FibroQ: An Easy and Useful Noninvasive Test for Predicting Liver Fibrosis in Patients with Chronic Viral Hepatitis

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Background: Liver biopsy–the gold standard in assessing liver histology–is recommended before all antiviral treatment. However, this procedure may cause complications, is costly, and is limited by sampling errors. Hence, noninvasive tests have been proposed to assess the severity of hepatic fibrosis. We propose a novel noninvasive index for predicting liver fibrosis, named fibro-quotient (FibroQ), and compared the diagnostic accuracies of FibroQ, aspartate aminotransferase (AST)-to-platelet ratio index (APRI), and AST/alanine aminotransferase (ALT) ratio (AAR).

Methods: This retrospective cohort study included 140 consecutive patients with chronic viral hepatitis who had undergone percutaneous liver biopsy before treatment at the Chang Gung Memorial Hospital, Chiayi from May 2005 through December 2007. The clinical data including sex, age, AST, ALT, platelet count, prothrombin time (PT) international normalized ratio (INR), and the Metavir fibrosis score (F0 to F4) of liver histology were recorded. APRI, AAR, and FibroQ were calculated. Receiver operating characteristic (ROC) curves were constructed to compare the accuracies of these three noninvasive tests in predicting significant fibrosis in patients with chronic viral hepatitis.

Results: FibroQ performed better than APRI, but was equal to AAR, in the prediction of significant fibrosis [area under the receiver operating characteristic curve (AUC): 0.783 vs 0.631 ($p = 0.02$) and 0.783 vs 0.733 ($p = 0.26$), respectively] and cirrhosis (AUC: 0.791 vs 0.634 ($p = 0.03$), and 0.791 vs 0.782 ($p = 0.47$), respectively). Using FibroQ below the lower cutoff value (0.6) and above the higher cutoff value (1.6), 108 of 140 (77.1%) patients could be identified correctly to have or not have significant fibrosis.

Conclusion: FibroQ, a novel noninvasive test, is an useful and easy tool to evaluate liver fibrosis in patients with chronic viral hepatitis and has better accuracy than APRI and is equal to AAR. Further prospective studies are warranted to validate its efficacy.

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Key words: liver fibrosis, noninvasive test, FibroQ, aspartate aminotransferase/alanine aminotransferase ratio (AAR), aspartate aminotransferase-to-platelet ratio index (APRI)

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Chronic viral hepatitis is one of the most common liver diseases in Taiwan, particularly in the face of a high prevalence of hepatitis C virus (HCV) infection in southern Taiwan.[1] It is known that patients with high degrees of fibrosis may progress rapidly to cirrhosis and hepatocellular carcinoma. Approximately 20% of patients with chronic viral hepatitis advance to cirrhosis and 5% of them develop hepatocellular carcinoma.[2,3] In contrast, patients with no fibrosis or with only portal fibrosis show slow progression to hepatocellular carcinoma.[4] To avoid the progression of the disease and complications, antiviral treatment is needed.[5] Since the risk of developing cirrhosis is closely related to the stage of fibrosis, liver biopsy is recommended before antiviral treatment. However, complications may occur and liver biopsy is costly and limited by sampling errors.[6,7] Hence, noninvasive tests have been proposed to access the severity of hepatic fibrosis in an attempt to replace biopsy. Aspartate aminotransferase (AST)-to-platelet ratio index (APRI)[8-12] and AST/alanine aminotransferase (ALT) ratio (AAR)[13-18] are known parameters that are based on laboratory test results and are therefore readily available in clinical practice. These two parameters have been reported to predict the presence of significant fibrosis and cirrhosis in a portion of patients.[8-18] Nearly all of the studies were conducted in western countries, and hence, it is questionable whether these two parameters could be used similarly for patients with chronic viral hepatitis in Taiwan. The initial aim of this study was to evaluate and compare the diagnostic accuracies of APRI and AAR for the prediction of significant fibrosis and cirrhosis in patients with chronic hepatitis in Taiwan. In addition, we found a novel index named fibrosis quotient (FibroQ) and compared the diagnostic accuracies of the three.

