Prediction of hepatocellular carcinoma development by aminotransferase to platelet ratio index in primary biliary cholangitis

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AIM
To investigate the usefulness of aspartate aminotransferase to platelet ratio index (APRI) in predicting hepatocellular carcinoma (HCC) risk in primary biliary cholangitis (PBC).

METHODS
We identified PBC patients between 2000 and 2015 by searching the electronic medical database of a tertiary center. The hazard ratio (HR) of HCC with different risk factors was determined by Cox proportional hazards model.

RESULTS
One hundred and forty-four PBC patients were recru-
Primary biliary cholangitis (PBC) is an immune-mediated, chronic cholestatic liver disease due to the destruction of small-sized biliary ducts with progressive liver fibrosis and hepatic necroinflammation or non-cirrhotic portal hypertension[6-9]. It has the potential to progress to cirrhosis. Traditionally, liver biopsy is regarded as the gold standard diagnostic method, but it may not be desirable in daily clinical practice due to its associated invasiveness which may lead to various complications[10].

The role of APRI, alone and in combination with other markers, in predicting adverse outcomes (liver transplantation, death) in PBC patients remains uncertain. We aimed to demonstrate the role of APRI, alone and in combination with treatment response, in predicting HCC development in PBC patients independent of UDCA response[12]. This is attributed to its ability to not only capture fibrosis/cirrhosis, but also to reflect other biologically significant pathways like hepatic necroinflammation or non-cirrhotic portal hypertension[16-20]. Both APRI at baseline and APRI at 1 year after treatment (APRI-r1) have been shown to predict adverse outcomes (liver transplantation and/or death) in PBC patients[20,21]. In addition, when combined with the treatment response criteria, APRI-r1 can further stratify the risk of adverse outcomes and improve the predictive performances[26,29].

Recently, APRI is also found to be a prognostic marker in PBC patients independent of UDCA response[26]. This is attributed to its ability to not only capture fibrosis/cirrhosis, but also to reflect other biologically significant pathways like hepatic necroinflammation or non-cirrhotic portal hypertension[26-28]. Both APRI at baseline and APRI at 1 year after treatment (APRI-r1) have been shown to predict adverse outcomes (liver transplantation and/or death) in PBC patients[26]. In addition, when combined with the treatment response criteria, APRI-r1 can further stratify the risk of adverse outcomes and improve the predictive performances[26,29].

However, whether APRI can predict HCC risk in PBC patients remains uncertain. We aimed to demonstrate the role of APRI, alone and in combination with treatment response, in predicting HCC development in PBC patients receiving UDCA.

**MATERIALS AND METHODS**

**Study subjects**

PBC patients who followed up at the Clinic of Hepatology Unit of Queen Mary Hospital (QMH), a tertiary referral center, between January 2000 and October 2015 were recruited.

As all patients with PBC were prescribed with UDCA in QMH, we first identified patients receiving UDCA between 2000 and 2015 by searching the electronic
medical database of QMH. Subsequently, we excluded non-PBC cases by reviewing the patient records, based on the criteria described in the subsequent section. Other exclusion criteria included non-Chinese ethnicity, cases with UDCA prescription for less than 1 year, overlap syndrome \[30\] and other coexisting hepatic diseases including CHB and CHC infection, steatohepatitis, alcoholic liver disease, and Wilson’s disease. Figure 1 illustrates the patient recruitment process.

Ethics approval was issued by the Institutional Review Board, The University of Hong Kong and West Cluster of Hospital Authority, Hong Kong.

Diagnosis of PBC
A diagnosis of PBC was made if two out of the following three criteria were fulfilled: (1) cholestatic liver function pattern with raised alkaline phosphatase (ALP) \(\geq 1.5\) times the upper limit of normal (ULN); (2) presence of anti-mitochondrial antibody (AMA); and (3) liver biopsy showing the histology of “nonsuppurative destructive cholangitis with destruction of interlobular biliary ducts”\[5\]. For liver biopsy cases, histologic staging was reported in accordance with Ludwig et al\[31\].

The Paris II criteria were proposed by Corpechot et al\[13\] for predicting adverse events in PBC patients with early-stage disease. Early PBC can be defined either histologically (Ludwig’s stages I and II) or biochemically (normal levels of albumin and bilirubin).

Diagnosis of adverse events
Patients had regular follow-up every 3 to 6 mo to monitor the platelet count, liver biochemistry, prothrombin time (PT) and alpha-fetoprotein level. Patients were recommended for ultrasonography (USG) of the liver every 6 mo for HCC\[32\].

A diagnosis of HCC was made by histology and/or imaging features \(i.e.,\) arterial enhancement and venous wash-out on triphasic computed tomography (CT) scan or magnetic resonance imaging (MRI).

A diagnosis of cirrhosis was made by any one of the following: (1) imaging (USG, CT or MRI) showing small liver with surface nodularity, or signs of portal hypertension (including splenomegaly, ascites and varices); (2) fibrosis score > 16.9 kPa on transient elastography\[33\]; and (3) clinical features including thrombocytopenia, prolonged prothrombin time, ascites, varices, hepatic encephalopathy and hepatorenal syndrome.

