Fibrosis index based on four factors better predicts advanced fibrosis or cirrhosis than aspartate aminotransferase/platelet ratio index in chronic hepatitis C patients

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KEYWORDS
aspartate aminotransferase/platelet ratio index (APRI);
fibrosis index based on four factors (FIB-4);
hepatic C virus;
hepatic fibrosis

Abstract Background/Purpose: Liver biopsy is the gold standard to determine the severity of hepatic fibrosis despite its risk and invasiveness. The aspartate aminotransferase/platelet ratio index (APRI) could noninvasively predict the severity of hepatic fibrosis in chronic hepatitis C (CHC) patients. Whether fibrosis index based on four factors (FIB-4) could better predict the severity of hepatic fibrosis than APRI in CHC patients remains inconclusive.

Methods: This retrospective study enrolled 1473 CHC patients (784 men and 689 women) with liver biopsy and clinical data including age, aspartate aminotransferase, alanine aminotransferase, and platelet count. FIB-4 and APRI were calculated with a formula using the four clinical parameters. Hepatic fibrosis was staged using the Metavir classification system.

Results: The areas under the receiver operating characteristics of FIB-4 for the diagnosis of significant fibrosis (F2), advanced fibrosis (F3), and cirrhosis (F4) were 0.816 [95% confidence interval (CI), 0.795–0.836], 0.827 (95% CI, 0.806–0.849), and 0.849 (95% CI, 0.830–0.867), respectively, compared with those of APRI—0.799 (95% CI, 0.778–0.819), 0.791 (95% CI, 0.770–0.812), and 0.802 (95% CI, 0.781–0.922). In addition, the...
areas under the receiver operating characteristics of FIB-4 were significantly greater than those of APRI for patients with advanced fibrosis and cirrhosis, respectively ($p < 0.0001$).

Conclusion: FIB-4 could predict hepatic fibrosis in CHC patients. By adding two parameters (age and alanine aminotransferase), FIB-4 better predicts advanced fibrosis and cirrhosis than APRI in CHC patients.

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Introduction

Chronic hepatic C virus (HCV) infection is one of the common chronic liver diseases worldwide, leading to the complications such as cirrhosis, liver decompensation, and hepatocellular carcinoma. Chronic HCV infection can induce hepatic fibrogenesis, and the severity of hepatic fibrosis is closely associated with long-term prognosis in chronic hepatitis C (CHC) patients. In addition, advanced fibrosis is one of the factors associated with unfavorable response to standard of care using interferon and ribavirin. Thus, it is important to determine the severity of hepatic fibrosis in our clinical practice. However, the severity of hepatic fibrosis could not be easily measured by imaging modalities such as ultrasound or computed tomography. Although liver biopsy with subsequent histological examination is currently the gold standard to stage hepatic fibrosis, it is invasive and carries the risk of complications such as pain or bleeding. In addition, small sampling area and interobserver variability could decrease its accuracy.

Transient elastography, which was recently introduced to measure liver stiffness, can predict the severity of hepatic fibrosis even in dialysis CHC patients. Although transient elastography is noninvasive, the instrument is expensive and thus not widely available. The scores of aspartate aminotransferase/platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4) are easily obtained through a formula using four clinical parameters—ast aspartate aminotransferase (AST), platelet count, age, and alanine aminotransferase (ALT) levels. APRI has been confirmed to precisely predict the severity of hepatic fibrosis in patients or even hemodialysis patients with CHC. The FIB-4 score is derived by adding two parameters (age and ALT in the backbone of APRI), and it was first developed to predict hepatic fibrosis in a cohort of patients with HCV and human immunodeficiency virus (HIV) co-infection. Later on, its predictive value was further validated in HCV monoinfected patients. A previous study showed that FIB-4 was useful in predicting significant fibrosis after liver transplant, independent of etiology. Another report suggested that FIB-4 could predict liver-related death in a cohort of CHC patients with or without HIV infection. Nevertheless, whether FIB-4 is better than APRI in predicting the severity of hepatic fibrosis or cirrhosis in CHC patients remains unclear. Thus, we conducted a large-scale retrospective study to solve the clinically important and relevant issues.

