Validation of the TREAT-B score for hepatitis B treatment eligibility in a large Asian cohort: TREAT-B improves with age

To the Editor:

We read with interest the articles by Shimakawa et al. outlining a new score to determine treatment eligibility in Africans living with chronic hepatitis B (CHB) and by Johannessen et al. validating this score in a hospital-based Ethiopian cohort. The TREAT-B algorithm is a simple score using widely-available alanine aminotransferase (ALT) and HBeAg tests to determine CHB treatment eligibility and to overcome barriers to treatment assessment arising from limited access to HBV DNA nucleic acid testing and transient elastography. Both groups found WHO guidelines performed poorly for treatment eligibility. Given the high CHB prevalence in the Asia-Pacific (>115 million people affected) and urgent need for simplified treatment algorithms in low-resource countries within this region, we validated the TREAT-B algorithm in a large Asian-Pacific cohort of patients with CHB.

Complete clinical data for 1,358 treatment-naive patients with CHB from 2 prospective clinical studies conducted in Melbourne, Australia were analysed; 976 (72%) were recruited from a single large metropolitan hospital and 382 (28%) were recruited from primary practice sites. Patients with HIV, HCV or HDV coinfection, hepatocellular carcinoma, decompensated liver disease, or severe autoimmune hepatitis were excluded. We validated the TREAT-B algorithm against the gold standard EASL 2017 guidelines, which replaced the previous EASL 2012 guidelines against which TREAT-B was originally validated. EASL 2017 guidelines recommend treatment in patients with a) cirrhosis and a detectable viral load; b) F2 or greater fibrosis stage and viral load >2,000 IU/L; c) ALT greater than 80 IU/L and viral load >20,000 IU/L; d) Metavir score (liver biopsy) ≥A2 and viral load >2,000 IU/ml; e) HBeAg-positive, age >30 years-old and viral load >2,000 IU/L; and f) family history of hepatocellular carcinoma. To define severe fibrosis/cirrhosis for the purposes of treatment eligibility, we used a transient elastography (TE) cut-off of >12 kPa (Fibroscan®, Echosens, France) for those with elevated ALT and >9 kPa if normal ALT, in accordance with EASL guidelines (2017) or cirrhosis confirmed on liver histology. The TREAT-B score was derived by addition of HBeAg status (positive 1 point, negative 0 points) to ALT level (<20 IU/L, 0 points; 20–39 IU/L, 1 point; 40–79 IU/L, 2 points; ≥80 IU/L, 3 points) and an overall score ≥2 was deemed eligible for treatment. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of TREAT-B was compared to EASL 2017 guidelines.

The hospital cohort was older (mean age 53 compared with 48 years, p < 0.001), predominantly male (63% hospital vs. 46% community, p < 0.001), HBeAg positive (26% hospital vs. 9% community, p < 0.001) and had a higher proportion with cirrhosis (4.1% hospital cohort, 1.0% community cohort, p = 0.01). Seventy percent of the hospital cohort and 93% of the community cohort were Asian; 5% of the hospital cohort were African and 2% were Indigenous Australians or Pacific Islanders.

Using the TREAT-B algorithm, 56% of hospital and 20% of community patients were eligible for treatment, compared to 35% of hospital and 14% of community patients using the EASL guidelines. Overall, TREAT-B had good sensitivity (88%) and specificity (72%), low PPV (56%) and high NPV (98%) and AUROC of 0.801 for determining EASL treatment eligibility in the whole cohort (Table 1). The TREAT-B algorithm had higher sensitivity (91%) but lower specificity (63%) in the hospital cohort compared with the community cohort (sensitivity 70%, specificity 88%) (Table 1).

Eighteen (42%) of 43 patients with severe fibrosis or cirrhosis, and 5 (20%) of 24 patients with cirrhosis (defined as TE >12 kPa or liver biopsy, and/or clinical evidence of cirrhosis) who were eligible by EASL 2017 treatment criteria were not eligible using the TREAT-B algorithm, all of whom were aged >30 years. When considering a higher cut-off for cirrhosis of 14 kPa, 5 of 19 patients (26%) were missed using the TREAT-B algorithm. We therefore re-analysed the data incorporating a new criterion (age >30 years and HBeAg positive regardless of ALT level) into the TREAT-B algorithm (TREAT-B-30). The TREAT-B-30 criteria increased sensitivity from 89% to 93%, specificity remained 72%, and NPV decreased slightly from 98% to 96%, AUROC 0.821 (Table 1). However, this change did not capture any of the patients with severe fibrosis or cirrhosis missed by the TREAT-B algorithm, as all were HBeAg negative. Of note, all had a detectable viral load; 8 (44%) had levels >2,000 IU/ml.

In this large multicentre, predominantly Asian cohort of Australian CHB patients, the TREAT-B algorithm had good sensitivity and specificity for treatment eligibility in accordance with EASL 2017 CHB guidelines. Incorporating age (>30 years) into the TREAT-B algorithm (TREAT-B-30) requires no additional resources and improved sensitivity for treatment eligibility without reducing specificity. However, 42% of cirrhotic patients who would most benefit from treatment were not eligible using either algorithm.

