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Performance of Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) score in classifying treatment eligibility under 2012 Asian Pacific Association for the Study of the Liver (APASL) guideline for chronic hepatitis B patients

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SUMMARY

Background
REACH-B [Risk Estimation for Hepatocellular Carcinoma (HCC) in Chronic Hepatitis B] scoring system was developed to predict the risk of HCC in noncirrhotic chronic hepatitis B (CHB) patients.

Aim
To evaluate the discriminatory performance of REACH-B scoring system in classifying anti-viral treatment eligibility of CHB patients according to the 2012 Asian Pacific Association for the Study of the Liver (APASL) treatment guideline.

Methods
A total of 904 noncirrhotic CHB were enrolled. Patients' age, gender, liver biochemistry, HBeAg status and HBV DNA levels were recorded.

Results
The minimum REACH-B risk score for patients to be eligible for anti-viral treatment was 7 for HBeAg-positive and 6 for HBeAg-negative patients. Among them, increasing REACH-B score was not significantly associated with eligibility for treatment [adjusted odds ratio (OR): 1.210, 95% confidence interval (CI): 0.979–1.494, $P = 0.078$] in HBeAg-positive patients, as shown by logistic regression analysis after adjusting for gender. In HBeAg-negative patients, REACH-B score significantly predicted the treatment eligibility (adjusted OR: 1.783, 95% CI: 1.607–1.979, $P < 0.001$). Discriminatory ability of REACH-B score to classify eligibility was poor for HBeAg-positive patients ≥ 40 years [area under receiver operating characteristic (AUC): 0.664, 95% CI: 0.533–0.795], but good/excellent for HBeAg-positive patients <40 years (AUC: 0.903; 95% CI: 0.841–0.964), HBeAg-negative patients ≥ 45 years (AUC: 0.883; 95% CI: 0.848–0.917) and HBeAg-negative patients <45 years (AUC: 0.907; 95% CI: 0.874–0.940).

Conclusion
The discriminatory performance of the REACH-B scoring system in classifying anti-viral treatment eligibility based on the 2012 APASL guideline was good/excellent, except for ≥ 40 years old HBeAg-positive patients.

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INTRODUCTION

More than 400 million people are chronically infected with hepatitis B virus (HBV) globally[1, 2] and chronic hepatitis B (CHB) is one of the most common causes of hepatocellular carcinoma (HCC) in the world. The use of anti-viral therapy among high-risk patients could reduce the development of cirrhosis and HCC.[3, 4] Clinicians are all eager for a useful scoring system that can provide accurate risk stratification for HCC development and help them make evidence-based decisions when managing their CHB patients.

The REACH-B (Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B) study aimed to develop a simple, clinically useful long-term prediction score to identify the risk of progression to HCC in non-cirrhotic CHB patients.[5] A 17-point risk-score was developed comprising of five non-invasive clinical parameters predictive of HCC [gender, age, alanine aminotransferase (ALT) level, HBeAg status, and serum HBV DNA level]. Although the development of original REACH-B scoring system used a community-based natural history cohort from Taiwan, the scoring system was validated in a hospital-based composite cohort from other Asian countries.[5]

There are currently three major regional guidelines for the treatment of CHB patients, published by the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Asian Pacific Association for the Study of the Liver (APASL).[6–8] Available information suggests that patients with normal to minimally raised ALT usually have mild histological changes and respond poorly when treated with currently available drugs. Accordingly, published guidelines suggested that only patients with active HBV replication and significantly raised ALT levels are candidates for treatment. Therefore, the treatment recommendations by the society guidelines are based on the effect of anti-viral drug instead of providing insight into the assumed HCC risk.

Treatment decisions by these society guidelines rely heavily on HBV viral loads, HBeAg status and ALT levels, and all these three variables partly form the composites of REACH-B score. Two other important HCC risk factors endorsed by REACH-B but not utilised by the society treatment guidelines are age and gender.[5–8] Papatheodoridis *et al.* demonstrated that, even under anti-viral treatment and achieving viral remission, older age and male gender are still associated with HCC development.[9] Therefore, without taking age and gender into consideration, there might exist a wide discrepancy between treatment eligibility that applies the current guidelines and their corresponding absolute HCC risk.

In the research that we presented here, we aimed to evaluate the discriminatory performance of using REACH-B score to classify CHB treatment eligibility based on 2012 APASL treatment guideline from one real-world cohort.