Methods

Study overview

Between 2006 and 2013, a total of 1473 CHC adult patients who received percutaneous liver biopsy prior to antiviral treatment in Taipei Tzu Chi Hospital and National Taiwan University Hospital in Taipei, Taiwan were retrospectively recruited in the study. All patients had positive anti-HCV antibody and detectable HCV RNA for at least 6 months. They had no other known causes of hepatitis such as alcoholism or use of hepatotoxic drug, and were negative for hepatitis B virus or HIV co-infection. The exclusion criteria were as follows: (1) patients had hepatocellular carcinoma; (2) patients received liver transplantation; and (3) patients received platelet transfusion recently. Demographic, biochemical, and virological data including age, sex, AST, ALT, HCV RNA, genotype, and platelet count were obtained from each patient at the time of liver biopsy. The formula used for APRI is:

$$\text{AST level} / \text{platelet count} \times 100, \quad (1)$$

and the formula used for FIB-4 is:

$$\text{age} \times \text{AST} / \left( \text{platelet count} \times \text{ALT}^{1/2} \right). \quad (2)$$

Biochemical and virological tests

The biochemical data were measured with an autoanalyzer (ROCHE ANALYTICS; Roche Professional Diagnostics, Penzberg, Germany). The upper limit of normal ALT level is 34 U/L for females and 45 IU/L for males. The upper limit of normal AST is 40 IU/L for both males and females. The HCV RNA level and genotype were determined as previously described.

Histological evaluations of liver biopsy specimens

Echo-guided percutaneous liver biopsy was performed from the right hepatic lobe using a 16-gauge biopsy needle (Temno Evolution, Allegiance, McGaw Park, IL, USA). The sampling tissues were fixed with formalin, embedded with paraffin, and stained with hematoxylin and eosin. All biopsy samples were evaluated by experienced pathologists who were blinded to the clinical data of the patients. The
severity of hepatic fibrosis was staged using the Metavir fibrosis score, ranging from F0 to F4. Significant fibrosis, advanced fibrosis, and cirrhosis were defined as fibrosis stage /C21 F2, /C21 F3, and F4, respectively. Most patients followed at the National Taiwan University Hospital had >1 liver biopsies. However, only biopsy results obtained prior to interferon plus ribavirin therapy were included for analysis in this study.

Ethical considerations

The study was performed in accordance with the principles of the 1975 Declaration of Helsinki and approved by the Ethical Committee of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, which waived the requirement for study design-specific informed consent.

Statistical analysis

Continuous variables including age, AST, ALT, platelet count, APRI, FIB-4, and HCV RNA were expressed as mean (standard deviation). Categorical variables were expressed by patient number and percentages. The diagnostic accuracy of APRI and FIB-4 were evaluated using receiver operating characteristics (ROC) curves, and the areas under the ROC curves (AUROCs) for APRI and FIB-4 were expressed as mean [95% confidence interval (CI)] and compared by c statistics.19 Furthermore, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+, and negative likelihood ratio (LR−) of FIB-4 were further evaluated by choosing the selected cutoff values. Statistical analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA). All tests were two-tailed, and p < 0.05 was considered statistically significant.

Results

Patients

Overall, 784 men and 689 women were enrolled in the study. Their mean age was 54.4 ± 11.5 years. The mean serum AST and ALT levels were 92 IU/L and 134 IU/L, respectively. With regard to hepatic fibrosis, 27 (1.8%), 352 (23.9%), 541 (36.7%), 186 (12.6%), and 367 (24.9%) of these patients were staged as F0, F1, F2, F3, and F4, respectively. Among these patients, 1364 (92.6%) had available data for HCV RNA level and genotype. The mean viral load was 3.16 × 10^6 IU/mL. Most patients (93.2%) had HCV genotype 1 and/or 2 infection (Table 1). The APRI and FIB-4 scores of patients with different stages of hepatic fibrosis are shown in Table 2.

Comparison of diagnostic accuracy between APRI and FIB-4

The AUROCs of FIB-4 were significantly greater than those of APRI in patients with advanced fibrosis [0.827 (95% CI, 0.806–0.849) vs. 0.791 (95% CI, 0.770–0.812), p < 0.0001] and cirrhosis [0.849 (95% CI, 0.830–0.867) vs. 0.802 (95% CI, 0.781–0.867), p < 0.0001] (Figure 1). However, the AUROC of FIB-4 tended to be greater than that of APRI in patients with significant fibrosis [0.816 (95% CI, 0.795–0.836) vs. 0.799 (95% CI, 0.778–0.819), p = 0.06].

