The ratio of aminotransferase to platelets is a useful index for predicting hepatic fibrosis in hemodialysis patients with chronic hepatitis C

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Percutaneous liver biopsy is the gold standard for staging hepatic fibrosis of hemodialysis patients with chronic hepatitis C before renal transplantation or antiviral therapy. Concerns exist, however, about serious post-biopsy complications. To evaluate a more simple approach using standard laboratory tests to predict hepatic fibrosis and its evolution, we studied 279 consecutive hemodialysis patients with chronic hepatitis C and a baseline biopsy. Among them, 175 receiving antiviral therapy underwent follow-up biopsy to evaluate the histological evolution of fibrosis. Multivariate analysis of routine laboratory tests at baseline showed the aspartate aminotransferase-to-platelet ratio index was an independent predictor of significant hepatic fibrosis. The areas under curves of this ratio to predict fibrosis stages F2-4 were 0.83 and 0.71 in the baseline and follow-up sets; and 0.75 and 0.80 respectively, for patients with sustained or non-sustained virological response groups in the follow-up sets. By a judicious setting of cut-off levels for the baseline and non-sustained groups, and the sustained virological response group, almost half and 60 percent of the baseline and follow-up sets could be correctly diagnosed without biopsy. Our study found the aminotransferase-to-platelet ratio index is accurate and reproducible for assessing hepatic fibrosis in hemodialysis patients with chronic hepatitis C. Applying this simple index could decrease the need of percutaneous liver biopsy in this clinical setting.

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Chronic hepatitis C (CHC) remains common in hemodialysis (HD) patients with the estimated prevalence of 3–80%.[1] Although these patients usually present with mildly elevated serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, several studies indicated that they harbored high risks of liver-related morbidity and mortality at both maintenance dialysis and post-renal transplantation stages.[2–4]

Currently, percutaneous liver biopsy (PLB) is the gold standard for staging hepatic fibrosis.[5] Evaluating the severity of liver histology for HD patients with CHC can help clinicians determine the eligibility of renal transplantation, the long-term prognosis, and the necessity of initiating interferon-based therapy.[1,6–10] However, PLB is costly and may cause serious hemorrhage in HD patients.[11–15] Furthermore, sampling and interpretation variability is often encountered.[16,17] A noninvasive test to evaluate the hepatic fibrosis is thus required, particularly in monitoring HD patients with CHC over time.

Noninvasive tests using routine biochemical indices, including AST-to-platelet ratio index (APRI) or Forns' score, have shown to be useful in evaluating the severity of hepatic fibrosis in ordinary CHC patients.[18–20] However, the value of using routine biochemical indices to predict the severity of hepatic fibrosis in HD patients with CHC remains disputed and deserves further validation.[15,21,22] Furthermore, data to predict the evolution of hepatic fibrosis by biochemical indices in these patients are still lacking. We therefore aimed to confirm and validate the usefulness of routine biochemical indices in predicting the severity of hepatic fibrosis in HD patients with CHC before renal transplantation

or antiviral therapy, and evaluate its role in correlating with the evolution of hepatic fibrosis in those with paired liver biopsies.

RESULTS

Patient characteristics

Of the 292 patients screened, 13 were excluded from the study because of hepatitis B virus co-infection in seven, hepatocellular carcinoma in two, decompensated cirrhosis in two, and declining PLB in two. The clinical characteristics of the remaining 279 eligible patients are summarized in Table 1. The mean length of the biopsy samples was 18.1 ± 1.4 mm without fragmentation. Of the 279 eligible patients with baseline PLB, 101 (36.2%) had significant hepatic fibrosis ($\geqslant$F2). Two hundred forty-two patients (86.7%) received 6 to 12 months of interferon-based therapy, and the overall sustained virologic response (SVR) rate was 53.2%. Of the 192 patients who completed follow-up after the discontinuation of antiviral therapy, 175 (91.1%) received follow-up PLB to evaluate the evolution of hepatic fibrosis and 58 of them (33.1%) had significant hepatic fibrosis ($\geqslant$F2). Furthermore, the proportion of significant hepatic fibrosis at follow-up PLB did not statistically differ in patients with SVR than those without SVR (32.2% versus 34.1%, $P = 0.79$). The complication rates of the 454 liver biopsies included local pain at the biopsy puncture site in 88 (19.4%), shoulder soreness in 52 (11.5%), biopsy puncture site oozing in 60 (13.2%), intrahepatic hematoma in 6 (1.3%) and hemoperitoneum in 1 (0.2%).