PATIENTS AND METHODS

Real-world setting in Taiwan and our daily practice

Since October 2003, the Bureau of National Health Insurance (BNHI) in Taiwan instituted the 'Trial of Reinforced Treatment for Patients with Chronic Hepatitis B' which reimburses the cost of anti-viral medications for a finite treatment course [for example, nucleos(t)ide analogues (NUCs) treatment for 18–36 months only was allowed] in noncirrhotic CHB patients. After July 2010, patients can avail of free HBV DNA viral nucleic acid amplification tests (NAT) provided by BNHI if their biochemical data meet the BNHI criteria for treatment [persistently elevated ALT $\geq 2 \times$ upper limit of normal (ULN) within a 6-month observation period, measured on two occasions at least 3 months apart]; otherwise, patients who wish to have their HBV NAT checked must do so at their own expense. Understandably, HBV DNA test was neither routinely checked nor imperative for asymptomatic CHB patients in our daily practice.

Studied subjects and methods

Between January 2006 and May 2012, a total of 4762 consecutive patients with positive HBsAg tests visited hepato-gastroenterology clinics at one nontertiary regional hospital in Taiwan. After excluding 275 patients with coexisting hepatitis C infection, 4487 mono-HBV infected patients were identified. We focused on 1502 patients who had at least one HBV NAT measurement available for further analyses. We then excluded patients with HCC ($n = 144$), cirrhosis ($n = 194$), aged <30 ($n = 163$) or >65 years ($n = 77$) and patients with other malignancies ($n = 20$). Finally, the remaining 904 subjects were enrolled into this analysis. The study was carried out in accordance with the provisions of the 1975 Declaration of Helsinki and with the approval of the Institutional Review Board of our hospital.

HBV DNA levels were measured using the Cobas TaqMan 48 Analyser (Roche Diagnostics, Basel, Switzerland), with a detectable lower limit of 6 IU/mL (or 32 copies/mL, 1 IU is equivalent to 5.26 copies/mL). According to our laboratory reference, the ULN of ALT

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level is 40 IU/L. For patients with multiple measurements of ALT, we selected the highest level for further analysis; at the same time, patient demographics, HBV DNA levels and hepatitis B serology were recorded retrospectively. Cirrhosis was judged by the ultrasonography-based quantitative scoring system, derived from the appearance of the liver surface, liver parenchymal texture, intrahepatic blood vessel size and splenic size, with 74.8% accuracy.[10.]

The treatment guideline proposed in 2012 by APASL had been published elsewhere.[8] A total of 438 patients with obviously active CHB were selected as candidates for treatment in this study, and the treatment eligibility was briefly summarised as: (i) HBeAg-positive patients, HBV DNA $\geq 10^5$ copies/mL and ALT $\geq 2 \times$ ULN, (ii) HBeAg-negative patients, HBV DNA $\geq 10^4$ copies/mL and ALT ≥ 2 x ULN. We did not consider '*persistently*' elevated ALT levels ($\geq 2 \times$ ULN at least 3 months between observations, as stated by APASL guideline) as a criteria for eligibility here. In addition, we also did not consider histological evidences of significant fibrosis as the criteria for treatment eligibility in patients with minimally elevated ALT, because: (i) REACH-B scoring system did not include invasive parameters such as liver biopsy, (ii) although we were aware that the APASL guideline suggests liver biopsy in those patients aged ≥ 40 years, with ALT 1–2 $\times$ ULN on serial testing and significant viraemia (defined as HBV DNA $\geq 10^5$ copies/mL in HBeAg-positive and $\geq 10^4$ copies/mL in HBeAg-negative patients), our BNHI did not make such a recommendation and liver biopsy is not performed routinely in our daily practice for treatment decisions. Actually, 16.1% (75/466) of ineligible patients in the current study should have had liver biopsy as recommended by the APASL guideline, but only two of them finally accepted such an invasive procedure. We also faithfully recorded the drug persistence rate and virological response for patients who had ever received anti-viral therapies. Treatment-persistence of NUCs was defined as continued acquisition of prescription as noted in patients' medical records.

Statistical analysis

The descriptive statistics used were mean $\pm$ standard deviation (s.d.) and proportion for categorical variables. Analysis was conducted using two-sample *t*-test, Pearson's Chi-squared test and Fisher exact test when appropriate. The Spearman correlation was used to measure the degree of association between two quantitative variables. Linear trend analyses were based on mean values. Logistic regression models were used to evaluate predictors of eligibility, and results were reported as odds ratio (OR) and their 95% confidence intervals (CI). To make more use of the information from risk scores in terms of classification, it would be helpful to summarise it. A popular way of summarising the information about classification is to plot a receiver operating characteristic (ROC) curve.[11–13] The area under the ROC curve (AUC) was measured to show how well a parameter can recognise concordance between two groups. Kaplan–Meier methodology was used for time to event calculation. All statistical testing was two-tailed at the 5% level. The analysis software used was the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 17.0.