APRI was calculated by the following formula proposed by Wai et al\[16\]: \([\text{AST} \text{ value}/\text{ULN}/\text{platelet} \ (10^9/L)] \times 100\).

Suboptimal treatment response to UDCA
For the initial analysis, we used the Rotterdam criteria (abnormal levels of bilirubin or albumin).
to define suboptimal treatment response. This is because the Rotterdam criteria were shown to have better predictive performances than other treatment response criteria in predicting requirement for liver transplantation and death in Chinese PBC patients\cite{24,34,35}. Analyzes by using other treatment response criteria were also performed. Table 1 illustrates the description of other prognostic models\cite{26}. Combination of APRI-r1 with treatment response could further stratify PBC patients into low-risk (APRI-r1 $\leq 0.54$ with treatment response), intermediate-risk (APRI-r1 $< 0.54$ with suboptimal treatment response, or APRI-r1 $> 0.54$ with treatment response) and high-risk (APRI-r1 $> 0.54$ with suboptimal treatment response) groups developing adverse events in terms of liver transplantation or death.

**Statistical analysis**

Statistical analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing) statistical software. We expressed continuous variables in terms of median and interquartile range (IQR). The correlation between continuous variables was assessed by Spearman’s bivariate correlation. We used Mann-Whitney U-test to assess the difference in continuous variables of two groups. We used $\chi^2$ test or Fisher’s exact test for the comparison of categorical variables. The hazard ratio (HR) of HCC with different variables was derived from the Cox proportional hazards model. Patients not meeting the clinical endpoint (HCC) were censored at latest follow-up or death. The follow-up duration was calculated from the date of diagnosis to the censored date. Missing data in the Cox model were handled by multiple imputation, wherein 50 complete datasets were constructed by imputing the missing values\cite{36}. The development of HCC was analyzed by the Kaplan-Meier method, and statistical significance was determined by the log-rank test. By plotting “sensitivity” against “1-specificity”, the receiver operating curve was generated. The performances of different models were expressed by area under the receiver operating curve (AUROC), with the 95% CI being deduced from bootstrapping by sampling with replacement from the original dataset and repeating the process by 1000 times. A two-sided $P$-value of $<0.05$ was used to define statistical significance.

**RESULTS**

**Characteristics of study patients**

One hundred and forty-four PBC patients were recruited, and 127 were female (88.2%). Table 2 shows the patient characteristics, laboratory and histology results. Patients were diagnosed at a median age of 57.8 years (IQR: 48.7 to 71.5 years). The median follow-up duration was 6.9 years (range: 1.0 to 26.3 years), making a total of 1136 patient-years. Twelve patients developed HCC, with an incidence rate of 10.6 cases per 1000 patient-years. Ten patients underwent liver transplantsations, and there were 40 deaths (21 were liver-related and 19 were non-liver-related).

Cirrhosis was noted in 41 patients (28.5%) before treatment commencement, while the median APRI and APRI-r1 levels of the cohort were 1.00 (0.60 to 1.84) and 0.22 (0.13 to 0.43), respectively. A significantly higher proportion of patients who developed HCC had baseline cirrhosis compared with the non-HCC group (66.7% vs 25.0%, $P = 0.005$). The HCC group also had a higher median APRI-r1 level (0.54 vs 0.20, $P = 0.002$), with a larger proportion having APRI-r1 $> 0.54$ (50.0% vs 16.7%, $P = 0.013$). The difference in median APRI levels between the two groups was of borderline significance (2.02 vs 0.97, $P = 0.050$), while no significant difference existed for the proportions of patients with APRI $> 0.54$ (90.0% vs 77.5%, $P = 0.689$). For other prognostic scores, the HCC group had a higher median Mayo risk score (5.1 vs 4.6, $P = 0.022$), while no significant differences existed for the model for end-stage liver disease (MELD) or Child-Pugh (CP) scores between the two groups.

Patients were prescribed with UDCA at a median dose of 750 mg. The number of patients who had suboptimal treatment response was as follows: 61 (42.4%; Rotterdam criteria), 52 (36.1%; Paris I criteria), 48 (33.3%; Barcelona criteria) and 50 (38.8%; Toronto criteria). None of our patients received fibrin acid derivatives.

Liver biopsies were performed in 62 patients. Out of the 52 patients with histology reports available, 21 were regarded as having early-stage PBC. If only the biochemical criteria were considered, 52 patients had early-stage disease. None of these patients developed HCC, and therefore analysis could not be performed using the Paris II criteria.

**Correlation between baseline APRI and other variables**

APRI had positive correlations with levels of AST ($r = 0.86$, $P < 0.001$), ALT ($r = 0.68$, $P < 0.001$), bilirubin.