METHODS

The departmental files of the Department of Gastroenterology, Chang Gung Memorial Hospital, Chiayi, were reviewed using the computer records of patients who had undergone percutaneous liver biopsy from May 2005 through December 2007. Patients with chronic viral hepatitis were included. The diagnoses of viral hepatitis (including hepatitis B, hepatitis C, and hepatitis B and C) were defined as the presence of HBsAg or anti-HCV Ab using the EIA methods (Abbott Architect, I 2000). Patients with the following conditions were excluded from the study: co-infected with human immunodeficiency virus (HIV), alcohol consumption in excess of 20 g/d, hepatocellular carcinoma, prior history of having undergone liver transplantation, prior antiviral or immunosuppressive therapy, metabolic liver disease, insufficient liver tissue for staging of fibrosis, recent warfarin or other anticoagulant usage, and incomplete data on liver function tests or platelet count within 1 month from the date of biopsy. We found 140 patients with chronic viral hepatitis who fulfilled our criteria. The clinical data were reviewed and the following parameters were recorded: sex, age, AST, ALT, platelet count, prothrombin time (PT) (international normalized ratio) (INR), albumin, hemoglobin, white blood cell (WBC), serum creatinin (Cr), free hormone of thyroxine (FT4), thyroid-stimulating hormone (TSH), and Metavir fibrosis score[19] (F0 to F4) of liver histology. Significant liver fibrosis was defined as a Metavir fibrosis score of > 1 (F2–4), and cirrhosis was defined as Metavir fibrosis score 4 (F4).

Statistical analysis was performed using the SPSS software version 12.0 (SPSS Inc., Chicago, IL, U.S.A.). Patient characteristics have been represented as the mean ± standard deviation (SD). Bivariate Spearman's rank correlation coefficient (R) was calculated in order to measure the relationship between the variables. Receiver operating characteristic (ROC) curves were constructed for each test. To evaluate the diagnostic accuracies of the simple fibrosis prediction tests, their sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and the area under the receiver operating characteristic curves (AUC) were calculated.

RESULTS

Patient characteristics

The characteristics of the 140 patients are summarized in Table 1. The ages of the patients ranged from 19 to 76 years at the time of undergoing biopsy (53.3 ± 11.4 years). The AST ranged from 17 to 307 U/L (95.7 ± 51.7 U/L). The ALT ranged from 15 to 442 U/L (152.7 ± 86.4 U/L). The platelet count ranged from 61–373 x 10^3/μL (170.5 ± 52.3 x 10^3/μL). The APRI ranged from 0.681–2.737 (1.872

Table 1. Patients' Characteristics

		(N = 140)			
M/F		91/49			
Etiology					
HBsAg (+)		18			
HCV Ab (+)		113			
HBsAg (+) & HCV Ab (+)		9			
Age (years)		53.2 ± 11.4			
AST (U/L)		95.7 ± 51.7			
ALT (U/L)		152.7 ± 86.4			
PT INR		1.042 ± 0.075			
PLT (x 10^3/μL)		170.5 ± 52.3			
Albumin (g/dL)		4.23 ± 0.33			
Hemoglobin (g/L)		14.6 ± 1.48			
WBC (x 10^9/L)		5.93 ± 1.83			
Cr (mg/dL)		0.96 ± 0.22			
FT4 (μg/dL)		1.12 ± 0.18			
TSH (mU/mL)		1.85 ± 1.82			
APRI		1.872 ± 1.243			
AAR		0.687 ± 0.259			
FibroQ		2.668 ± 1.723			
		N (%)	APRI	AAR	FibroQ
Metavir fibrosis stage	F1	24 (17.1%)	1.367 ± 0.784	0.535 ± 0.186*†	1.429 ± 0.899*‡
	F2	57 (40.7%)	1.811 ± 1.462	0.676 ± 0.269	2.429 ± 1.501§
	F3	53 (37.9%)	2.142 ± 1.148	0.744 ± 0.250*	3.311 ± 1.854*§
	F4	6 (4.3%)	2.080 ± 0.625	0.891 ± 0.214†	4.202 ± 1.597‡

Abbreviations: INR: international normalized ratio; AAR: AST/ALT ratio; APRI: AST-to-platelet ratio index; FibroQ: 10 x (Age x AST x PT INR/ALT x platelet count); *: $p < 0.01$, F1 vs. F3; †: $p < 0.05$, F1 vs. F4; ‡: $p < 0.01$, F1 vs. F4; §: $p < 0.05$, F2 vs. F3.