### Table 1  Baseline patient characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (N = 1473)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>54.4 (11.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>784 (53.2)</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>92 (75)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>134 (106)</td>
</tr>
<tr>
<td>Platelet count (10^9/L)</td>
<td>172 (59)</td>
</tr>
<tr>
<td>APRI</td>
<td>1.91 (2.09)</td>
</tr>
<tr>
<td>FIB-4</td>
<td>3.15 (2.82)</td>
</tr>
<tr>
<td>Fibrosis stage (Metavir), n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27 (1.8)</td>
</tr>
<tr>
<td>1</td>
<td>352 (23.9)</td>
</tr>
<tr>
<td>2</td>
<td>541 (36.7)</td>
</tr>
<tr>
<td>3</td>
<td>186 (12.6)</td>
</tr>
<tr>
<td>4</td>
<td>367 (24.9)</td>
</tr>
<tr>
<td>HCV genotype, n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>804 (58.9)</td>
</tr>
<tr>
<td>2</td>
<td>465 (34.1)</td>
</tr>
<tr>
<td>Mixed 1 and 2</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>3</td>
<td>76 (5.6)</td>
</tr>
<tr>
<td>6</td>
<td>14 (1.0)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>HCV RNA level (IU/mL)</td>
<td>3,155,404 (6,092,998)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) unless otherwise indicated.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; APRI = AST/platelet count ratio index; FIB-4 = fibrosis index based on four factors; HCV = hepatitis C virus; SD = standard deviation.

### Table 2  Distribution of hepatic fibrosis stage according to the Metavir classification.

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>27 (1.8)</td>
<td>352 (23.9)</td>
<td>541 (36.7)</td>
<td>186 (12.6)</td>
<td>367 (24.9)</td>
</tr>
<tr>
<td>APRI</td>
<td>0.82 ± 0.72</td>
<td>0.93 ± 0.80</td>
<td>1.65 ± 2.32</td>
<td>2.24 ± 1.89</td>
<td>3.14 ± 2.12</td>
</tr>
<tr>
<td>FIB-4</td>
<td>1.47 ± 0.61</td>
<td>1.56 ± 0.91</td>
<td>2.63 ± 2.74</td>
<td>3.46 ± 2.16</td>
<td>5.42 ± 3.09</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) unless otherwise indicated.

APRI = aspartate aminotransferase to platelet ratio index; SD = standard deviation.
Comparison of diagnostic accuracy between APRI and FIB-4 categorized by HCV genotype 1 or 2

In 804 patients with chronic genotype 1 HCV infection, the AUROCs of FIB-4 were significantly greater than those of APRI in patients with advanced fibrosis [0.834 (95% CI, 0.807–0.859) vs. 0.807 (95% CI, 0.778–0.834), p = 0.0087] and cirrhosis [0.858 (95% CI, 0.832–0.881) vs. 0.817 (95% CI, 0.789–0.843), p = 0.0001]. However, the AUROC of FIB-4 was not different with that of APRI in patients with significant fibrosis [0.813 (95% CI, 0.784–0.839) vs. 0.799 (95% CI, 0.769–0.826), p = 0.28]. In 465 patients with chronic genotype 2 HCV infection, the AUROCs of FIB-4 were significantly greater than those of APRI in patients with advanced fibrosis [0.806 (95% CI, 0.767–0.841) vs. 0.770 (95% CI, 0.729–0.807), p = 0.0193] and cirrhosis [0.818 (95% CI, 0.78–0.852) vs. 0.767 (95% CI, 0.726–0.804), p = 0.0029]. However, the AUROC of FIB-4 was not significantly different from that of APRI in patients with significant fibrosis [0.817 (95% CI, 0.779–0.851) vs. 0.803 (95% CI, 0.764–0.838), p = 0.32].

Selective cutoff values of FIB-4 for different stages of hepatic fibrosis

If FIB-4 was <1.45, the NPV was 92.7% and the sensitivity was 95.1% for advanced fibrosis (Table 3). If FIB-4 > 3.25, the PPV was 71.4% and the specificity was 84.9% for advanced fibrosis.

Discussion

In this study, 1473 CHC patients with mainly genotype 1 and/or 2 infection were enrolled. By using AUROC analysis, our data show that both FIB-4 and APRI can predict the severity of hepatic fibrosis in CHC patients. In addition, FIB-4 can better predict advanced fibrosis and cirrhosis than APRI (p < 0.0001).
FIB-4 better than APRI in chronic hepatitis C

Table 3  Selective cutoff values of FIB-4 for different stages of hepatic fibrosis.

