the predicting accuracy of TE in AIH patients is controversial, since elevated alanine aminotransferase (ALT) levels may affected the accuracy of TE in identifying liver fibrosis [11]. In addition, the high cost of TE equipment also limits the widely use of TE in clinical practice [12]. Two classical NITs, aspartate transaminase (AST) to platelet (PLT) ratio index (APRI) and the fibrosis-4 score (FIB-4), were initially proposed to assess liver fibrosis with relatively high accuracy in patients with chronic

hepatitis C (CHC) [13, 14]. APRI and FIB-4 are also recommended to assess significant fibrosis and cirrhosis in both chronic hepatitis B (CHB) and CHC patients by WHO [12, 15]. However, the predicting accuracy of APRI and FIB-4 was unsatisfied in AIH patients [16, 17].

A simpler NIT, red cell distribution width (RDW) to PLT ratio (RPR), was initially reported by Chen et al. to assess liver fibrosis and cirrhosis in CHB patients [18]. The area under the receiver operating characteristic curves (AUROCs) of RPR were 0.825 and 0.884 for diagnosing significant fibrosis and cirrhosis in CHB patients, which were significantly higher than that of FIB-4 and APRI [18]. In addition, the predicting performance of RPR for liver fibrosis was also relatively high in other liver diseases [19]. Wang, et al. reported that the diagnosis accuracy of RPR for significant fibrosis was higher than APRI and FIB-4 in patients with primary biliary cirrhosis (PBC) [19]. However, whether RPR could be used to predict the fibrosis stages in AIH patients remains unclear. Thus, in the present study, we aimed to analyze the diagnostic accuracy of RPR for liver fibrosis in AIH patients. Furthermore, we compared the predicting accuracy of RPR with APRI and FIB-4 for identifying liver fibrosis.

Methods

Patients

We retrospectively included 119 AIH patients who underwent liver biopsy from three medical centers (Nanjing Drum Tower Hospital, The Second Hospital of Nanjing and Huai'an No. 4 People's Hospital) between July 2016 and June 2019. The diagnostic criteria of AIH was according to the guideline of the American Association for the Study of Liver Diseases [4]. All patients did not received immunosuppressive therapy before liver biopsy. Patients were excluded based on the exclusion criteria as follows: 1) co-infected with viral hepatitis; 2) co-existence of nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease, PBC and hereditary metabolic liver disease; 3) co-existence of cancers including HCC and other malignant tumors.

All patients signed informed consent before liver biopsy was performed. The study was conducted according to the ethics principles of the Declaration of Helsinki and approved by the Ethics Committees of Nanjing Drum Tower Hospital, The Second Hospital of Nanjing and Huai'an No. 4 People's Hospital.

Liver biopsy and laboratory test

Liver biopsy was performed using a 16G puncture needle guided by ultrasound. Liver fibrosis was staged according to the Scheuer scoring system [20]. Liver fibrosis was divided into five stages: S0 to S4 [20]. The stages of S2-S4, S3-S4 and S4 are defined as significant liver fibrosis, advanced liver fibrosis and liver cirrhosis, respectively. Demographic and clinical data within one week before liver biopsy were retrospectively recorded, including age, sex, blood routine, biochemistry and immunology tests.

Computational formula of NITs

The computational formulas of NITs in our study were as follows: APRI: (AST (U/L)/ULN of AST)/PLT count (10^9/L) ×100 [13]; FIB-4: (age (years)×AST (U/L))/ ((PLT count (10^9/L) × (ALT (U/L))$^{1/2}$) [14]; RPR: RDW (%)/PLT count (10^9/L) [18].

Statistical analyses

Continuous variables were shown as median (interquartile range (IQR)) and categorical variables were presented as percentages. The differences of continuous parameters between groups were compared using the Student's t-test or Mann-Whitney U test. Chi-square test or Fisher's exact test was used to compare the differences of categorical variables. The correlation analysis was performed by Spearman's rank correlation test. The predictive accuracy of different NITs was compared based on receiver operating characteristic (ROC) curves. Differences among the AUROCs were compared using the z-test. The cut-off value was confirmed by the Youden's index which was the optimal combination of sensitivity and specificity. Differences were statistically significant at $P < 0.05$. Data analyses were carried out by using the SPSS statistical software version 22.0 (SPSS Inc., Chicago, IL, United States).