**Table 1** Descriptions of prognostic risk models for primary biliary cholangitis

| Time of evaluation | Definition of suboptimal treatment response |
|--------------------|---------------------------------------------|
| Rotterdam | 1 yr Abnormal bilirubin and/or albumin |
| Paris I | 1 yr ALP $> 1$ ULN or AST $> 1.5$ ULN |
| Paris II | 1 yr ALP $> 1$ ULN or AST $> 1.5$ ULN |
| Barcelona | 1 yr ALP $> 1$ ULN and decrease in ALP $< 40\%$ |
| Tokyo | 2 yr $ALP > 1.67 \times ULN$ |
| APRI | Baseline AST/ULN of AST/platelet ($\times 10^3$) $> 100$ |
| APRI-r1 | 1 yr AST/ULN of AST/platelet ($\times 10^3$) $> 100$ |

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; APRI: AST to platelet ratio index; APRI-r1: APRI at 1-year; AST: Aspartate aminotransferase; PBC: Primary biliary cholangitis; ULN: Upper limit of normal.
Figure 2  Cumulative hepatocellular carcinoma incidence. A: Whole cohort; B: Stratified by APRI-r1. APRI-r1: AST/platelet ratio index at 1-year.

Table 2  Baseline characteristics of the study cohort

| Variable                  | Whole cohort, \( n = 144 \) | Patients with HCC, \( n = 12 \) | Patients without HCC, \( n = 132 \) | \( P \) value |
|---------------------------|-------------------------------|----------------------------------|-----------------------------------|-------------|
| Age, yr \((\text{yr})\)   | 57.8 (48.7-71.5)              | 68.1 (56.2-74.6)                 | 57.0 (48.2-70.7)                  | 0.278       |
| Female sex                | 127 (88.2)                    | 9 (75.0)                         | 118 (89.4)                       | 0.153       |
| Duration of follow-up, yr | 6.0 (5.5-10.4)                | 8.9 (5.3-11.4)                   | 6.8 (5.5-10.4)                   | 0.499       |
| Ursodeoxycholic acid, mg  | 750 (750-750)                 | 750 (750-750)                    | 750 (750-750)                    | 0.576       |
| Suboptimal treatment response, | 61 (42.5)                    | 9 (75.0)                         | 52 (39.4)                       | 0.017       |
| Rotterdam criteria        |                               |                                  |                                   |             |
| Diabetes                  | 29 (20.1)                     | 6 (50.0)                         | 23 (17.4)                        | 0.016\(^1\) |
| Smoking\(^2\)             | 13 (9.3)                      | 4 (33.3)                         | 9 (6.8)                          | 0.011\(^2\) |
| Alcohol\(^3\)             | 17 (13.7)                     | 2 (16.7)                         | 15 (11.4)                        | 0.623       |
| Cirrhosis                 | 41 (28.5)                     | 8 (66.7)                         | 33 (25.0)                        | 0.005\(^3\) |
| Histological stage 3-4\(^4\) | 23 (44.2)                  | 3 (50.0)                         | 20 (43.5)                        | 1.00        |
| Platelet, \(10^9/\text{L}\) | 216 (152-262)                | 133 (95-150)                     | 229 (175-266)                    | < 0.001\(^1\) |
| Creatinine, \(\mu\text{mol}/\text{L}\) | 69 (60-82)               | 73 (60-79)                        | 68 (60-82)                       | 0.047\(^3\) |
| Albumin, \(\text{g}/\text{L}\) | 40 (36-42)                  | 24 (14-30)                        | 40 (36-42)                       | 0.087       |
| Bilirubin, \(\mu\text{mol}/\text{L}\) | 14 (10-26)                 | 30 (19-55)                        | 14 (10-26)                       | < 0.001\(^1\) |
| ALP (U/L)                 | 284 (196-484)                 | 343 (227-362)                    | 273 (196-496)                    | 0.991       |
| ALT, U/L\(^1\)            | 74 (54-130)                   | 85 (64-109)                      | 74 (53-133)                      | 0.563       |
| AST, U/L\(^1\)            | 68 (51-113)                   | 76 (56-109)                      | 68 (51-115)                      | 0.741       |
| GGT, U/L\(^1\)            | 517 (256-771)                 | 626 (333-843)                    | 490 (224-760)                    | 0.285       |
| PT, s                     | 11.3 (10.5-11.7)              | 11.8 (11.7-12.5)                 | 11.2 (10.5-11.7)                 | 0.007\(^5\) |
| AMA positivity            | 119 (82.6)                    | 8 (66.7)                         | 111 (84.1)                       | 0.223       |
| Globulin, \(\text{mg}/\text{dL}\) | 41 (37-46)                  | 40 (37-44)                        | 41 (37-46)                       | 0.337       |
| IgM, \(\text{mg}/\text{dL}\) | 363 (250-502)                | 446 (282-579)                    | 359 (250-478)                    | 0.563       |
| Mayo risk score\(^1\)     | 4.7 (3.8-5.5)                 | 5.1 (4.8-6.6)                    | 4.6 (3.8-5.4)                    | 0.022       |
| MELD score                | 6 (6-8)                       | 8 (6-9)                          | 6 (6-7)                          | 0.097       |
| CP score\(^1\)            | 5 (5-6)                       | 6 (5-6)                          | 5 (5-6)                          | 0.125       |
| CP class B/C\(^1\)        | 29 (20.1)                     | 2 (16.7)                         | 25 (19.2)                        | 1.00        |
| APRI                       | 1.00 (0.60-1.84)              | 2.02 (1.05-3.34)                 | 0.97 (0.59-1.72)                 | 0.05\(^5\) |
| APRI > 0.54\(^1\)         | 102 (78.5)                    | 9 (90.0)                         | 93 (77.5)                        | 0.689       |
| APRI-r1 > 0.54\(^1\)      | 0.22 (0.13-0.43)              | 0.54 (0.31-0.70)                 | 0.20 (0.13-0.38)                 | 0.002\(^5\) |