Table 1 | Baseline characteristics of hemodialysis patients with chronic hepatitis C

Characteristics	HD patients with CHC (*n*=279)
Age (years)	47.4 ± 9.8
Male gender, *n* (%)	166 (59.5)
BMI (kg/m^2)	23.5 ± 3.4
Hemoglobin (g/l)	11.7 ± 1.8
White blood cell count ($\times 10^9$/l)	6.4 ± 1.8
Platelet count ($\times 10^9$/l)	194 ± 58
Prothrombin time (INR)	0.94 ± 0.21
Albumin (g/dl)	4.1 ± 0.3
Bilirubin total (mg/dl)	0.4 ± 0.4
AST (/ULN)	1.0 ± 0.9
ALT (/ULN)	1.4 ± 1.3
ALP (/ULN)	1.1 ± 0.7
γ-GT (/ULN)	2.9 ± 1.6
Creatinine (mg/dl)	10.0 ± 3.2
HCV RNA, $\log_{10}$ (IU/ml)	5.7 ± 0.9
HCV genotype, n (%)	
1a/1b	179 (64.2)
2a/2b	98 (35.1)
6	2 (0.7)
Indications for liver biopsy, n (%)	
Before renal transplantation	37 (13.3)
Before anti-viral therapy	242 (86.7)
Standard IFN	32
Pegylated IFN	107
Pegylated IFN plus RBV	103
Length of biopsy samples (mm)	18.1 ± 1.4
Fibrosis score (METAVIR), n (%)	
F0	82 (29.4)
F1	96 (34.4)
F2	64 (22.9)
F3	25 (9.0)
F4	12 (4.3)
Overall SVR rate after antiviral therapy, *n* (%)[a]	102 (53.2)
Patients with follow-up liver biopsy, *n* (%)[b]	175 (62.7)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHC, chronic hepatitis C; HCV, hepatitis C virus; HD, hemodialysis; IFN, interferon; INR, international normalized ratio; IU, international unit; RBV, ribavirin; SVR, sustained virological response; ULN, upper limit of normal; γ-GT, γ-glutamyl transpeptiase.
[a]By intention-to-treat (ITT) analysis; data from the 192 patients with known end point, and the remaining 50 patients were on treatment or on post-treatment follow-up.
[b]17 of the 192 patients (8.9%) receiving anti-viral therapy with known end point declined follow-up percutaneous liver biopsy.

Prediction factors for significant hepatic fibrosis

Table 2 shows the univariate and multivariate analyses of various baseline factors to predict HD patients with CHC harboring significant hepatic fibrosis. In univariate analysis, age, platelet count, AST, total bilirubin, γ-GT, and APRI were associated with patients with significant hepatic fibrosis. When these factors were put in multivariate analysis, APRI was the only independent factor predicting patients with significant hepatic fibrosis (OR: 1.08, CI: 1.03–1.13, $P = 0.003$).

Diagnostic accuracy of APRI to predict significant hepatic fibrosis

By multivariate analysis, APRI was considered useful to predict HD patients with CHC presenting significant hepatic fibrosis. ROC curve was constructed to evaluate the overall diagnostic accuracy. Furthermore, we also evaluated the reproducibility of APRI for the 175 patients (62.7%) who received follow-up PLB after the discontinuation of anti-viral therapy. The areas under curves (AUCs) to predict significant hepatic fibrosis for patients undergoing baseline and follow-up PLB were 0.83 (95% CI 0.78–0.88) and 0.71 (95% CI 0.65–0.77), respectively (Figures 1a and b). We further evaluated the differences of the diagnostic accuracy of APRI in predicting significant hepatic fibrosis in patients with SVR or non-SVR, and the AUCs for SVR and non-SVR groups were 0.75 (95% CI 0.69–0.81) and 0.80 (95% CI 0.69–0.91), respectively (Figures 1c and d).