± 1.243). The AAR ranged from 0.548–1.133 (0.687 ± 0.259). There were 24 (17.1%) patients with F1 fibrosis, 57 (40.7%) patients with F2 fibrosis, 53 (37.9%) patients with F3 fibrosis, and six (4.3%) patients with F4 fibrosis. The AAR scores increased significantly as the fibrosis advanced (ANOVA test; $p = 0.002$). The APRI scores also tended to increase as the fibrosis advanced, although they were not statistically significant (ANOVA test; $p = 0.07$).

Predictors of significant fibrosis and formulation of a new index

Bivariate Spearman's rank correlation coefficient (R) was calculated to measure the relationship between individual serum markers and the Metavir fibrosis score (Table 2). Liver fibrosis correlated with age ($p = 0.008$) and prothrombin time (PT INR) ($p = 0.001$), whereas a strong correlation was found between liver fibrosis and the platelet count ($p < 0.001$). Although AST and ALT lacked any correlation with liver fibrosis, AAR (AST/ALT) correlated with the fibrosis score ($p < 0.001$). Other factors such as albumin, hemoglobin, WBC, serum creatinin, FT4, TSH, lacked any correlation with liver fibrosis ($p > 0.05$).

As shown in Table 3 and Fig. 1, the AUCs of APRI and AAR is not so good in predicting significant fibrosis as reported by other authors. We hypothesized that an index combined more significantly correlated parameters would have a better prediction efficacy. For this reason, we put the positive correlation parameters (age, PT INR and AAR) in the numerator and negative correlation parameters

Table 2. Correlation of Fibrosis Severity with the Variables

	Bivariate Spearman's rank correlation coefficient (95% CI)	*p* value
Age (years)	0.224 (0.060, 0.376)	0.008
AST (U/L)	0.133 (–0.034, 0.292)	0.117
ALT (U/L)	–0.129 (–0.288, 0.038)	0.129
PT INR	0.278 (0.117, 0.424)	0.001
Platelet count (x 10^3/μL)	–0.378 (–0.512, –0.226)	< 0.001
Albumin	–0.164 (–0.321, 0.002)	0.271
Hb	–0.136 (–0.295, 0.030)	0.109
WBC	–0.154 (–0.312, 0.012)	0.071
Cr	–0.165 (–0.322, 0.001)	0.053
FT4	–0.157 (–0.315, 0.009)	0.101
TSH	–0.025 (–0.190, 0.141)	0.791
AAR	0.362 (0.208, 0.498)	< 0.001
APRI	0.273 (0.112, 0.420)	0.001
FibroQ	0.465 (0.324, 0.586)	< 0.001

Abbreviations: INR: international normalized ratio; AAR: AST/ALT ratio; APRI: AST-to-platelet ratio index; FibroQ: 10 x (Age x AST x PT INR/ALT x platelet count). We used Fisher's Z-transform to compute asymmetric confidence limits for the Spearman's rank correlation coefficients.

(platelet) in the denominator to formulate a novel index. We named it the fibrosis quotient, FibroQ = [(10 x age x AST x PT INR)/(PLT x ALT)]. The FibroQ ranged from 0.328 to 10.155 (2.668 ± 1.723) and increased as the fibrosis advanced (ANOVA test: $p < 0.001$).

Predicting significant fibrosis

ROC curves evaluating the diagnostic accuracies of FibroQ, AAR, APRI were constructed to predict significant fibrosis (Fig. 1). Comparison of the AUCs for continuous variables (FibroQ, AAR, APRI) via the procedures described by Hanley[20] showed a superior diagnostic accuracy of FibroQ