In low-resource settings that cannot afford to follow international guidelines, the cost of treating patients unlikely to benefit from treatment must be carefully weighed against the risk of hepatocellular carcinoma and death in untreated cirrhotic patients with CHB. Simplified treatment algorithms must have high sensitivity for detecting cirrhotic patients to have an impact on global CHB-related mortality; to achieve this, additional biomarkers for cirrhosis may be required.
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Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

Authors’ contributions
JH conceived and led the project, performed the analysis and wrote the paper. DA, AT and MH mentored the project and provided intellectual input into all aspects of the project, assisted with manuscript writing and approved the final draft. YX and CvG provided intellectual input in study design, assisted with manuscript writing and approved the final draft. SB, JL and WK conducted the CATCH study, provided data for the community cohort, contributed to writing of the manuscript and approved the final draft. JW prepared the data for the hospital cohort. SB, CC, BD, PD, SH, JAH, TH, LL, TP, MR and KV provided clinical data for the hospital cohort, assisted with manuscript writing and approved the draft.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.06.031.

Table 1. Accuracy of the TREAT-B and TREAT-B-30 algorithm to determine hepatitis B treatment eligibility in accordance with EASL 2017 guidelines in hospital-based and community-based hepatitis B cohorts.

<table>
<thead>
<tr>
<th></th>
<th>EASL 2017 eligible</th>
<th>EASL 2017 not eligible</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>AUROC</th>
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<td>TREAT-B eligible</td>
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</table>

AUROC, area under the receiver operator curve; NPV, negative predictive value; PPV, positive predictive value.

References

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Letters to the Editor

TREAT-B and TREAT-B-30 scores to identify HBV-infected African patients eligible for antiviral treatment according to the EASL 2017 guidelines

To the Editor:

We read with interest the letter by Howell and colleagues which validated the TREAT-B (Treatment Eligibility in Africa for the HBV) score in 1,358 patients with chronic HBV infection in Australia.1 To eliminate HBV infection by 2030, improving diagnostic capacities in resource-limited countries with high HBV burden is essential.2 However, conventional tools to assess treatment eligibility, particularly HBV DNA PCR and liver biopsy/FibroScan®, remain unaffordable in these countries.3 In a validation dataset of 327 Africans, the AUROC, sensitivity and specificity of TREAT-B were 0.85, 85%, and 77%, respectively.4

In 2017, EASL updated its guidelines and further clarified that the following conditions require treatment: i) HBV-HBeAg-positive and high viremia and age >30 years; ii) family history of hepatocellular carcinoma (HCC)/cirrhosis; and iii) extrahepatic manifestations (Table S1). Upper limit of normal (ULN) for ALT became explicitly defined as 40 IU/L. The following thresholds for liver stiffness measurement (LSM) were recommended to diagnose severe fibrosis or cirrhosis: >9 kPa for those with normal ALT and >12 kPa for elevated ALT.6

By applying these new criteria as a reference, Howell et al.6 reported that the AUROC, sensitivity and specificity of TREAT-B to indicate EASL 2017 treatment criteria were 0.80, 88.2% and 71.7%, respectively.1

Since our original work referred to the EASL 2012 criteria, and applied LSM threshold values that were locally optimized7 and ULNs of ALT recommended by the American guidelines at that time (men: 30 IU/L; women: 19 IU/L) to develop and validate TREAT-B,8 we re-analyzed the same dataset by applying the EASL 2017 criteria with the new thresholds for LSM6 and ALT (40 IU/L for both sexes), as performed by Howell et al. The numbers meeting the EASL 2012 and 2017 criteria were 58 (7.2%) and 54 (6.7%) in 804 Gambians, and 58 (17.7%) and 53 (16.2%) in 327 other Africans, respectively. The majority had a concordance between the 2012 and 2017 criteria. However, 32 Gambians and 9 other Africans had a discordance: 16 patients, ineligible based on the 2012 criteria were eligible based on the 2017 criteria because of “HBeAg-positive and high viremia and age >30 years” (n = 14) and the change in the LSM thresholds (n = 2); 25 lost their eligibility due to the change in the ULN for ALT (n = 18) and the change in the LSM cut-offs (n = 7). Family history was not considered due to poor ascertainment of HCC/cirrhosis in Africa.8 No case had extrahepatic manifestations.

Despite these changes, the performance of TREAT-B did not substantially change between the EASL 2012 and 2017 guidelines (Table 1). In addition, the AUROC, sensitivity, and specificity to select patients meeting the 2017 criteria in our dataset were quite similar to those reported by Howell and colleagues.

Importantly, Howell et al. indicated that the performance of TREAT-B was modest in a subset of patients with severe fibrosis/cirrhosis, and therefore they proposed a new algorithm called “TREAT-B-30” incorporating an additional criterion “HBeAg-positive patients aged >30 years irrespective of their ALT levels” into the TREAT-B score.9 We thus assessed TREAT-B-30 in 69 African patients with severe fibrosis/cirrhosis defined by EASL’s LSM thresholds1; in this subgroup TREAT-B performed as well as TREAT-B-30 to identify HBV-infected patients fulfilling the EASL 2017 criteria (Table 1). TREAT-B and TREAT-B-30 performed similarly well in African patients. As suggested by Howell et al. TREAT-B could be used in areas with limited access to PCR or FibroScan®.

Keywords: Hepatitis B; Diagnostic score; Patient care management; Validation studies; Sensitivity and specificity; Africa; Elimination; TREAT-B.

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Reply to: “Validation of the TREAT-B score for hepatitis B treatment eligibility in a large Asian cohort: TREAT-B improves with age”

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