RESULTS

Among 904 patients enrolled, 217 (24%) were HBeAg-positive and 687 (76%) were HBeAg-negative. Almost all (99.7%, 901/904) patients had at least two measurements of ALT tests (range: 1–21, median 7 tests). The demographic and laboratory data of the overall population are summarised in Table 1. Compared with their HBeAg-negative counterparts, HBeAg-positive patients tended to be younger [40.6 ($\pm$9.1) vs. 45.9 ($\pm$8.6) years, $P < 0.001$], with higher ALT level [401 ($\pm$494) vs. 257 ($\pm$503) IU/L, $P < 0.001$], and higher HBV DNA level [7.4 ($\pm$2.7) vs. 4.4 ($\pm$2.7) copies/mL in $\log_{10}$, $P < 0.001$; an arbitrary value of 16 copies/mL was assigned to samples with undetectable HBV DNA]. There was a male predominance in this study (69.0%) but no gender difference was noted between HBeAg-positive and HBeAg-negative subjects ($P = 0.139$).

The proportion of age, gender, ALT and HBV DNA stratified into different levels according to REACH-B scoring system were also summarised in Table 1. The total REACH-B score was higher by one point for HBeAg-positive patients than their HBeAg-negative counterparts [9.4 ($\pm$2.5) vs. 8.4 ($\pm$2.9), $P < 0.001$].

Impacts of gender and age upon REACH-B score

The mean REACH-B score of the men was higher than that of the women by 1.4 point [9.1 ($\pm$2.8) vs. 7.7 ($\pm$2.8), $P < 0.001$].

We followed the REACH-B scoring system and the study population was stratified into seven different age groups as: 30–34, 35–39, 40–44, 45–49, 50–54, 55–59 and 60–65 years. The distributions of mean REACH-B score across the different ages were summarised in Figure 1. There were graded relationships between increasing patient age and increments of REACH-B scores in both

Table 1 | Demographic and laboratory data for all patients ($N = 904$). Mean ± s.d. or *n* (%)

Characteristics	REACH-B score	HBeAg-positive $N = 217$	HBeAg-negative $N = 687$	*P*
Age				
Mean ± s.d., years		40.6 ± 9.1	45.9 ± 8.6	<0.001
Median, years		39.0	46.0	
30–34 years	0	72 (33%)	79 (11%)	
35–39 years	1	43 (20%)	93 (14%)	
40–44 years	2	37 (17%)	143 (21%)	
45–49 years	3	26 (12%)	128 (19%)	
50–54 years	4	15 (7%)	118 (17%)	
55–59 years	5	15 (7%)	81 (12%)	
60–65 years	6	9 (4%)	45 (6%)	
Gender				0.139
Female	0	76 (35.0%)	204 (29.7%)	
Male	2	141 (0%)	483 (70.3%)	
ALT, IU/L				
Mean ± s.d., IU/L		401 ± 494 IU/L	257 ± 503 IU/L	<0.001
Median, IU/L		219 IU/L	99 IU/L	
<15	0	0 (0%)	5 (0.7%)	
15–44	1	21 (9.7%)	127 (15.8%)	
45 or more	2	196 (90.3%)	555 (80.8%)	
HBV DNA level (copies/mL)				
Mean ± s.d.,* $\log_{10}$		7.4 ± 2.7 $\log_{10}$	4.4 ± 2.7 $\log_{10}$	<0.001
Median, $\log_{10}$		8.0 $\log_{10}$	4.6 $\log_{10}$	
<9999	0	27 (12.4%)	278 (40.5%)	
10 000–99 999	3	14 (6.5%)	105 (15.3%)	
100 000–999 999	5	8 (3.7%)	105 (15.3%)	
$>10^6$ or more	4	168 (77.4%)	199 (29.0%)	
Total REACH-B score (range: 0–17)		9.4 ± 2.5	8.4 ± 2.9	<0.001
Patients eligible under APASL treatment guideline		154 (71.0%)	284 (41.3%)	<0.001

ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of the Liver; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; s.d., standard deviation.