Results

Study Population

A total of 127 AIH patients were retrospectively included in the study. Of these patients, 5 patients co-infected with hepatitis B virus and 2 patients co-infected with hepatitis C virus. One patient with insufficient data were also excluded. 119 AIH patients were included for the final analysis. The baseline characteristics of patients were presented in Table 1. 99 (83.2%) patients were female and the median age was 52.5 (IQR 44.5, 59.8) years old. The median levels of PLT, RDW, ALT and IgG were 156.5 (IQR 118.3, 196.5) × 10^9/L, 13.7 (IQR 12.9, 15.6) %, 81.6 (IQR 40.0, 204.7) U/L and 15.9 (IQR 12.8, 20.8) g/L, respectively. 82 (68.9%) patients were positive for antinuclear antibody (ANA) positive and 17 (14.3%) patients were positive for anti-smooth muscle antibody (ASMA). The proportions of different liver fibrosis stages were: S0, 4 (3.4%) patients; S1, 33 (27.7%) patients; S2, 48 (40.3%) patients; S3, 22 (18.5%) patient and S4, 12 (10.1%) patients. The median values of APRI, FIB-4 and RPR were 1.32 (IQR 0.56, 2.64), 2.69 (IQR 1.35, 5.10) and 0.09 (IQR 0.07, 0.13), respectively.

Table 1

Baseline characteristics of study patients.

Variables	AIH (n = 119)
Age (y) (IQR)	52.5 (44.5, 59.8)
Female (%)	99 (83.2)
PLT (× 10^9/L) (IQR)	156.5 (118.3, 196.5)
RDW (%) (IQR)	13.7 (12.9, 15.6)
ALT (U/L) (IQR)	81.6 (40.0, 204.7)
AST (U/L) (IQR)	68.8 (33.8, 157.5)
GGT (U/L) (IQR)	121.3 (57.5, 216.1)
TB (μmol/L) (IQR)	22.7 (12.5, 36.6)
ALB (g/L) (IQR)	37.5 (34.0, 39.7)
IgG (g/L) (IQR)	15.9 (12.8, 20.8)
IgM (g/L) (IQR)	1.5 (1.1, 2.1)
ANA (+) (%)	82 (68.9)
ASMA (+) (%)	17 (14.3)
AMA (+) (%)	8 (6.7)
APRI (IQR)	1.32 (0.56, 2.64)
FIB-4 (IQR)	2.69 (1.35, 5.10)
RPR (IQR)	0.09 (0.07, 0.13)
Stage of liver fibrosis	
S0 (%)	4 (3.4)
S1 (%)	33 (27.7)
S2 (%)	48 (40.3)
S3 (%)	22 (18.5)
S4 (%)	12 (10.1)

AIH, autoimmune hepatitis; RDW, red cell distribution width; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; TB, total bilirubin; ALB, albumin; IgG immunoglobulin G; IgM immunoglobulin M; PT, prothrombin time; ANA antinuclear antibody; ASMA anti-smooth muscle antibody; IQR, interquartile range.