Selective cut-off levels of APRI to predict significant hepatic fibrosis

Table 3 shows the diagnostic accuracy to predict significant hepatic fibrosis in both baseline and follow-up PLBs by different cut-off levels. When we chose <0.40 and $\geqslant 0.80$ to predict the absence and presence of significant hepatic fibrosis for patients with baseline PLB, 84.4% (136 of 161) patients with APRI tested within this range could be correctly diagnosed, and 48.7% (136 of 279) patients could avoid invasive PLB. When we chose <0.30 and $\geqslant 0.60$, and chose <0.40 and $\geqslant 0.80$ to predict the absence and presence

Table 2 | Univariate and multivariate analyses with Wald tests of baseline factors in predicting patients with significant hepatic fibrosis (⩾F2)

	Univariate analysis			Multivariate analysis[a]		
Variables	Patients with significant hepatic fibrosis (n=101)	Patients without significant hepatic fibrosis (n=178)	P-value	s.e.	OR (95% CI)	P-value
Age (years)	49.2 ± 8.8	46.3 ± 10.2	0.02	0.02	1.01 (0.97–1.04)	0.59
Gender (male, %)	63	57	0.32	—	—	—
BMI (kg/m^2)	23.8 ± 3.4	23.4 ± 3.5	0.40	—	—	—
Hemoglobin (g/l)	11.7 ± 1.4	11.6 ± 1.0	0.66	—	—	—
White blood cell count ($\times 10^9$/l)	6.5 ± 1.8	6.4 ± 1.9	0.67	—	—	—
Platelet count ($\times 10^9$/l)	174 ± 62	205 ± 53	<0.001	0.003	0.98 (0.97–0.99)	0.95
Prothrombin time (INR)	0.95 ± 0.09	0.95 ± 0.25	0.33	—	—	—
Albumin (g/dl)	4.1 ± 0.3	4.0 ± 0.4	0.35	—	—	—
Bilirubin total (mg/dl)	0.4 ± 0.2	0.4 ± 0.1	0.01	1.02	3.29 (0.45–24.24)	0.28
AST (/ULN)	1.3 ± 0.8	0.8 ± 0.4	<0.001	0.39	12.54 (5.84–26.94)	0.31
ALT (/ULN)	1.6 ± 1.3	1.3 ± 1.3	0.15	—	—	—
ALP (/ULN)	1.1 ± 0.7	1.0 ± 0.7	0.17	—	—	—
γ-GT (/ULN)	2.1 ± 3.7	1.3 ± 2.4	0.02	0.05	1.06 (0.96–1.18)	0.22
Creatinine (mg/dl)	10.3 ± 3.3	9.8 ± 3.1	0.19	—	—	—
APRI[a] 100[b]	78.8 ± 43.8	41.5 ± 18.4	<0.001	0.03	1.08 (1.03–1.13)	0.003

Abbreviations: CI, confidence interval; OR, odds ratio; s.e., standard error.
[a]Factors with a P-value <0.05 by univariate analysis entered into multivariate analysis.
[b]Aspartate aminotransferase-to-platelet ratio index multiplied by 100 to facilitate multivariate regression analysis.