* An arbitrary value of 16 copies/mL was assigned to samples with undetectable HBV DNA for the statistical comparison.

HBeAg-positive ($P_{trend} < 0.001$) and HBeAg-negative patients ($P_{trend} < 0.001$). Further correlation analysis also showed that age (every 1-year increment) was positively correlated to REACH-B scores (per 1-point increase) not only for HBeAg-positive ($r = 0.695$, $P < 0.001$) but also for HBeAg-negative patients ($r = 0.586$, $P < 0.001$).

Treatment eligibility under APASL treatment guideline

The numbers of patients being eligible vs. ineligible for treatment under APASL treatment guideline, stratified according to REACH-B score, were delineated in Figure 2. Compared with their HBeAg-negative counterparts, more HBeAg-positive patients were eligible for treatment (71.0% vs. 41.3%, $P < 0.001$, see Table 1). In HBeAg-positive patients, the REACH-B score was higher for patients eligible for treatment than their ineligible counterparts [10.1 (±1.9) vs. 7.8 (±2.9), $P < 0.001$]. In a similar manner, in HBeAg-negative patients, the REACH-B score was also higher for patients eligible for treatment than their ineligible counterparts [10.5 (±1.8) vs. 6.9 (±2.6), $P < 0.001$].

Impact of gender difference upon eligibility for APASL treatment guideline. Regarding gender difference, the proportion of patients eligible for treatment was not different between men and women (50.2% vs. 44.6%, $P = 0.125$).

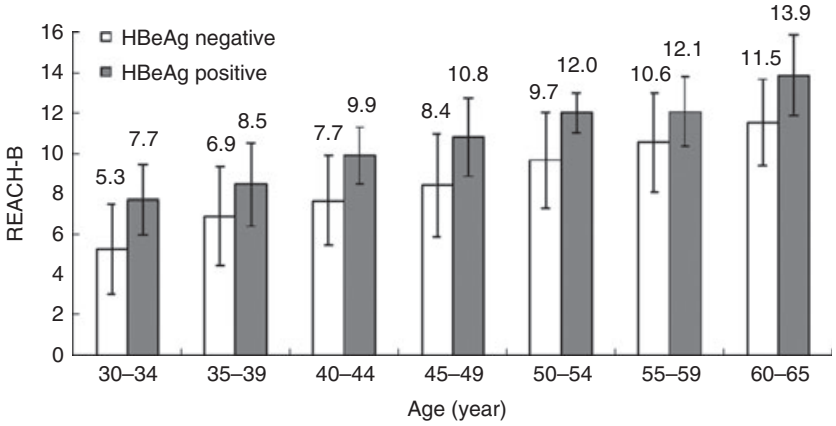

Figure 1 | Distribution of mean REACH-B score according to HBeAg status stratified by different age groups. There were graded relationships between increasing patient age and increments of REACH-B scores in both HBeAg-positive ($P_{trend} < 0.001$) and HBeAg-negative patients ($P_{trend} < 0.001$). REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B.

Impact of age upon eligibility for APASL treatment guideline. Using logistic regression analysis, increasing patient age (for every 5-year increment) was *not* significantly associated with treatment eligibility in HBeAg-positive patients [crude odds ratio (OR): 0.996, 95% confidence interval (CI): 0.845–1.175, $P = 0.965$; and adjusted OR: 1.000, 95% CI: 0.848–1.180, $P = 0.999$ after adjusting for sex difference). On the contrary, in HBeAg-negative patients, increasing age did significantly predict the treatment eligibility (crude OR: 1.094, 95% CI: 1.001–1.196, $P = 0.046$; and adjusted OR: 1.115, 95% CI: 1.019–1.221, $P = 0.018$ after adjusting for sex difference).

Using REACH-B score to predict treatment eligibility under APASL treatment guideline. The minimum REACH-B risk score for patients to be eligible for treatment was 7 for HBeAg-positive and 6 for HBeAg-negative patients in this study. We further analysed the association between risk scores and treatment eligibility among these subjects. Using logistic regression analysis, increasing REACH-B score (for every 1-point increment) was *not* significantly associated with eligibility for treatment (crude OR: 1.155, 95% CI: 0.954–1.399, $P = 0.139$; and adjusted OR: 1.210, 95% CI: 0.979–1.494, $P = 0.078$ after adjusting for sex difference) in HBeAg-positive patients. On the contrary, in HBeAg-negative patients, increasing REACH-B score significantly predicted the treatment eligibility (crude OR: 1.769, 95% CI: 1.595–1.961, $P < 0.001$; and adjusted OR: 1.783, 95% CI: 1.607–1.979, $P < 0.001$ after adjusting for gender difference).