Comparisons of NITs among different liver fibrosis stages

Figure 1 showed APRI, FIB-4 and RPR levels in different fibrosis stages. The RPR values in patients with S2-S4 (0.10, IQR 0.08–0.15), S3-S4 (0.10, IQR 0.09–0.14) and S4 (0.14, IQR 0.09–0.19) were significantly higher than that of patients with S0-S1 (0.07, IQR 0.06–0.08, P < 0.001), S0-S2 (0.08, IQR 0.06–0.12, P = 0.018) and S0-S3 (0.09, IQR 0.07–0.13, P = 0.011), respectively. However, there were no significant differences of APRI values between patients with S0-S1 (1.31, IQR 0.48–3.24) and S2-S4 (1.37, IQR 0.57–2.52, P = 0.991), patients with S0-S2 (1.44, IQR 0.49–3.24) and S3-S4 (1.03, IQR 0.57–1.90, P = 0.261), S0-S3 (1.41, IQR 0.55–2.82) and S4 (0.89, IQR 0.58–1.40, P = 0.332). A higher value of FIB-4 was observed in patients with S2-S4 (3.22, IQR 1.58–6.41) compared to patients with S0-S1 (1.83, IQR 1.22–3.76, P = 0.017), whereas there were no significant differences of FIB-4 values between patients with S0-S2 (2.62, IQR 1.26–5.18) and S3-S4 (2.99, IQR 1.53–5.06, P = 0.713), S0-S3 (2.69, IQR 1.29–5.10) and S4 (3.28, IQR 1.72–5.97, P = 0.689). RPR level was positively correlated with fibrosis stages (r = 0.412, P < 0.001), while APRI (r = -0.061, P = 0.511) and FIB-4 (r = 160, P = 0.083) was not significantly correlated with fibrosis stages (Fig. 2).

Comparisons of the diagnostic accuracy of different NITs

ROC curves were used to compare the accuracy of different NITs in identifying fibrosis and cirrhosis (Fig. 3). The AUROCs of RPR in diagnosing significant fibrosis, advanced fibrosis and cirrhosis were 0.780 (95%CI 0.696 to 0.865), 0.639 (95%CI 0.530 to 0.748) and 0.724 (95%CI 0.570 to 0.878), respectively. The corresponding cut-off values of RPR were 0.083, 0.084 and 0.127, respectively. The AUROCs of APRI in predicting significant fibrosis, advanced fibrosis and cirrhosis were 0.499 (95%CI 0.379 to 0.620, P = 0.991), 0.434 (95%CI 0.329 to 0.539, P = 0.261) and 0.414 (95%CI 0.262 to 0.567, P = 0.332).The AUROCs of FIB-4 in predicting significant fibrosis, advanced fibrosis and liver cirrhosis were 0.639 (95%CI 0.529 to 0.748, P = 0.017), 0.522 (95%CI 0.410 to 0.634, P = 0.713) and 0.535 (95%CI 0.372 to 0.699, P = 0.689), respectively. The AUROCs of RPR were significantly higher than APRI and FIB-4 in diagnosing significant fibrosis, advanced fibrosis and liver cirrhosis (Table 2).

Table 2

Diagnostic accuracy of different indexes for predicting liver fibrosis in autoimmune hepatitis patients.

	Optimized cutoff	Sensitivity (%)	Specificity (%)	AUC (95%CI)	LR +	LR -	P value	P value of ROC contrast test*
Significant liver fibrosis (S2-S4)								
RPR	0.083	75.61	77.78	0.780 (0.696, 0.865)	3.403	0.314	< 0.001	-
APRI	0.271	98.78	11.11	0.499 (0.379, 0.620)	1.111	0.110	0.991	< 0.001
FIB-4	2.055	70.73	58.33	0.639 (0.529. 0.748)	1.697	0.502	0.017	0.002
Advanced liver fibrosis (S3-S4)								
RPR	0.084	79.41	51.19	0.639 (0.530, 0.748)	1.627	0.402	0.018	-
APRI	0.381	94.12	19.05	0.434 (0.329, 0.539)	1.163	0.309	0.261	< 0.001
FIB-4	3.928	44.12	66.67	0.522 (0.410, 0.634)	1.324	0.838	0.713	0.005
Liver cirrhosis (S4)								
RPR	0.127	66.67	77.36	0.724 (0.570, 0.878)	2.945	0.431	0.011	-

*Compared with RPR.

AUC, area under the receiver operating characteristic curve; CI, confidence interval; LR-, negative likelihood ratio; LR+, positive likelihood ratio.