Data are presented as \( n \) (%), and all continuous variables are expressed as median (interquartile range). 1Missing data: smoking (7), alcohol (3), platelet (10), creatinine (1), albumin (2), bilirubin (2), ALT (2), AST (6), GGT (2), globulin (6), IgM (20), Mayo risk score (2), CP score (2), APRI (14), APRI-r1 (6). 2Sixty-two patients had liver biopsies done, with reports available for review for 52. 3\( ^{\text{P}} \) values < 0.05. All continuous variables expressed in median (interquartile range). ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AMA: Anti-mitochondrial antibody; APRI: AST/platelet ratio index; APRI-r1: APRI at 1 year after treatment; AST: Aspartate aminotransferase; CP: Child-Pugh; GGT: Gamma-glutamyl transferase; IgM: Immunoglobulin M; MELD: Model for end-stage liver disease; PT: Prothrombin time.
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Figure 3 Cumulative hepatocellular carcinoma incidence stratified by treatment response. A: Rotterdam criteria; B: Paris I criteria; C: Barcelona criteria; D: Toronto criteria.

(r = 0.43, P < 0.001), ALP (r = 0.31, P < 0.001) and gamma-glutamyl transferase (GGT) (r = 0.31, P < 0.001). It had negative correlations with platelet counts (r = -0.43, P < 0.001) and albumin levels (r = -0.27, P = 0.002). The correlation between APRI and PT was of borderline significance (r = 0.17, P = 0.052). For the correlations with other prognostic models, there were positive correlations between APRI and Mayo risk score (r = 0.32, P < 0.001) and CP score (r = 0.43, P < 0.001), but not for the MELD score (r = 0.12, P = 0.664).

HCC risk factors

Table 3 shows the association between HCC development and various factors. On univariate analysis, significant factors for HCC development included older age, male sex, presence of cirrhosis, hypoalbuminemia and suboptimal treatment response (defined by the Rotterdam criteria). On multivariate analysis, only older age (HR = 1.07; 95%CI: 1.02-1.12), cirrhosis (HR = 4.38; 95%CI: 1.06-18.14) and APRI-r1 > 0.54 (HR = 3.94; 95%CI: 1.04-14.94) were independent risk factors (Table 4). Suboptimal treatment response was
In the multivariate analyses, albumin was not included as this variable was already included in the Rotterdam criteria. \(^1\) Values < 0.05. ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AMA: Anti-mitochondrial antibody; APRI: AST to platelet ratio index; APRI-r1: APRI at 1 year after treatment; AST: Aspartate aminotransferase; CI: Confidence interval; GGT: Gamma-glutamyl transferase; HR: Hazard ratio; IgM: Immunoglobulin M; PT: Prothrombin time.

### Table 3 HRs and 95%CIs for the association between hepatocellular carcinoma development and different variables

| Variables                          | Univariate analysis | Multivariate analysis |
|------------------------------------|---------------------|-----------------------|
|                                    | HR 95%CI            | P value               | HR 95%CI             | P value               |
| Age, yr                            | 1.06 1.01-1.11      | 0.016\(^2\)           | 1.07 1.02-1.12       | 0.004\(^2\)           |
| Male sex                           | 5.22 2.17-21.44     | 0.022\(^2\)           | 3.67 0.69-19.56      | 0.128                 |
| Diabetes mellitus                  | 3.01 0.96-9.44      | 0.058                 | 2.35 0.27-21.99      | < 0.001\(^1\)         |
| Cirrhosis                          | 8.02 0.43-27.19     | 0.243                 | 4.50 1.69-14.53      | 0.003\(^2\)           |
| APRI > 0.54                        | 3.43 0.43-27.19     | 0.243                 | 3.94 1.04-14.94      | 0.043\(^2\)           |
| APRI-r1 > 0.54                     | 5.10 1.64-15.86     | 0.005\(^2\)           | 4.38 1.06-18.14      | 0.041\(^2\)           |
| Creatinine, µmol/L                 | 1.02 0.99-1.05      | 0.222                 |                     |                       |
| Albumin, g/L                       | 0.85 0.75-0.96      | 0.007\(^2\)           |                     |                       |
| Bilirubin, µmol/L                  | 1.01 0.98-1.03      | 0.514                 |                     |                       |
| ALP, U/L                           | 0.997 0.994-1.00    | 0.104                 |                     |                       |
| ALT, U/L                           | 0.996 0.987-1.00    | 0.331                 |                     |                       |
| AST, U/L                           | 0.996 0.975-1.01    | 0.467                 |                     |                       |
| GGT, U/L                           | 1.00 0.999-1.001    | 0.975                 |                     |                       |
| PT, s                              | 1.40 0.99-1.98      | 0.066\(^2\)           |                     |                       |
| AMA positivity                      | 0.52 0.16-1.75      | 0.292                 |                     |                       |
| Globulin, mg/dL                    | 0.99 0.90-1.08      | 0.804                 |                     |                       |
| IgM, mg/dL                         | 1.00 0.997-1.002    | 0.830                 |                     |                       |
| Suboptimal treatment response, Rotterdam criteria\(^1\) | 5.95 1.59-22.26 | 0.008\(^2\) | 2.18 0.45-10.58 | 0.334 |