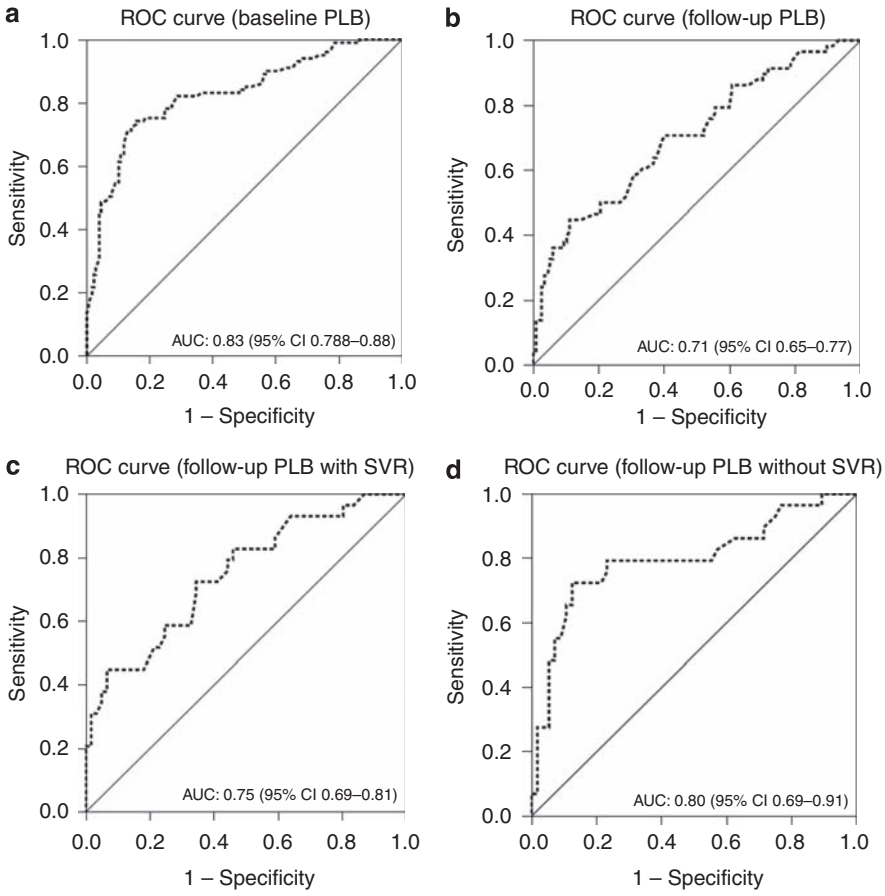

Figure 1 | ROC curves of APRI in predicting HD patients with CHC presenting significant hepatic fibrosis (⩾F2).

of significant hepatic fibrosis for patients with follow-up PLB, 76.9% (90 of 117) and 74.8% (104 of 139) patients with APRI tested within this range could be correctly diagnosed, and 51.4% (90 of 175) and 59.4% (104 of 175) patients could avoid invasive PLB, respectively. Because the two different cut-off levels showed equivocal diagnostic value for follow-up

Table 3 | Selective cut-off values of APRI for sensitivity, specificity, positive predictive value, and negative predictive value to predict significant hepatic fibrosis (⩾F2) in patients with baseline and follow-up percutaneous liver biopsies

	Baseline (*n*=279)							Follow-up (*n*=175)						
	Patients tested *n* (%)	Actual fibrosis *n* (%)						Patients tested *n* (%)	Actual fibrosis *n* (%)					
APRI	All (*n*=279)	⩾F2 (*n*=101)	<F2 (*n*=178)	Sen (%)	Spe (%)	PPV (%)	NPV (%)	All (*n*=175)	⩾F2 (*n*=58)	<F2 (*n*=117)	Sen (%)	Spe (%)	PPV (%)	NPV (%)
<0.30	44 (16)	3 (3)	41 (23)	97	23	42	93	78 (45)	14 (24)	64 (55)	76	55	45	82
⩾0.30	235 (84)	98 (97)	137 (77)					97 (55)	44 (76)	53 (45)				
<0.40	107 (38)	16 (16)	91 (51)	84	51	49	85	114 (65)	29 (50)	85 (73)	50	73	48	75
⩾0.40	172 (62)	85 (84)	87 (49)					61 (35)	29 (50)	32 (27)				
<0.60	199 (71)	39 (39)	160 (90)	61	90	78	80	136 (78)	32 (55)	104 (89)	45	89	67	76
⩾0.60	80 (29)	62 (61)	18 (10)					39 (22)	26 (45)	13 (11)				
<0.80	225 (81)	56 (55)	169 (95)	45	95	83	75	150 (86)	39 (67)	111 (95)	33	95	76	74
⩾0.80	54 (19)	45 (45)	9 (5)					25 (14)	19 (33)	6 (5)				
<0.95	240 (86)	69 (68)	171 (96)	32	96	82	71	165 (94)	50 (86)	115 (98)	14	98	80	70
⩾0.95	39 (14)	32 (32)	7 (4)					10 (2)	8 (14)	2 (2)				

Abbreviations: APRI, aspartate aminotransferase to platelet ratio index; NPV, negative predictive value; PPV, positive predictive value; Sen, sensitivity; Spe, specificity.