	Optimized cutoff	Sensitivity (%)	Specificity (%)	AUC (95%CI)	LR +	LR -	P value	P value of ROC contrast test*
APRI	0.547	83.33	24.53	0.414 (0.262, 0.567)	1.104	0.680	0.332	< 0.001
FIB-4	2.212	75.00	42.45	0.535 (0.372, 0.699)	1.303	0.589	0.689	< 0.001
*Compared with RPR.								
AUC, area under the receiver operating characteristic curve; CI, confidence interval; LR-, negative likelihood ratio; LR+, positive likelihood ratio.								

Discussion

Accurately identifying the severity of liver fibrosis is essential to guide the clinical management of AIH. Although several NITs were proposed to predict liver fibrosis with high accuracy in patients with viral hepatitis [13, 18, 21], the diagnosis performance of these NITs in AIH patients is not yet clear.

APRI and FIB-4 as two most widely used NITs of diagnosing liver fibrosis were recommend by WHO for predicting liver fibrosis in CHB and CHC patients in resource-limited settings [12, 15, 22–24]. However, few studies reported the accuracy of APRI and FIB-4 for predicting liver fibrosis in AIH patients. Yuan et al. reported the AUROCs of APRI and FIB-4 were 0.798 and 0.881 for diagnosing liver cirrhosis in AIH patients [25]. Similar study was reported by Zeng et al. which showed that APRI and FIB-4 could diagnose liver cirrhosis with moderate accuracy in AIH patients [16]. However, these two studies only investigated the accuracy of APRI and FIB-4 in predicting liver cirrhosis in AIH patients. Compared to the diagnosis of liver cirrhosis, evaluating early stages of liver fibrosis may be more critical for the management of AIH patients [3]. Moreover, the sample sizes are small in these two studies [16, 25]. In the present study, we investigated the diagnostic accuracy of these two NITs for liver fibrosis in AIH patients with larger sample sizes. However, our results indicated that APRI could not predict significant liver fibrosis, advanced liver fibrosis and liver cirrhosis. FIB-4 could only identifying significant liver fibrosis with a very low AUROC of 0.639. Our study suggested that APRI and FIB-4 are not good NITs for staging liver fibrosis in AIH patients.

In the present study, we further investigated a novel NIT, RPR, for staging liver fibrosis in AIH patients. The diagnostic accuracy of RPR for different liver fibrosis stages was significantly higher than that of APRI and FIB-4. RPR was initially established to estimate liver fibrosis in CHB patients [18]. Previous study reported that RPR could predict significant fibrosis and cirrhosis with relatively high accuracy, which was superior to APRI and FIB-4 in CHB patients [18]. Since then, numerous studies have validated the accuracy of RPR for predicting liver fibrosis in chronic liver diseases [19, 26–28]. A retrospective study from Korean

indicated that the diagnostic performance of RPR for predicting advanced liver fibrosis and cirrhosis was comparable to FIB-4 and superior to APRI in CHB patients [26]. A meta-analysis also reported that RPR had similar diagnostic performance compared to APRI and FIB-4 in identifying significant liver fibrosis, while was comparable with APRI and inferior to FIB-4 in staging advanced liver fibrosis and cirrhosis in chronic liver diseases [27]. In nonviral liver diseases, Cengiz et al. found that the diagnostic accuracy of RPR was comparable with APRI and FIB-4 for predicting significant liver fibrosis, advanced liver fibrosis and cirrhosis in NAFLD patients [28]. Wang et al., reported that RPR had a higher accuracy than APRI and FIB-4 for predicting advanced fibrosis in treatment-naïve PBC patients [19].

Recently, Liu et al investigated the predicting accuracy of RPR for advanced liver fibrosis in patients with AIH [17]. They found that RPR had the highest accuracy compared to other NITs for predicting advanced liver fibrosis [17]. However, the sample size is relatively small with only 45 AIH patients included. In addition, this study only investigated the accuracy of RPR in predicting advanced liver fibrosis in AIH patients. Consisted with the study by Liu et al, our study also demonstrated that RPR could predict advanced liver fibrosis with high accuracy. Furthermore, we also investigated the diagnostic accuracy of RAR for significant liver fibrosis and cirrhosis in AIH patients. Our results showed that PRR could predicted significant fibrosis and liver cirrhosis with relative high accuracy.