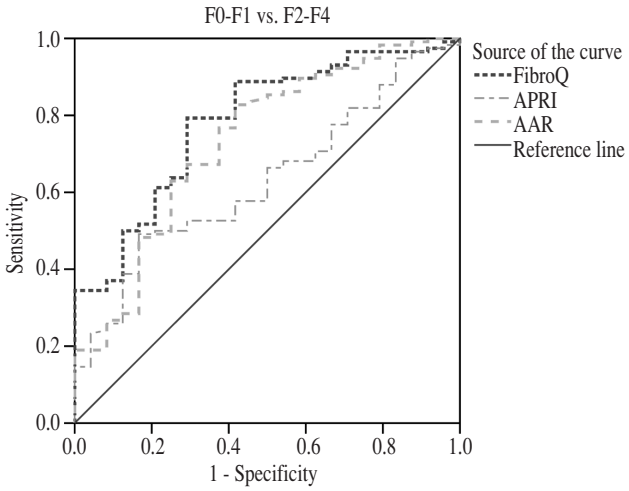

Fig. 1 Receiver operating characteristic (ROC) curves of the simple noninvasive tests for prediction of significant fibrosis (F2–4) according to the Metavir system in 140 patients with chronic viral hepatitis. ROC curves are shown for the fibrosis stage as assessed by the pathologist. Abbreviations used: FibroQ: 10 x (Age x AST x PT INR/ALT x platelet count); AAR: AST/ALT ratio; APRI: AST-to-platelet ratio index.

Table 3. Performance of Simple Fibrosis Prediction Tests for Significant Fibrosis (F2–4) and Cirrhosis (F4)

Metavir fibrosis score vs.	AUC (F2–4)	AUROC (F4)
AAR	0.733 (95% CI: 0.618–0.848)	0.782 (95% CI: 0.597–0.967)
APRI	0.631 (95% CI: 0.521–0.741)	0.634 (95% CI: 0.507–0.761)
FibroQ	0.783 (95% CI: 0.687–0.880)	0.791 (95% CI: 0.680–0.902)

Abbreviations: AUC: area under the receiver operating characteristic curve (confidence intervals are given in parentheses); AAR: AST/ALT ratio; APRI: AST-to-platelet ratio index; FibroQ: 10 x (Age x AST x PT INR / ALT x platelet count).

(AUC = 0.783) over APRI (AUC = 0.631; $p = 0.02$, statistically significant), but equal to AAR (AUC = 0.733; $p = 0.26$, not statistically significant), in the prediction of significant fibrosis (Table 3).

To compare our results with those of previous reports, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the simple fibrosis prediction tests were calculated using cutoff values exactly as originally described (Table 4). However, the accuracy of the original cutoff value (AAR, 1.0; APRI, ≤ 0.5 or > 1.5) was not found to be optimal. We then selected the most balanced cutoff value for FibroQ (1.6), AAR (0.5), and APRI (1.2) from the ROC analysis in order to predict significant liver fibrosis. It is evident that FibroQ has better accuracy than AAR and APRI. Using a cutoff value of the FibroQ score of > 1.6, the presence of significant fibrosis could correctly be identified with a high accuracy (93% PPV) in 92 (65%) of the 140 patients.

Predicting cirrhosis

ROC curves evaluating the diagnostic accuracies of FibroQ, AAR, and APRI were constructed to predict cirrhosis (Fig. 2). Comparison of the AUCs for the continuous variables (FibroQ, AAR, APRI) via the procedures described by Hanley[20] showed a superior diagnostic accuracy of FibroQ over APRI ($p = 0.03$, statistically significant), but equal to AAR ($p = 0.47$, not statistically significant), in the prediction of cirrhosis (Table 3).

To compare our results with those of the previous reports, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the simple fibrosis prediction tests were calculated using cutoff values exactly as originally described (Table 5). However, the accuracy of the original cutoff value (AAR, 1.0; APRI, ≤ 1.0 or > 2.0) was not found to be optimal. We then selected the most balanced cutoff value for the FibroQ (2.6), AAR (0.75), and APRI (1.5) from the ROC analysis in order to predict liver cirrhosis. It is evident that FibroQ had better accuracy than AAR and APRI. Using a cutoff value of a FibroQ score of > 2.6, the presence of cirrhosis was totally excluded with 100%