Performance of discriminatory ability between REACH-B score and treatment eligibility under APASL treatment guideline

We plotted ROC curves for four subgroups according to HBeAg status as stratified by high- vs. low-age groups (dichotomised by median split). As shown in Figure S1 (published online, graphs A–D), the discriminatory ability was poor for HBeAg-positive patients older than 40 years (AUC: 0.664, 95% CI: 0.533–0.795), but good/excellent for HBeAg-positive patients younger than 40 years (AUC: 0.903, 95% CI: 0.841–0.964), HBeAg-negative patients older than 45 years (AUC: 0.883, 95% CI: 0.848–0.917) and HBeAg-negative patients younger than 45 years (AUC: 0.907, 95% CI: 0.874–0.940).

We summarised sensitivity, specificity and accuracy in Table 2 for these four subgroups using the optimal cutoff points determined by ROC analyses: (i) score 8 for HBeAg-positive, <age 40, (ii) score 11 for HBeAg-positive, age 40 and above, (iii) score 8 for HBeAg-negative, age < 45; (iv) score 11 for HBeAg-negative, age 45 and above. Of important note, in using cutoff score of 11 for HBeAg-positive patients age 40 and above, the specificity was only 53.6%; it meant that 13 of 28 patients (46.4%, false negative rate) would be erroneously excluded from treatment according to APASL treatment guideline. We detailed the HBV viral loads of these 13 patients and found that, although their HBV DNA levels lay in the range of 1.49×10^4–2.11×10^8 copies/mL, their ALT level never exceeded $2 \times$ ULN even after frequent blood tests (numbers of ALT measurements: range 2–12, median 5).

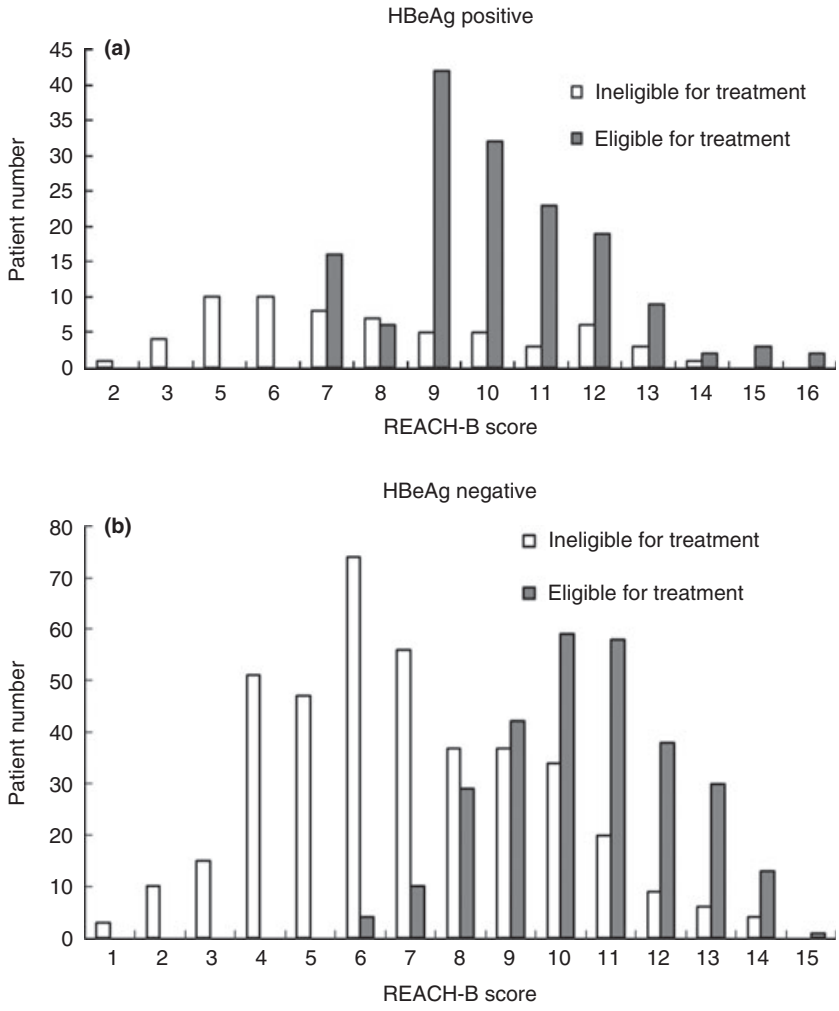

Figure 2 | Number of patients eligible vs. ineligible under APASL treatment guideline according to strata of REACH-B score: (a) for HBeAg-positive patients, (b) for HBeAg-negative patients. APASL, Asian Pacific Association for the Study of the Liver; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B.