<table>
<thead>
<tr>
<th>Prevalence (%)</th>
<th>≥ F2</th>
<th>≥ F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>74.2</td>
<td>37.5</td>
<td>24.9</td>
<td></td>
</tr>
<tr>
<td>Cutoff value</td>
<td>0.75</td>
<td>2.15</td>
<td>1.45</td>
</tr>
<tr>
<td>PPV</td>
<td>77.6</td>
<td>91.0</td>
<td>47.6</td>
</tr>
<tr>
<td>NPV</td>
<td>82.7</td>
<td>46.3</td>
<td>92.7</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>98.7</td>
<td>67.6</td>
<td>95.1</td>
</tr>
<tr>
<td>Specificity</td>
<td>17.7</td>
<td>80.7</td>
<td>37.1</td>
</tr>
<tr>
<td>LR+</td>
<td>1.20</td>
<td>3.51</td>
<td>1.51</td>
</tr>
<tr>
<td>LR−</td>
<td>0.07</td>
<td>0.40</td>
<td>0.13</td>
</tr>
</tbody>
</table>

FIB-4 = fibrosis index based on four factors; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

These findings hold true in either genotype 1 or 2 CHC patients. In clinical practice, if FIB-4 was < 1.45, the NPV for advanced hepatic fibrosis was 92.7%. If the FIB-4 index was > 2.15, the PPV of significant fibrosis (≥ F2) was 91%.

Hepatic fibrosis is one of the important factors associated with the long-term prognosis of CHC patients. If noninvasive methods could accurately predict the severity of hepatic fibrosis, the majority of liver biopsies could be avoided. In recent years, transient elastography has been accepted as an alternative method to assess the severity of hepatic fibrosis. However, several limitations could affect its clinical usefulness. The cost of transient elastography may preclude its widespread availability, and it has a decreased accuracy in specific population groups including obese patients or patients with ascites or hepatits flare. To the best of our knowledge, this study is the first one in Asian CHC patients. Thus, we can validate the power of FIB-4 for predicting hepatic fibrosis in clinical practice, and serial data can be obtained to follow up on disease progression.

Taking these data together, we suggest using FIB-4 instead of APRI to predict hepatic fibrosis in clinical practice, and urge practicing physicians to measure platelet count in addition to routine AST, ALT, and AFP testing as well as ultrasound examination for the regular follow-up of CHC patients. Just like the role of estimated glomerular filtration rate (eGFR) (formula \( \frac{186.3 \times \text{serum creatinine} - 1.154 \times \text{age} - 0.203 \times (0.742 \text{if female}) \times (1.212 \text{if black})}{186.3 \times \text{serum creatinine} - 1.154 \times \text{age} - 0.203 \times (0.742 \text{if female}) \times (1.212 \text{if black})} \)) in the prediction of renal function, if FIB-4 index can be automatically calculated with the aid of a computer, we can easily understand the status of hepatic fibrosis and its progression.

This study has several unique features. First, this is the first validation of FIB-4 in Asian CHC patients. Thus, we can validate the power of FIB-4 for predicting hepatic fibrosis in Asian patients. Second, the sample size is large, and different severity levels of hepatic fibrosis—including significant, advanced fibrosis, or cirrhosis—were analyzed using AUROC between APRI and FIB-4. Thus, we could understand the performance of FIB-4 in different severity levels of hepatic fibrosis compared with APRI. Third, diagnostic accuracy between FIB-4 and APRI was compared not only in the overall population but also in subgroups categorized by HCV genotype 1 or 2. However, several limitations are also noted. First, although a small proportion of patients (7.4%) lacked data on HCV RNA and genotype, the percentage was acceptable. Second, the possible interobserver variability between different pathologists in determining the severity of hepatic fibrosis could not be avoided.

In summary, the FIB-4 index is validated to noninvasively predict the severity of hepatic fibrosis, and compared with APRI it better predicts advanced fibrosis and cirrhosis in Asian CHC patients. It is noninvasive, simple, and widely available in clinical practice. Just like eGFR for predicting renal function, it can help physicians to understand the severity of hepatic fibrosis and follow up on disease progression in CHC patients.

Acknowledgments

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References