Table 4 | Selective cut-off values of APRI for sensitivity, specificity, positive predictive value, and negative predictive value to predict significant hepatic fibrosis (⩾F2) in patients with and without sustained virological response

	With SVR (*n*=90)							Without SVR (*n*=85)						
	Patients tested *n* (%)	Actual fibrosis *n* (%)						Patients tested *n* (%)	Actual fibrosis *n* (%)					
APRI	All (*n*=90)	⩾F2 (*n*=29)	<F2 (*n*=61)	Sen (%)	Spe (%)	PPV (%)	NPV (%)	All (*n*=85)	⩾F2 (*n*=29)	<F2 (*n*=56)	Sen (%)	Spe (%)	PPV (%)	NPV (%)
<0.30	69 (76)	13 (45)	56 (90)	55	90	76	81	9 (11)	1 (3)	8 (12)	97	14	37	89
⩾0.30	21 (24)	16 (55)	5 (10)					76 (89)	28 (97)	48 (88)				
<0.40	82 (92)	24 (83)	58 (95)	17	95	63	71	32 (38)	5 (17)	27 (48)	83	48	45	84
⩾0.40	8 (8)	5 (17)	3 (5)					53 (62)	24 (83)	29 (52)				
<0.60	87 (97)	26 (90)	61 (100)	10	100	100	70	48 (56)	6 (21)	43 (77)	79	77	62	90
⩾0.60	3 (3)	3 (10)	0 (0)					37 (44)	23 (79)	13 (23)				
<0.80	90 (100)	29 (100)	61 (100)	0	100	—[a]	68	60 (71)	10 (34)	50 (89)	65	89	76	83
⩾0.80	0 (0)	0 (0)	0 (0)					25 (29)	19 (66)	6 (11)				
<0.95	90 (100)	29 (100)	61 (100)	0	100	—[a]	68	75 (88)	21 (72)	54 (96)	28	96	80	72
⩾0.95	0 (0)	0 (0)	0 (0)					10 (12)	8 (28)	2 (4)				

Abbreviations: APRI, aspartate aminotransferase to platelet ratio index; SVR, sustained virological response.
[a]Not applicable because no patients in SVR group had APRI⩾0.80 at follow-up percutaneous liver biopsy.

PLB, and the AUC in the follow-up set was inferior to the AUC in the follow-up set either with SVR or without SVR (Figures 1b vs c or d), we further analyzed the diagnostic accuracy of APRI by patients with SVR or non-SVR separately (Table 4). When we chose either <0.30 and ⩾0.60, or <0.40 and ⩾0.80 to predict the absence and presence of significant hepatic fibrosis for SVR or non-SVR group, 81.7% (58 of 71) in the SVR group, and 80.7% (46 of 57) patients in the non-SVR group with APRI tested within this range could be correctly diagnosed, and 64.4% (58 of 90) and 54.1% (46 of 85) patients could avoid invasive PLB, respectively. Therefore, if we stratified the cut-off levels by patients with or without SVR, 59.4% (104 of 175) patients could be correctly staged for hepatic fibrosis by using the APRI alone, without performing PLB. Table 5 illustrates the post-test probability of patients with significant hepatic fibrosis on the basis of different age and APRI values calculated from the logistic regression model: Logit $(P \geqslant F2) = -4.357 + 0.054\,(\text{APRI} \times 100) + 0.017\,(\text{age})$.

DISCUSSION

The use of simple and non-invasive tests to evaluate the severity of hepatic fibrosis in HD patients with CHC is important, because the staging PLB potentially bears higher risks of serious complications. A useful non-invasive tool to evaluate the stage of hepatic fibrosis would be helpful, particularly in monitoring the evolution of hepatic fibrosis for these patients. Previous reports using various biochemical indices to predict the hepatic fibrosis showed divergent results probably due to small sample size or retrospective study design.[15,22] Recently, Schiavon *et al.*[21] retrospectively enrolled a sizable number of HD patients with CHC who underwent PLB, with laboratory tests performed within 6 months from the date of biopsies. They found that APRI could accurately predict the severity of hepatic fibrosis and about 52% of the patients could be correctly diagnosed without PLB. Despite APRI to predict hepatic fibrosis is valuable to ordinary CHC patients, no studies have validated the diagnostic accuracy of APRI in HD patients with CHC.