\(^1\) In the multivariate analyses, albumin was not included as this variable was already included in the Rotterdam criteria. \(^2\) Values < 0.05. ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AMA: Anti-mitochondrial antibody; APRI: AST to platelet ratio index; APRI-r1: APRI at 1 year after treatment; AST: Aspartate aminotransferase; CI: Confidence interval; GGT: Gamma-glutamyl transferase; HR: Hazard ratio; IgM: Immunoglobulin M; PT: Prothrombin time.

### Table 4 Adjusted HRs and 95%CIs for the association between hepatocellular carcinoma development and different variables

| Criteria                      | HR 95%CI      | P value |
|-------------------------------|---------------|---------|
| Rotterdam                     |               |         |
| Age                           | 1.07 1.02-1.12| 0.004\(^1\) |
| Male sex                      | 3.67 0.69-19.56| 0.128  |
| Cirrhosis                     | 4.38 1.06-18.14| 0.041\(^1\) |
| APRI-r1 > 0.54                | 3.94 1.04-14.94| 0.043\(^1\) |
| Suboptimal treatment response | 2.18 0.45-10.58| 0.334  |
| Paris I                       |               |         |
| Age                           | 1.07 1.02-1.12| 0.003\(^1\) |
| Male sex                      | 3.04 0.54-17.12| 0.207  |
| Albumin                       | 0.94 0.80-1.09| 0.386  |
| Cirrhosis                     | 4.37 1.07-17.75| 0.039\(^4\) |
| APRI-r1 > 0.54                | 3.92 1.06-14.54| 0.041\(^1\) |
| Suboptimal treatment response | 1.7 0.41-7.03  | 0.466  |
| Barcelona                     |               |         |
| Age                           | 1.07 1.02-1.12| 0.005\(^5\) |
| Male sex                      | 3.26 0.56-18.96| 0.188  |
| Albumin                       | 0.93 0.80-1.07| 0.307  |
| Cirrhosis                     | 4.44 1.08-18.56| 0.041\(^1\) |
| APRI-r1 > 0.54                | 4.47 1.26-15.93| 0.021\(^1\) |
| Suboptimal treatment response | 1.22 0.33-4.49  | 0.768  |
| Toronto                       |               |         |
| Age                           | 1.07 1.02-1.13| 0.003\(^1\) |
| Male sex                      | 3.22 0.56-18.50| 0.19  |
| Albumin                       | 0.94 0.80-1.09| 0.425  |
| Cirrhosis                     | 4.56 1.09-19.17| 0.038\(^1\) |
| APRI-r1 > 0.54                | 4.16 1.10-15.69| 0.036\(^1\) |
| Suboptimal treatment response | 1.46 0.31-6.89  | 0.631  |

\(^1\)P values < 0.05. The adjusted HR for suboptimal response was derived by multivariate analysis with other significant variables in Table 3 (age, male sex, cirrhosis and albumin) included. Separate multivariate analysis was performed for each criteria in defining suboptimal response. In the multivariate analyses, albumin was not included for the Rotterdam criteria. APRI-r1: AST/platelet ratio index at 1-year; HR: Hazard ratio.

### HCC cumulative incidence

The 5-, 10- and 15-year cumulative incidences of HCC were 2.3% (95%CI: 0%-4.8%), 8.4% (95%CI: 1.8%-14.5%) and 21.6% (6.8%-34.1%), respectively (Figure 2A).

Cumulative incidence of HCC was significantly higher for patients with APRI-r1 > 0.54 (log rank P = 0.002; Figure 2B). Among patients with APRI-r1 ≤ 0.54, the 5-, 10- and 15-year cumulative incidences of HCC were 2.5%(95%CI: 0%-3.0%), 6.7%(95%CI: 0%-13.1%) and 18.3% (95%CI: 0.4%-33.0%), respectively. Among patients with APRI > 0.54, the 5-, 10- and 15-year cumulative incidences of HCC development were 8.3% (95%CI: 0%-18.7%), 18.5% (95%CI: 0%-37.2%) and 49.0% (95%CI: 0%-75.2%).