Table 2 | Determining sensitivity, specificity and accuracy using optimal cutoff REACH-B score by ROC analysis to identify APASL treatment guideline eligibility for subgroups stratified by age and HBeAg status, *n/N* (%)

	Sensitivity	Specificity	Accuracy
HBeAg-positive and age <40 years, score 1–7 vs. 8–17 (N = 115)	64/80 (80.0%)	26/35 (74.3%)	90/115 (78.3%)
HBeAg-positive and age ≥40 years, score 1–10 vs. 11–17 (N = 102)	58/74 (78.4%)	15/28 (53.6%)	73/102 (71.6%)
HBeAg-negative and age <45 years, score 1–7 vs. 8–17 (N = 315)	108/122 (88.5%)	163/193 (84.5%)	271/315 (86.0%)
HBeAg-negative and age ≥45 years, score 1–10 vs. 11–17 (N = 372)	132/162 (81.5%)	174/210 (82.9%)	306/372 (82.3%)

APASL, Asian Pacific Association for the Study of the Liver; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; ROC, receiver operating characteristic.

Persistence of anti-viral treatment and its virological response in real-life clinical practice

Currently, our BNHI reimburses the cost of pegylated interferon and four NUCs [lamivudine (LAM), entecavir (ETV), telbivudine (LdT), and tenofovir disoproxil fumarate (TDF)] as the first-line treatments for patients with active chronic hepatitis B (defined as the presence of persistently elevated ALT ≥2 × ULN on two occasions and at least 3 months apart, plus viremia as defined in APASL statement and/or available histological evidence). For the 438 patients already eligible for treatment under APASL guideline, 265 (60.5%) had previously received some kind of anti-viral therapies while 173 (39.5%) had never been treated, with corresponding REACH-B score of 10.4 (±1.9) and 10.2 (±1.8), respectively, (P = 0.206). Sixteen patients (14 HBeAg-positive, two HBeAg-negative) were treated with pegylated interferon and 249 patients (110 HBeAg-positive, 139 HBeAg-negative) were

treated with NUCs (LAM, n = 68; ETV, n = 157; LdT, n = 19; TDF 19). Three interferon-treated patients and 10 NUCs-treated patients achieved HBeAg loss during anti-viral therapies.

We were particularly interested in the drug persistence rate of 249 patients treated with NUCs. As shown in Figure 3a, the persistence rates were 93.3%, 80.5% and 79.2% at year 1, 2 and 3 respectively. It should be noted that, 22.4% (13/58) of the patients decided to terminate therapy by the end of year 3 as our BNHI no longer reimburses free medications after 3 years of treatment for noncirrhotic patients. Inevitably, drug persistence rate abruptly declined to 58.0% after 3 years of treatment. If we excluded 10 NUCs-treated patients who achieved HBeAg loss during treatment, further subanalysis (N = 239) showed that the persistence rate was 58.8% after 3 years of treatment.

A Kaplan–Meier analysis was used to analyse the cumulative probability of complete virological response, defined as achieving HBV-DNA undetectability for the first time (Figure 3b). There were 43.6%, 71.4%, 79.4% and 88.8% of patients who achieved complete virological response at year 1, 2, 3 and 4, respectively; and the median time to HBV-DNA undetectability was 14 months.