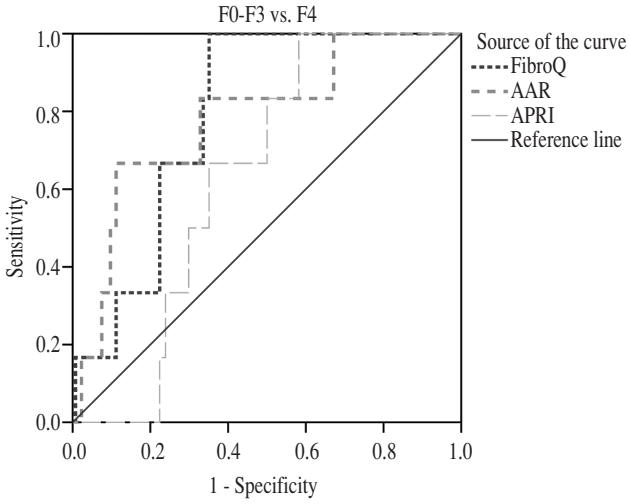

Fig. 2 Receiver operating characteristic (ROC) curves of the simple noninvasive tests for the prediction of cirrhosis (F4) according to the Metavir system in 140 patients with chronic viral hepatitis. ROC curves are shown for the fibrosis stage as assessed by the pathologist. FibroQ: 10 x (Age x AST x PT INR/ALT x platelet count); AAR: AST/ALT ratio; APRI: AST-to-platelet ratio index.

Table 4. Diagnostic Accuracies of Simple Fibrosis Prediction Tests for Significant Fibrosis (Metavir fibrosis score, F2–4)

	FibroQ	AAR		APRI		
Cutoff value	1.6	0.54	1	1.2	0.5	1.5
Sensitivity	0.79	0.77	0.10	0.66	0.97	0.54
Specificity	0.71	0.63	1.00	0.50	0.13	0.58
PPV	0.93	0.91	1.00	0.87	0.84	0.86
NPV	0.41	0.36	0.19	0.24	0.43	0.21

Abbreviations: FibroQ: fibro-quotient, 10 x (Age x AST x PT INR/ALT x platelet count); AAR: AST/ALT ratio; APRI: AST-to-platelet ratio index; PPV: positive predictive value; NPV: negative predictive value.

Table 5. The Diagnostic Accuracies of Simple Fibrosis Prediction Tests for of Cirrhosis (Metavir fibrosis score, F4)

	FibroQ	AAR		APRI		
Cutoff value	2.6	0.75	1.0	1.5	1.0	2.0
SEN	1.000	0.833	0.33	0.833	1.000	0.500
SPE	0.649	0.672	0.925	0.500	0.299	0.649
PPV	0.113	0.102	0.167	0.069	0.060	0.060
NPV	1.000	0.989	0.969	0.985	1.000	0.967

Abbreviations: FibroQ: fibro-quotient, 10 x (Age x AST x PT INR/ALT x platelet count); AAR: AST/ALT ratio; APRI: AST-to-platelet ratio index; PPV: positive predictive value; NPV: negative predictive value.

NPV in 87 (62.1%) of the 140 patients.

DISCUSSION

The gold standard for assessment of chronic viral hepatitis is the pathological grade and stage that are determined through liver biopsy. However, liver biopsy has its own limitations, risks, and costs.[6,7] Therefore, several noninvasive biomarkers, models, and tests have been proposed to attempt to predict the severity of liver disease, particularly the degree of fibrosis, in order to avoid unnecessary liver biopsy.[21-25] Some of the noninvasive means are expensive, need complicated calculations, or involved tests that are generally not a part of the routine monitoring and investigations of patients with chronic liver disease. For these reasons, such tests are only available in some research centers and cannot be widely used in clinical practice. We think that an ideal noninvasive test for assessing liver fibrosis should be reliable, reproducible, and based on readily available tests and parameters. Since APRI and AAR fulfilled these criteria, we used these two measures to evaluate patients with chronic viral hepatitis. The initial aim was to validate the usefulness of these two simple tests in a community hospital with hyperendemic hepatitis B and C virus infections.

In light of the limited availability and high cost of many fibrosis markers, Wai et al.[8] derived and validated the APRI in a cohort of 270 patients with chronic viral hepatitis C. In their study, the AUCs of APRI for predicting significant fibrosis and cirrhosis were 0.80~0.88 and 0.89~0.94, respectively. By using two different cutoff values for the exclusion and prediction of significant fibrosis (≤ 0.5 or > 1.5), a negative predictive value (NPV) of 86% and a positive predictive value (PPV) of 88% were calculated. Based on these high predictive values, the authors concluded that APRI obviated liver biopsy in approximately 50% of patients. Subsequently, numerous researchers have attempted to validate these findings; however, the results have been controversial.[8-12] The differences in the patient populations, including the prevalence of significant fibrosis, and in the reference ranges for AST may explain these discrepancies. In a recent systematic review, Shaheen and Myers[26] concluded that the summarized AUCs of APRI for predicting significant fibrosis and cirrhosis were 0.76 (95% CI: 0.74–0.79) and 0.82 (95% CI: 0.79–0.86), respectively. At a 40% prevalence of significant fibrosis, the cutoff values of < 0.5 had a negative predictive value of 80%, but could reduce the necessity of liver biopsy by only 35%. The results of our current study showed the AUC of APRI for predicting significant fibrosis and cirrhosis were only 0.631 and 0.634, respectively, which were lower than those reported previously. It has been mentioned that when using APRI, researchers had difficulties in differentiating intermediate fibrosis.[26] The majority of patients in our study belonged to the intermediate fibrosis groups (F2-3). This kind of population distribution might explain the low AUC values of APRI in our study.