Cumulative incidence of HCC was significantly higher for patients who had suboptimal biochemical response by using the Rotterdam (log rank P = 0.003) and Paris I criteria (log rank P = 0.038). The difference was of borderline significance by using the Barcelona criteria (log rank P = 0.061), while there was no significant difference by using the Toronto criteria (log
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Using the combination of APRI-r1 and biochemical response to define low-, intermediate- and high-risk groups further stratified HCC risk (all log rank $P < 0.05$), with the exception for the Toronto criteria (log rank $P = 0.120$) (Figure 4A-D). When APRI-r1 was combined with treatment response as defined by the Rotterdam criteria, the 5-, 10- and 15-year cumulative incidences of HCC were 0%, 4.3% (95%CI: 0%-10.0%) and 10.3% (95%CI: 0%-22.0%), respectively among the low-risk group. For the intermediate-risk group, the 5-year, 10- and 15-year cumulative incidences of HCC were 2.7% (95%CI: 0%-7.8%), 11.5% (95%CI: 0%-27.2%) and 33.7% (95%CI: 0%-63.5%), respectively. The high-risk group was at the highest risk, with the 5-, 10- and 15-year cumulative incidences of HCC being 10.2% (95%CI: 0%-22.7%), 21.4% (95%CI: 0%-41.9%) and 58.1% (95%CI: 0%-84.0%), respectively.

Predictive performances of various prognostic models

Table 6 shows the predictive performances of various prognostic models. APRI-r1 had the best performance in predicting HCC development (AUROC = 0.77, 95%CI: 0.64-0.88), although the 95%CI overlapped with that of Mayo risk score (AUROC = 0.70, 95%CI: 0.54-0.84), cirrhosis (AUROC = 0.71, 95%CI: 0.56-0.86) and thrombocytopenia (< 150 $\times$ 10$^9$/L) (AUROC = 0.75, 95%CI: 0.58-0.90). APRI, MELD CP scores and hyperbilirubinemia (> 17 $\mu$mol/L) did not
have satisfactory performances, as the AUROCs were less than 0.70, with the 95%CI crossing 0.50. The performances of various treatment response criteria were also unsatisfactory (all AUROCs less than 0.70), with the Rotterdam and Paris I criteria showing comparable AUROCs (around 0.68), while the 95%CI of the AUROCs of the Barcelona and Toronto criteria crossed 0.50. The Rotterdam criteria had the highest sensitivity and negative predictive value.

**DISCUSSION**

In the current study, a total of 144 Chinese PBC patients with UDCA use were recruited. A study with the same cohort of patients assessed by different prognostic models for prediction of long-term transplant-free survival was recently published\[^{34}\].

Our patients were diagnosed at a slightly older age than that reported in the West (median: 57.8 vs 54.5 years)\[^{37}\]. The female preponderance (88% of our cohort) and the treatment response (33%-42%) were consistent with those reported in the West\[^{5,12}\].

APRI is widely used in the assessment of fibrosis/cirrhosis in various kinds of hepatic diseases (CHB and CHC infection, alcoholic liver disease and non-alcoholic fatty liver disease)\[^{16-22}\]. A recent study proposed that APRI could be used to predict adverse outcomes in PBC patients\[^{26}\]. However, its potential role in HCC prediction in PBC patients is still not clear. A meta-analysis reports an 18.8-fold increase of HCC risk in PBC patients compared with the general population\[^{38}\], but it suggests that HCC may not be as common in PBC patients compared with other liver diseases\[^{39}\]. Therefore, a non-invasive test that is simple and cost-

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*Table 5  Prediction of hepatocellular carcinoma development by APRI-r1 in combination with suboptimal treatment response*

| Criteria | Univariate analysis | Multivariate analysis\(^{1}\) |
|----------|---------------------|-------------------------------|
|          | HR                  | 95%CI            | P value | P trend | HR       | 95%CI            | P value | P trend |
| Rotterdam |                     |                  |         |         |          |                  |         |         |
| Low-risk  | Ref                 |                  |         |         | Ref      |                  |         |         |
| Intermediate-risk | 2.81      | 0.56-14.01 | 0.208   | <0.001\(^{2}\) | 1.54     | 0.25-9.63          | 0.644   | 0.006\(^{2}\) |
| High-risk | 10.29               | 2.55-41.48       | 0.01\(^{2}\) |         | 7.95     | 1.56-40.45        | 0.012\(^{2}\) |         |
| Paris I   |                     |                  |         |         |          |                  |         |         |
| Low-risk  | Ref                 |                  |         |         | Ref      |                  |         |         |
| Intermediate-risk | 2.81      | 0.63-12.60 | 0.177   | 0.003\(^{2}\) | 2.34     | 0.40-13.60         | 0.345   | 0.013\(^{2}\) |
| High-risk | 8.38                | 1.99-35.21       | 0.004   |         | 7.28     | 1.45-36.71        | 0.016\(^{2}\) |         |
| Barcelona |                     |                  |         |         |          |                  |         |         |
| Low-risk  | Ref                 |                  |         |         | Ref      |                  |         |         |
| Intermediate-risk | 1.28      | 0.29-5.72       | 0.75    | 0.002\(^{2}\) | 0.53     | 0.08-3.34          | 0.496   | 0.038\(^{2}\) |
| High-risk | 10.66               | 2.85-39.89       | <0.001\(^{2}\) |         | 5.54     | 1.29-23.71        | 0.021\(^{2}\) |         |
| Toronto  |                     |                  |         |         |          |                  |         |         |
| Low-risk  | Ref                 |                  |         |         | Ref      |                  |         |         |
| Intermediate-risk | 3.25      | 0.81-13.06      | 0.097   | 0.052   | 4.4      | 0.97-19.90         | 0.055   | 0.061   |
| High-risk | 4.22                | 0.85-20.97       | 0.079   |         | 4.77     | 0.78-29.24        | 0.091   |         |