RPR only contained two routine blood routine parameters and the computational formula is very simple. Previous studies reported that RDW levels were associated with severity of chronic liver diseases [29–31]. A retrospective study by Karagoz et al. reported that RDW levels were significantly elevated in CHB patients and can be used as an independent predictor of liver fibrosis [29]. Our previous study also found significantly elevated RDW in patients with CHB related cirrhosis [30]. Kim et al. reported that elevated RDW was associated with advanced liver fibrosis in a large cohort of NAFLD patients [31]. RDW was also demonstrated to be an independent predictor of cirrhosis in AIH [16, 17]. The elevation of RDW in AIH patients can be interpreted as follows. Firstly, hypersplenism caused by portal hypertension may increase the destruction of red blood cells [17]. In addition, various inflammatory cytokines may inhibit red blood cells maturation in AIH patients, which may induce the immature red blood cells into peripheral blood [32]. Moreover, chronic inflammation may impact the iron metabolism, restrain the production of erythropoietin and decrease red blood cells lifetime, which together result in the increase of RDW [33, 34]. PLT is also a well-known independent predictor for liver fibrosis in chronic liver diseases. The decreased PLT may be caused by hypersplenism and the decreased thrombopoietin production associated with damaged liver cells in liver fibrosis [35, 36].

Our study has several limitations. First, the patients were retrospective enrolled and the simple size was relatively small. Thus, the diagnostic value of RPR for liver fibrosis in AIH patients needs to be validated in the future. Second, we did not compare the predicting performance between RPR and TE since TE was not a routine measurement in our clinics. Third, whether RPR could predict long-term outcome of AIH deserves further investigation.

In conclusion, the RPR is a more accurate NIT than APRI and FIB-4 for staging liver fibrosis in AIH patients. The RPR represents a simple and inexpensive alternative NIT to liver biopsy for the management of AIH patients in clinic setting.

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Abbreviations

AIH, autoimmune hepatitis; IgG, immunoglobulin G; HCC, hepatic carcinoma; LB, liver biopsy; NITs, non-invasive tests; TE, transient elastography; ALT, alanine aminotransferase; AST, aspartate transaminase; PLT, platelet; APRI, AST to PLT ratio index; FIB-4, fibrosis-4 score; CHC, chronic hepatitis C; CHB, chronic hepatitis B; RDW, red cell distribution width; RPR, RDW to PLT ratio; AUROCs, receiver operating

characteristic curves; PBC, primary biliary cirrhosis; NAFLD, nonalcoholic fatty liver disease; IQR, interquartile range; ROC, receiver operating characteristic.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethics principles of the Declaration of Helsinki and was approved by the Ethics Committee of Nanjing Drum Tower Hospital, The Second Hospital of Nanjing and Huai'an No. 4 People's Hospital. All subjects provided written informed consent for the liver biopsy.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study will be available from the corresponding author on reasonable request.

Competing interests

The authors have declared that no conflicts of interest exist.

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Authors' Contributions

Rui Huang, Chao Wu and Yongfeng Yang designed the study and revised the manuscript;

Huali Wang and Jian Wang analyzed the data and wrote the manuscript; Juan Xia, Xiaomin Yan, Yanhong Feng, Lin Li, Jun Chen, Duxian Liu and Weimao Ding collated the data.

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Not applicable.

Figures

Figure 1

Comparisons of the APRI (A), FIB-4 (B) and RPR (C) levels according to different liver fibrosis stages in AIH patients.

Figure 2

Correlations between different noninvasive tests and liver fibrosis stages.

Figure 3

Receiver operating characteristic curve of different noninvasive tests for predicting significant liver fibrosis (A) advanced liver fibrosis (B) and liver cirrhosis (C) in AIH patients.