



Performance of two simplified HBV treatment criteria (TREAT-B score and WHO guidelines) in Burkina Faso, West Africa

To the Editor:

To achieve the World Health Organization (WHO)'s global strategy of eliminating hepatitis B virus (HBV) infection by 2030, it is vital to scale up screening, clinical staging and treatment services in low- and middle-income countries (LMICs) which account for the largest proportion of people living with chronic HBV infection worldwide.¹ Although both screening tests for hepatitis B surface antigen (HBsAg) and generic antiviral medicines are now available at affordable prices in LMICs, access to the conventional diagnostic tests to examine treatment eligibility (liver biopsy/FibroScan[®]/HBV DNA) is still limited and non-affordable.² Consequently, the WHO guidelines provided simplified criteria specific for LMICs where HBV DNA quantification is inaccessible: cirrhosis (clinical diagnosis or aspartate aminotransferase-to-platelet ratio index (APRI) >2.0), or persistently elevated alanine aminotransferase (ALT), defined by 3 ALT determinations over a period of 6–12 months.³ Recently, using the data from the PROLIFICA (Prevention of Liver Fibrosis and Cancer in Africa) Study in The Gambia, West Africa, we developed TREAT-B (Treatment Eligibility in Africa for the Hepatitis B Virus), a novel simple score free from HBV DNA and based on solely ALT level and hepatitis B e antigen (HBeAg) sero-status. The total TREAT-B score is obtained by adding HBeAg score (negative (0 point) or positive (1 point)), and ALT score (<20 IU/L (0 point), 20–39 (1 point), 40–79 (2 points) or ≥80 (3 points)). TREAT-B ranged from 0 (HBeAg-negative and ALT <20 IU/L) to 4 (HBeAg-positive and ALT ≥80 IU/L). TREAT-B had high diagnostic accuracy for the selection of treatment eligible patients (area under the receiver operating characteristic curve [AUROC] 0.85; sensitivity 84.5%; specificity 77.3%), based on the reference tests used in the European Association for the Study of the Liver (EASL) guidelines, performed in the validation dataset from other African populations.⁴

Since the publication of the original work, further validation of TREAT-B and the simplified WHO criteria was performed, using the EASL guidelines as a reference. In the UK and Germany, among predominantly migrant populations from Africa or Asia, the AUROC of TREAT-B (0.84; 95% CI 0.80–0.88) was significantly higher than the WHO criteria (0.67; 95% CI 0.63–0.70), with sensitivity and specificity of 82.9% and 73.7% for TREAT-B and 92.4% and 41.0% for WHO.⁵ In Ethiopia, Johannessen and colleagues showed that the AUROC of TREAT-B (0.73; 95% CI 0.68–0.78) was again significantly better than the WHO criteria (0.62; 95% CI 0.56–0.68), with sensitivity and specificity of 53.0% and 83.4% for TREAT-B and 56.7% and 67.4% for the WHO criteria.⁶

Here, we report the performance of TREAT-B and simplified WHO criteria evaluated in an independent dataset from Burkina Faso. Of 1,313 HBsAg-positive patients evaluated at the Yalgado Ouédraogo University Hospital, Ouagadougou, in 2006–2012, there were 255 treatment-naïve patients who had ≥3 ALT measurements, in addition to the comprehensive baseline assess-

ment including HBeAg (Elecsys[®], Roche Diagnostics), HBV DNA PCR (Cobas[®] Taqman) and fibrosis assessment (liver biopsy [n = 78], FibroScan [n = 8], and FibroTest [n = 169]). For FibroScan, significant fibrosis (≥F2) and cirrhosis (F4) were defined as ≥7.9 kPa and ≥9.5 kPa, respectively.⁷ After excluding patients coinfecting with HCV/HDV/HIV, decompensated cirrhosis, or hepatocellular carcinoma, 222 were finally included in the analysis.

Table 1 shows their baseline characteristics. Median age was 34 years (interquartile range: 28–40), and 150 (67.6%) were men. HBeAg was positive in 36 (16.2%). Treatment was indicated in 63 (28.4%), 91 (41.0%), and 73 (32.9%) patients, based on the reference tests used in the EASL 2017 criteria,⁸ TREAT-B, and simplified WHO criteria, respectively. Table 2 presents the performance of TREAT-B and WHO criteria to diagnose treatment eligibility, as determined by the EASL guidelines. The AUROC of TREAT-B (0.76; 95% CI 0.69–0.83) was significantly higher than that of the WHO criteria (0.68; 95% CI 0.61–0.75), using the Wald statistic ($p = 0.03$).⁹ The sensitivity and specificity were 69.8% and 70.4% for TREAT-B with a cut-off of ≥2, and 58.7% and 77.4% for the simplified WHO criteria.