\(^{1}\)The adjusted HR for suboptimal response was derived by multivariate analysis with other significant variables in Table 3 (age, male sex, cirrhosis and albumin) included; \(^{2}\)P-values < 0.05. Separate multivariate analysis was performed for each criteria in defining suboptimal response. In the multivariate analyses, albumin was not included for the Rotterdam criteria, as this variable was already included in the criteria. APRI-r1: AST/platelet ratio index at 1-year; CI: Confidence interval; HR: Hazard ratio.

*Table 6  Predictive performances of prognostic models for hepatocellular carcinoma development*

| Categorical variable | Rotterdam | Paris I | Barcelona | Toronto | Cirrhosis | Thrombocytopenia, < 150 × 10\(^{9}\)/L | Hyperbilirubinemia, > 17 mmol/L |
|----------------------|-----------|---------|-----------|---------|-----------|--------------------------------------|----------------------------------|
| AUROC                | 0.66      | 0.67    | 0.64      | 0.64    | 0.71      | 0.75                                 | 0.64                             |
| (95%CI)              | (0.52-0.80) | (0.52-0.81) | (0.48-0.78) | (0.47-0.78) | (0.56-0.86) | (0.58-0.90) | (0.49-0.77) |
| Sensitivity          | 75.00%    | 66.60%  | 58.30%    | 63.60%  | 66.70%    | 70.00%                               | 66.70%                           |
| Specificity          | 60.60%    | 66.60%  | 68.90%    | 63.60%  | 75.00%    | 79.00%                               | 60.80%                           |
| PPV                  | 14.80%    | 15.40%  | 14.60%    | 14.00%  | 19.50%    | 21.20%                               | 13.60%                           |
| NPV                  | 96.40%    | 95.70%  | 94.80%    | 94.90%  | 96.10%    | 97.00%                               | 84.90%                           |
| Continuous variable  |          |         |           |         |           |                                      |                                  |
| AUROC                | 0.68      | 0.77    | 0.7       | 0.63    | 0.62      |                                      |                                  |
| (95%CI)              | (0.49-0.87) | (0.64-0.88) | (0.54-0.84) | (0.45-0.79) | (0.47-0.76) |                                  |
| Sensitivity          | -         | -       | -         | -       | -         |                                      |                                  |
| Specificity          | -         | -       | -         | -       | -         |                                      |                                  |
| PPV                  | -         | -       | -         | -       | -         |                                      |                                  |
| NPV                  | -         | -       | -         | -       | -         |                                      |                                  |

APRI: AST to platelet ratio index at baseline; APRI-r1: APRI at 1-year; AUROC: Area under receiver operating curve; CP: Child-Pugh; MELD: Model for end-stage liver disease; NPV: Negative predictive value; PPV: Positive predictive value.
effective will be of significant clinical importance in the management of PBC patients.

Our study showed that APRI correlated with adverse liver function (in terms of both laboratory parameters and also traditional PBC prognostic models - Mayo risk score and CP score). In addition, a higher APRI-r1 level was associated with a higher HCC risk. Although being regarded as a fibrosis/cirrhosis marker, APRI-r1 retained the association with HCC development despite the inclusion of cirrhosis into the multivariate analysis (adjusted HR = 3.94). This is likely because APRI has an additional role of reflecting other pathological pathways including liver inflammation and non-cirrhotic portal hypertension.

Suboptimal treatment response was not an independent risk factor, in contrary to that reported by Trivedi et al. There are a few possible reasons to account for this. First, as disease stage is known to affect the treatment response, the effect of treatment response on HCC risk would be attenuated by including APRI and cirrhosis into the multivariate analysis. Second, our study might not be adequately powered to detect this effect given the limited number of events. However, by combining both factors (APRI-r1 and treatment response), the HCC risk of individuals could be further stratified into low-risk, intermediate-risk and high-risk.

Hyperbilirubinemia was recognized to be a risk factor for liver transplantation and death in PBC patients in previous studies, but was not a significant independent risk factor for HCC development in the current study. This is likely related to the fact that hyperbilirubinemia in patients with PBC can also be due to cholestasis, while APRI is more specifically related to fibrosis/cirrhosis.

Our study also determined the predictive performances of APRI and APRI-r1 in addition to the traditional prognostic models and treatment response criteria. We showed that APRI-r1 had a satisfactory performance, with an AUROC of 0.77. It appears that APRI-r1 outperformed other prognostic models, although the result should be interpreted with caution as there was overlapping of the 95% CIs of some models (e.g., Mayo risk score) due to the relatively small sample size of our cohort.