The clinical use of AAR in the diagnostic workup of patients with chronic liver disease is supported by studies conducted in several countries evaluating populations with varied epidemiological and ethnic backgrounds.[13,14] Nevertheless, the use of

AAR as a clinical decision-making aid in patients with chronic liver disease has been a matter of debate.[15,16] We also attempted to use AAR to detect either significant fibrosis or cirrhosis and found it to be useful in our patient population. The AUCs of the ROC curve in differentiating significant fibrosis and cirrhosis were 0.733 and 0.782, respectively. In contrast to the results of previous studies which suggested that APRI was superior to AAR in predicting significant fibrosis and cirrhosis,[10,12] the results of our present study showed that AAR performed better than APRI (but, $p > 0.05$, not statistically significant) in this regard.

Recently, researchers from a hospital in Taiwan also demonstrated a low accuracy of APRI and AAR for predicting significant fibrosis in viral hepatitis C carriers with persistently normal ALT levels.[27] The AUCs of the ROC curve in differentiating significant fibrosis were only 0.673 for APRI and 0.504 for AAR in their study. In order to optimize the usefulness of simple noninvasive tests for our patient population, we formulated a novel index, named FibroQ. We found that the FibroQ, formulated by combining age, AST, PT INR, ALT, and platelet count, performed better than APRI ($p < 0.05$, statistically significant), and had similar results to AAR ($p > 0.05$, not statistically significant), in the prediction of significant fibrosis (AUC, 0.783) and cirrhosis (AUC, 0.791). Among patients with a FibroQ score of 0.6 or less, five of nine (55.6%) did not have significant fibrosis. Among the 116 patients who had significant fibrosis, only four patients had FibroQ scores of 0.6 or less. Among patients with FibroQ scores of > 1.6, 92 of 99 (92.9%) had significant fibrosis, and only seven patients without significant fibrosis were classified incorrectly. Together, using the FibroQ below the lower cutoff value (0.6) and above the higher cutoff value (1.6), 108 of the 140 patients (77.1%) were identified correctly as with or without significant fibrosis. In this regard, these results were similar to that of APRI as described by Wai et al.[8]

In conclusion, the results of our current study demonstrated that FibroQ proved to be a better biomarker than APRI, and equal to AAR, for predicting significant fibrosis in patients with chronic viral hepatitis. Further prospective studies involving a greater number of patients are warranted to validate the usefulness of FibroQ in clinical practice.

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用 FibroQ 來評估病毒性肝炎患者之肝纖維化程度

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前 言： 肝臟切片是評估肝纖維化程度的標準方式，然而有其危險性。非侵入性的評估方式，如 AAR、APRI 因而被提出，來取代肝臟切片。我們在此提出一個新的非侵入性的評估系統 FibroQ。

方 法： 本次回溯性研究，收集嘉義長庚醫院從 2005 年 5 月至 2007 年 12 月，共 140 位接受肝臟切片的慢性病毒性肝炎患者的年齡、生化及血液等臨床資料，並用以計算 AAR、APRI 和 FibroQ，進而比較這三種非侵入性方式推測肝纖維化之準確度。

結 果： FibroQ 比 APRI 有更好的 AUROC (AUROCs: 0.783 vs. 0.631, $p = 0.02$)；和 AAR 相比較，則沒有顯著差異 (AUROCs: 0.783 vs. 0.733, $p = 0.26$)。

結 論： FibroQ 是一個有效又簡單的非侵入性評估肝纖維化方式。

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關鍵詞： 肝纖維化，非侵入性檢查，FibroQ，AAR，APRI

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