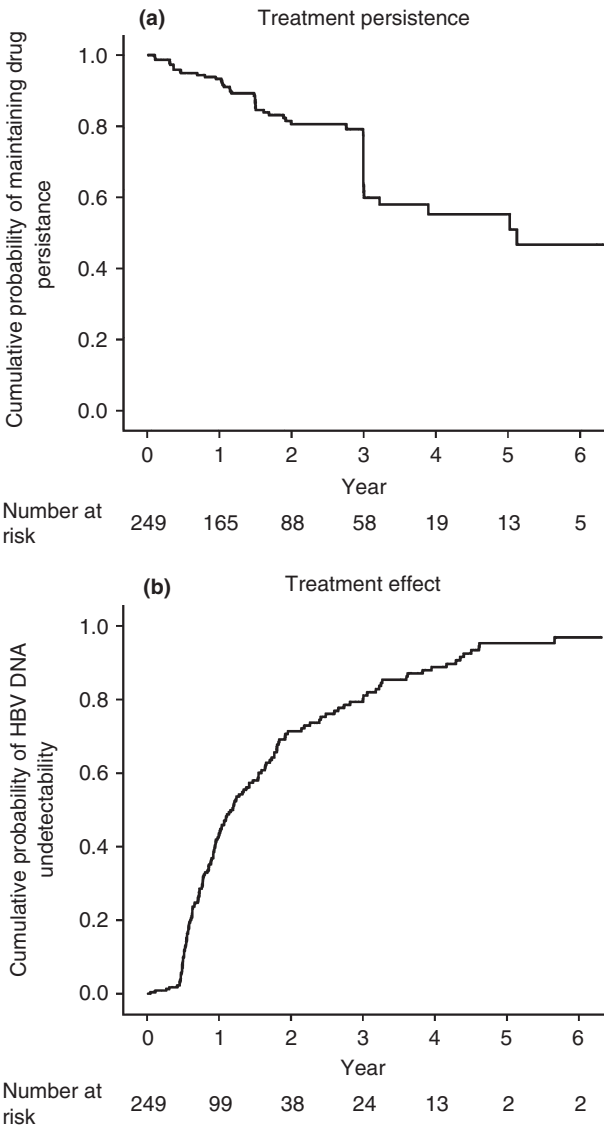

Figure 3 | (a) Kaplan–Meier method was used to analyse probability of treatment persistence with nucleos(t)ide analogues for 249 patients with chronic hepatitis B. Of note, 22.4% (13/58) patients decided to terminate treatment by the end of year 3, as our Bureau of National Health Insurance no longer reimburses free medications after 3-years treatment for noncirrhotic patients. This curve showed that drug persistence rate abruptly declined to 58.0% after 3 years of treatment. (b) Kaplan–Meier method was used to analyse treatment effect of nucleos(t)ide analogues for 249 chronic hepatitis B patients, and this figure showed the cumulative probability of complete virological response (defined as the first time to achieve HBV-DNA undetectability, <32 copies/mL).

DISCUSSION

Risk estimates can theoretically be used to raise people's awareness of certain diseases that can cause a significant burden of morbidity/ mortality, to impart knowledge to high-risk patients, and to motivate therapeutic adherence. Such topics have received much attention in cardiovascular risk prediction.[11] However, risk prediction in viral hepatitis is still in its infancy stage. The REACH-B scoring system is comprised of HBV viral loads, HBeAg status, ALT levels, age and gender. It can provide treatment guidance by focusing on disease-severity as reflected by long-term HCC risk, which are not covered in currently prevailing society recommendations. In this study, the mean risk score of patients eligible for treatment under 2012 APASL treatment guideline was 10, with a projected HCC risk of 0.9% at 3 years, 2.0% at 5 years and 5.2% at 10 years as estimated by the REACH-B scoring system.[5]

Although age and gender are important HCC risks, they are often neglected by the present treatment guidelines.[5–8] There was no difference in the sex ratio in terms of eligibility for treatment in this study. We next studied the impact of aging on REACH-B score and treatment eligibility. Increasing age paralleled higher REACH-B scores, not only for HBeAg-positive but also for HBeAg-negative patients. For HBeAg-negative patients, we were able to confirm that both age and REACH-B score increments significantly predicted eligibility for the treatment.