Table 5 | Post-test probability of significant hepatic fibrosis (⩾F2) based on different age and APRI values[a]

	Age				
APRI	18–25 years	26–35 years	36–45 years	45–55 years	56–65 years
0.06–0.10	2.7[b]	3.2	3.8	4.4	5.2
0.11–0.15	3.6	4.1	4.9	5.7	6.7
0.16–0.20	4.6	5.3	6.3	7.3	8.6
0.21–0.25	6.0	6.9	8.1	9.4	11.0
0.26–0.30	7.7	8.8	10.3	12.0	13.9
0.31–0.35	9.8	11.3	13.1	15.1	17.4
0.36–0.40	12.5	14.2	16.5	18.9	21.7
0.41–0.45	15.7	17.9	20.5	23.4	26.6
0.46–0.50	19.7	22.2	25.3	28.6	32.2
0.51–0.55	24.3	27.2	30.7	34.4	38.3
0.56–0.60	29.6	32.8	36.7	40.7	44.9
0.61–0.65	35.5	39.1	43.2	47.4	51.6
0.66–0.70	41.9	45.6	49.9	54.1	58.3
0.71–0.75	48.6	52.4	56.6	60.7	64.7
0.76–0.80	55.3	59.0	63.1	66.9	70.6
0.81–0.85	61.8	65.4	69.1	72.6	75.9
0.86–0.90	68.0	71.2	74.6	77.6	80.5
0.91–0.95	73.5	76.4	79.3	82.0	84.4
0.96–1.00	78.4	80.9	83.4	85.6	87.6
1.01–1.05	82.7	84.7	86.8	88.6	90.2
1.06–1.10	86.2	87.9	89.6	91.1	92.4
1.11–1.15	89.1	90.5	91.9	93.1	94.1
1.16–1.20	91.5	92.6	93.7	94.6	95.4

[a]Calculated based on APRI and age included in the multivariate logistic regression model: Logit ($P \geqslant F2$)=−4.357+0.054 (APRI × 100)+0.017 (age).
[b]Post-test probability was expressed in percentages.

Our results are in line with previous studies in both HD and ordinary CHC patients that AST levels and PLT count were independently associated with patients with significant hepatic fibrosis.[21,22] Furthermore, AUC of our patients (0.83) with baseline PLB is similar to that of Schiavon's ones (0.80).[21] Although the sensitivity, specificity, and NPV to predict significant hepatic fibrosis were similar in our and Schiavon's studies when the cut-off levels set at <0.40 and $\geqslant 0.95$, the PPV differed much between them. This discrepancy between Schiavon's study and ours could be reasoned by the following: (1) differences in the prevalence of the enrolled patient with significant hepatic fibrosis (23.7 versus 36.2%); (2) differences in the time interval between the PLB and the routine laboratory tests (within 6 months versus 2 weeks); (3) differences in the nature of study design (retrospective chart review versus prospective design); (4) differences in the mean length of biopsy specimen (13.7 ± 4.8 mm versus 18.1 ± 1.4 mm), affecting the biopsy interpretation. It is generally believed that the different prevalence of significant fibrosis is a more probable cause for these discrepancies. Shaheen *et al.*[19] conducted a systemic review of APRI for the prediction of hepatic fibrosis in ordinary CHC patients, and they concluded the major strength of APRI is to exclude patients with significant hepatic fibrosis, especially in the lower prevalence setting. Because the proportion of CHC patients receiving HD with significant hepatic fibrosis was lower than those with elevated ALT levels and similar to those with persistently normal ALT levels, setting APRI <0.40 was reliable to exclude HD patients with significant hepatic fibrosis.[15,21,23,24]