Cases were identified by searching the electronic database system of the hospital with subsequent review of the clinical records. This ensures the accurate and complete capture of all PBC cases. Another noticeable strength of the study is the long follow-up duration (up to 26 years), since a long lag time is usually required from PBC diagnosis to HCC development. Moreover, the inclusion of a homogenous group of Chinese patients and exclusion of concomitant liver diseases removed the confounding factors of ethnicity and hepatitis due to other liver diseases.

A few limitations are present in the current study. First, a relatively small sample size may render the study underpowered to confirm a significant association of some factors with HCC development (e.g., smoking and alcohol), although previous study also failed to show an association with these factors. Second, since this study was carried out in a tertiary center, selection bias may account for the higher HCC incidence rate in our cohort (10.6 cases per 1000 person-years). On the contrary, the study by Trivedi et al., which was a multi-center study involving 4565 patients, reported an incidence rate of only 3.4 cases per 1000 person-years. Third, our study recruited only Asian subjects, and therefore the applicability of this finding to other ethnicities remains to be investigated. Fourth, as this is only a single-center study with a relatively small sample size, validation studies from other centers are necessary. Lastly, while APRI was shown to be of both predictive and prognostic values in chronic viral hepatitis patients, studies on the usefulness of this marker in other chronic liver diseases are still lacking. Consistent findings are expected as fibrosis/cirrhosis is the major risk factor for HCC development, although further studies on other chronic liver diseases are warranted.

In conclusion, our study confirmed the usefulness of APRI-r1 in predicting HCC development in PBC patients receiving UDCA. The combination of APRI-r1 with treatment response allowed further stratification of HCC risk. Owing to its non-invasiveness and cost-effectiveness, APRI can be used as a marker to streamline the HCC surveillance protocol in PBC patients.

**ARTICLE HIGHLIGHTS**

**Research background**
No reliable predictive models exist for hepatocellular carcinoma (HCC) in primary biliary cholangitis (PBC). Aspartate aminotransferase (AST) to platelet ratio index (APRI) not only captures fibrosis/cirrhosis, but also reflects other biologically significant pathways like hepatic necroinflammation or non-cirrhotic portal hypertension. The usefulness of APRI in predicting HCC in PBC remains unknown.

**Research motivation**
A predictive marker for HCC development in PBC patients will help disease prognostication and streamline the follow-up and HCC surveillance strategy.

**Research objectives**
To investigate the usefulness of APRI in predicting HCC in PBC.

**Research methods**
The authors recruited all PBC patients who had follow-up in the Hepatology Clinic of Queen Mary Hospital (QMH) between January 2000 and October 2015. Patients were followed up every 3 to 6 mo with regular monitoring of platelet count, liver biochemistry, prothrombin time and alpha-fetoprotein level. In the analysis of the risk factors for adverse events, suboptimal response to UDCA was identified by using various treatment response criteria. APRI-r1 in combination with treatment response criteria enables further stratification of PBC patients into low-risk (biochemical response with APRI-r1 ≤ 0.54), intermediate-risk (suboptimal biochemical response with APRI-r1 > 0.54) and high-risk (suboptimal biochemical response with APRI-r1 > 0.54) groups of developing adverse
outcomes in terms of liver transplantation or death. The Cox proportional hazards model was used to determine the hazard ratio (HR) of HCC with different variables. The Kaplan-Meier method was used to analyze the development of HCC. The performances of various prognostic models were expressed in terms of area under the receiver operating curve (AUROC).

Research results
A total of 144 patients were identified. The median age at diagnosis was 57.8 years (interquartile range: 48.7-71.5 years), and 41 (28.5%) had baseline cirrhosis. The median follow-up duration was 6.9 years (range: 1.0-26.3 years), with a total of 1136 patient-years. Twelve patients developed HCC, with an incidence rate of 10.6 cases per 1000 patient-years. The overall 5-, 10- and 15-year probabilities of HCC development were 2.3% [95% confidence interval (CI): 0%-4.8%], 8.4% (95% CI: 1.8%-14.5%) and 21.6% (6.8%-34.1%), respectively. Independent risk factors for HCC development were older age (HR = 1.07), cirrhosis (HR = 4.38) and APRI at 1 year after treatment (APRI-r1) > 0.54 (HR = 3.94). APRI-r1 in combination with treatment response further stratified the risk of HCC development (log rank $P < 0.05$). The AUROC of APRI-r1 in predicting HCC was 0.77 (95% CI: 0.64-0.88).

Research conclusions
APRI-r1 can be used as a predictive marker for HCC development in PBC patients. Combination of APRI-r1 with treatment response can further stratify the HCC risk.

Research perspectives
Our study confirmed the usefulness of APRI-r1 in predicting HCC development in PBC patients receiving UDCA. The combination of APRI-r1 with treatment response allowed further stratification of HCC risk. Owing to its non-invasiveness and cost-effectiveness, APRI can be used as a marker to streamline the HCC surveillance protocol in PBC patients. Future multi-center studies with larger sample size are warranted to confirm our findings.

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