Intriguingly, for the HBeAg-positive counterparts, increasing age and higher REACH-B score were not able to predict treatment eligibility. The discrepancy in treatment eligibility with regards to the effect of aging on different HBeAg status could be best explained by one compelling study from Hong Kong by Fung *et al.,* which showed that HBeAg-negative CHB patients tend to have elevated ALT and higher viral load with increasing age.[14] Thus there were significantly higher proportions of HBeAg-negative patients with active disease who were candidates for treatment as they get older.[14] Simultaneously, Fung *et al.* also reported that HBeAg-positive patients had lower HBV DNA levels in the older age group than their younger counterparts, and the proportion of elevated ALT did not correlate with age.[14] Therefore, we could infer that increasing age and REACH-B score have nothing to do with treatment eligibility in HBeAg-positive patients, as shown in the current study. Our findings could be further illustrated by plotting ROC curve (Figure S1, graphs A–D; published online) and calculating the corresponding AUC, which is regarded as an important method in determining the utility or predictive ability of risk-estimation scheme.[12] We clearly showed the good/excellent discriminatory ability of REACH-B score in determining eligibility for treatment under the APASL treatment guideline in HBeAg-negative subjects as a whole and HBeAg-positive CHB patients younger than 40 years, as well as the poor discriminatory ability in HBeAg-positive patients aged 40 years and older. To illustrate, 46.4% of HBeAg-positive patients with age older than 40 years and high HCC risk as corroborated by a REACH score ≥ 11 (all were significantly viraemic) would be erroneously excluded from treatment as their ALT levels never exceeded $2 \times$ ULN even after frequent blood tests during follow-up. In this situation, we would suggest that the severity of liver fibrosis of these high-risk patients be evaluated through liver biopsy or complementary non-invasive tools such as liver stiffness measurement, rather than preclude them from treatment.[7, 8, 15] Therefore, our findings reinforced the statement of 2012 APASL treatment guideline: 'assessment of liver fibrosis is recommended in viremic patients with high normal or minimally raised ALT levels and patients older than 40 years'. In keeping with this viewpoint, leading experts recently made an appeal by advocating therapy in all patients even with high-normal ALT activity, because earlier treatment intervention may be beneficial in preventing disease progression in the long term.[16]

For patients already eligible for treatment under APASL guideline, only 60.5% had previously received some kind of anti-viral therapies in this study. The reasons for the unmet clinical needs are not clear. Patients' misperception that CHB is not a serious illness is one possible explanation. Most importantly, the rigid rules drafted by our BNHI only allowed patients with '*persistently*' elevated ALT levels $>2 \times$ ULN (observed on two occasions at least 3 months apart in a period of 6 months) to be treated. Although the APASL and AASLD treatment guidelines suggest a 1–3 month observation period to ensure the need for therapy, the EASL guideline does not have such recommendation.[6–8] We felt that adherence to 'persistently elevated ALT for 3 months' to be unrealistic when initiating treatment while the other guidelines (such as the one proposed by EASL) place more emphasis on histological severity of liver disease for viremic CHB patients, even if ALT levels are normal.[7]

In line with another real-life clinical investigation by Watcharasak *et al.*[17], the drug-persistence rate in our study during the first 3-year period was high among 249 patients treated with NUCs (Figure 3a), and continuous viral suppression could be achieved if patients were to be treated persistently (Figure 3b). Unfortunately, 22.4% of the patients decided to terminate therapy by the end of year 3 as our BNHI no longer reimburses free medications after this period. Perceivably, drug persistence rate dropped abruptly to 58.0% after 3 years of treatment. We hereby raised this important issue: without the full support of the healthcare provider, both the patients and physicians will never be satisfied with the anti-viral coverage rate.

There are several limitations in this study. This is a cross-sectional retrospective study, and therefore does not take into account the changes or fluctuation in viral load over time. Another limitation is the possible presence of referral bias, as we did not routinely check HBV DNA levels for all HBsAg-positive patients. Despite this possibility, the studied subjects in our real-life practice did not differ from other Asian hospital-based patients in terms of sex distribution, age, HBeAg status and HBV DNA levels.[5, 14] Accordingly, we are convinced that selection bias is at best minimal in this study.

To conclude, the REACH-B score, as an estimator of HCC risk, has the potential to be incorporated into a clinical decision-making about appropriate and timely therapeutic intervention under the 2012 APASL guideline. The discriminatory performance of REACH-B scoring system in classifying treatment eligibility for APASL treatment guideline was good/excellent; however, a noticeable portion of HBeAg-positive patients older than 40 years

with REACH-B score ≥ 11 would be erroneously excluded from treatment, due to their minimally elevated ALT. Whether the use of such risk-predicting model influences the guideline revision and improves patient outcomes should be an interesting subject for future studies.

AUTHORSHIP

Guarantor of the article: T.-M. Chen.

Author contributions: T-M Chen designed the research, collected and analysed the data, performed the research and wrote the paper. CF Wen analysed the data. CC Chang and PT Huang designed the research. CC Lin, as corresponding author, was responsible for the whole study design and communications between all co-authors. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. ROC curves for 4 subgroups according to HBeAg status stratified by high- vs low-age groups (dichotomized by median split). (a) HBeAg-positive and age <40 years; (b) HBeAg-positive and age 40 years or more; (c) HBeAg-negative and age <45 years; (d) HBeAg-negative and age 45 years or more.

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