With the high prevalence of HCV infection in HD patients and the improving responses to interferon-based therapies for chronically infected patients, monitoring the evolution of hepatic fibrosis after treatment is also important. However, few studies evaluated the value of APRI to predict the severity of hepatic fibrosis in patients with follow-up PLB. Our study also included 175 HD CHC patients with follow-up PLB after interferon-based therapy. Nevertheless, the AUC of APRI in the follow-up set to predict significant hepatic fibrosis was inferior to that in the baseline set (0.71 versus 0.83), and the predictive value by applying different cut-off levels were only modest. We speculated that the best cut-off levels of APRI for the SVR patients at baseline and follow-up may differ, probably because of the rapid decrease of AST levels after the treatment, whereas the regression of fibrosis may not be evident. In contrast, those for the non-SVR patients at baseline and follow-up were more likely to remain unchanged. When the diagnostic accuracy of APRI to predict significant hepatic fibrosis for patients with SVR and non-SVR were independently analyzed, both the AUCs were higher than that with combined analysis. By using different cut-off levels of APRI for the SVR (<0.30 and $\geqslant 0.60$) and non-SVR (<0.40 and $\geqslant 0.80$) patients, more patients tested for APRI fell within these ranges, and thus can be correctly diagnosed without performing PLB. Of particular note was the comparable AUC, sensitivity, specificity, PPV and NPV of APRI to predict significant hepatic fibrosis between baseline patients and follow-up patients without SVR, confirming the reproducibility of APRI to predict the severity of hepatic fibrosis in HD patients with CHC.

Although APRI is considered useful for the prediction of severity of hepatic fibrosis in this prospective cohort, limitations still exist. First, our study is based on the assumption that PLB, which takes only 1/50,000 the size of the liver, is the gold standard for the assessment of hepatic fibrosis. Although sampling and interpretation of variations might occur, our study took strict sampling and interpretation procedures with the mean length of the biopsy samples being 18.1 mm without tissue fragmentation, and with one experienced pathologist to review all the samples to minimize such errors. Second, about 42% of patients with APRI fell between these 2 cut-off levels, leaving the severity of hepatic fibrosis unclassified. Applying the post-test probability for significant hepatic fibrosis on the basis of specific APRI value can help clinicians determine whether a liver biopsy is warranted. Third, the accuracy of APRI to predict cirrhosis and its role to replace PLB for patients with cirrhosis cannot be evaluated in this study due to its low prevalence (4.3%). Fourth, the time interval between the baseline and the follow-up PLB in patients receiving anti-viral therapy is 12–18 months, when the changes of hepatic fibrosis stages may not be evident. Considering the slow regression of hepatic fibrosis and the persistently normalized AST levels in patients with SVR, the AUC of APRI to predict significant hepatic fibrosis

may be even higher if the time interval between the two biopsies could be longer. In contrast, the diagnostic accuracy of APRI to predict the long-term evolution of the hepatic fibrosis in patients without SVR might be similar, considering the consistency of AUCs for the baseline and follow-up sets. Fifth, because the variability of AUC is related to the prevalence of fibrosis stages, the AUCs in our study should be adjusted by the population-based sampling in HD patients with CHC.[25] To the best of our knowledge, there was no large-scaled study to evaluate the distribution of hepatic fibrosis stages in this special group of patients for standardization. On the other hand, our study consecutively enrolled patients in each participating center, which may reflect the naturally observed prevalence of different fibrosis stages. Further large studies are awaited to define the severity of hepatic fibrosis in these patients.

In conclusion, our data indicate that APRI is accurate and reproducible to evaluate significant hepatic fibrosis in HD patients with CHC before anti-viral therapy or renal transplantation. Applying this simple index in our clinical practice may reduce the need of staging PLB in this special clinical setting. Further large studies are needed to confirm the role of APRI in predicting the long-term evolution of hepatic fibrosis.

MATERIALS AND METHODS

Patients

From January 2005 to February 2009, a total of 292 consecutive HD patients aged between 18 and 65 years with CHC who were scheduled to receive renal transplantation or interferon-based therapy were prospectively evaluated at four academic centers in Taiwan. HD patients with CHC were defined as patients with creatinine clearance of less than 10 milliliter per minutes per 1.73 square meters of body surface area who received maintenance renal replacement therapy through vascular routes and harbored persistent anti-HCV (Abbott HCV EIA 2.0, Abbott Diagnostic, Chicago, IL, USA) as well as HCV RNA (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany) for more than 6 months. Patients who received interferon-based therapy had additional PLB 6 months after a course of 6 or 12 months of treatment to evaluate histological evolution. Patients who were co-infected with hepatitis B virus or human immunodeficiency virus, had a history of heavy alcohol use, neoplastic diseases or other causes of liver diseases, received immunosuppressive agents, had decompensated cirrhosis (Child-Pugh class B or C), and were contra-indicated for or declined PLB were excluded from this study. The study conformed to the principles of the Helsinki Declaration and was approved by the institutional review board of each participating center. Each patient gave informed consent before enrollment.

Methods

Baseline demographic data were recorded for all patients. Hemogram (including hemoglobin, white blood cell count, and platelet count), serum biochemical data (including albumin, total bilirubin, AST, ALT, alkaline phosphatase, γ-glutamyl transpeptidase, and serum creatinine), coagulation profiles, serological and virological data were collected before PLBs. The hemogram and the routine biochemistry were evaluated by the automated Sysmex XE-2100 hematology analyzer (Sysmex, Kobe, Japan) and the Toshiba TBA-120 FR analyzer (Toshiba, Tokyo, Japan), respectively. All serological data, including anti-HCV, HBsAg, anti-HBs, anti-HBc, and anti-human immunodeficiency virus, were tested by the commercial kits. HCV RNA (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH) and HCV genotyping (Inno-LiPA HCV II, Innogenetics, Ghent, Belgium) were tested for all patients at baseline and were tested 6 months after the anti-viral therapy to evaluate the sustained virological response (SVR). The AST-to-platelet ratio index (APRI) was calculated as AST/upper limit of normal (ULN) × 100/platelet count (10^9/l).[18]

All patients eligible for the study underwent PLBs within 2 weeks of the completion of blood tests. Ultrasound-guided liver biopsies from the right hepatic lobe were performed using 16-G biopsy needles (Temno Evolution, Allegiance, McGaw Park, IL, USA). The sampling tissues were fixed with formalin, embedded with paraffin, and stained with hematoxylin and eosin (H & E) and reticulin silver (Masson trichome method). The hepatic fibrosis was staged by the METAVIR scoring system, ranging from F0 to F4.[26] Significant hepatic fibrosis was defined as a fibrosis stage of $\geqslant$F2. All samples were evaluated by one experienced pathologist who was unaware of the clinical status of the study subjects.

Statistics

Statistical analyses were performed using Statistical Program for Social Sciences (SPSS 12.0 for windows; SPSS, Chicago, Illinois, USA). Patient characteristics were expressed as mean ± s.d. and percentage as appropriate. Two-sample *t*-test and χ^2 with Fisher's exact test for univariate analysis where appropriate and logistic regression with Wald test for multivariate analysis of the baseline hemogram and routine biochemistry were performed to find the independent factors for patients with significant hepatic fibrosis ($\geqslant$F2). The estimated sample size for multivariate regression model was 260 based on the following assumptions: type I error = 0.05; type II error = 0.10, estimated predictors = 3, and anticipated effect size (f^2) = 0.055, given a R^2 = 0.052. The diagnostic accuracy and reproducibility of APRI for baseline and follow-up PLBs to predict significant hepatic fibrosis were evaluated by the AUCs with 95% confidence intervals (CI), respectively. All statistical tests were two-tailed and results were considered statistically significant when a *P*-value was <0.05.

DISCLOSURE

D-SC is a consultant for Norvartis and Roche; D-SC is a consultant for Norvartis and GlaxoSmithKline; J-HK has recently received research funding from Vitagenomics; is a consultant for Bristol-Myers Squibb, GlaxoSmithKline, Norvartis, Omrix, Roche, and Schering-Plough; and is on the speaker's bureau for Roche, Bristol-Myers Squibb, GlaxoSmithKline, Norvartis, and Schering-Plough; all other authors declared no competing interests.

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