Despite substantial variation in sensitivity and specificity, all the previous external validation studies, including the one reported here, constantly showed that TREAT-B is better than the simplified WHO criteria at discriminating between patients who are eligible or ineligible for antiviral therapy. The sensitivity of TREAT-B observed in Ethiopia (53.0%) and in Burkina Faso (69.8%) may be suboptimal; nevertheless, from a public health perspective, reduced cost and improved operational characteristics can compensate for the low sensitivity of a test, which can lead to better access to diagnostic services. A modeling study of tuberculosis has shown that the diagnostic sensitivity was just one of multiple parameters in resource-limited countries; a point-of-care test with 40% sensitivity had a similar impact on population-level mortality to a molecular assay with 70% sensitivity, because the former improved the linkage to care.¹⁰ The advantage of TREAT-B is that both ALT and HBeAg can be potentially measured using a point-of-care test, although the detection limit of HBeAg rapid diagnostic tests needs to be improved.¹¹ A health-economic study using modeling is underway by our group to assess the effectiveness and cost-effectiveness of the simplified HBV treatment algorithms with varying diagnostic sensitivity and specificity in resource-limited settings.

Different approaches exist to simplify HBV treatment criteria. TREAT-B was derived through a purely statistical method: out of clinical, haematological, biochemical, and serological markers widely available in LMICs, an automated stepwise selection procedure identified a set of variables (ALT and HBeAg) that gave a good prediction of the treatment eligibility. Another approach is to replace each of the conventional reference tests used to define treatment eligibility with an affordable and available alternative. For example, liver fibrosis can be evaluated through APRI or gamma-glutamyltransferase to platelet ratio (GPR).⁷ Instead of real-time PCR, high HBV viral replication in treatment-naïve patients can be diagnosed

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

Table 1. Characteristics of the study participants (n = 222).

	All (n = 222)	Treatment eligible by EASL (n = 63)	Treatment ineligible by EASL (n = 159)	p value*
Median age (IQR), years	34 (28–40)	32 (26–40)	34 (28–40)	0.8
Male, n (%)	150 (67.6)	51 (81.0)	99 (62.3)	0.01
Median HBV DNA (IQR), log 10 IU/ml	3.0 (2.1–4.3)	5.8 (3.9–7.2)	2.4 (1.8–3.3)	<0.0001
Positive HBeAg, n (%)	36 (16.2)	22 (34.9)	14 (8.8)	<0.001
Median ALT (IQR), IU/L				
1st measurement	30 (20–53)	51 (28–77)	25 (18–42)	<0.0001
2nd measurement	29 (18–46)	43 (25–87)	26 (16–38)	<0.0001
3rd measurement	28 (19–47)	44 (27–77)	24 (17–37)	<0.0001
Liver fibrosis, n (%)				
No or mild (F0–1)	103 (46.4)	4 (6.4)	99 (62.3)	<0.001
Significant (F2)	82 (36.9)	32 (50.8)	50 (31.5)	
Severe (F3)	24 (10.8)	15 (23.8)	9 (5.7)	
Cirrhosis (F4)	13 (5.9)	12 (19.1)	1 (0.6)	
Treatment eligible by TREAT-B (score ≥2), n (%)	91 (41.0)	44 (69.8)	47 (29.6)	<0.001
Treatment eligible by the simplified WHO criteria, n (%)	73 (32.9)	37 (58.7)	36 (22.6)	<0.001

ALT, alanine aminotransferase; EASL, the European Association for the Study of the Liver; HBeAg, HBV e antigen; HBV, hepatitis B virus; WHO, World Health Organization. * p value was obtained using Wilcoxon rank-sum test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables.

Table 2. Performance of TREAT-B and the simplified WHO criteria (n = 222).

	TREAT-B	Simplified WHO criteria	p value*
AUROC (95% CI)	0.76 (0.69–0.83)	0.68 (0.61–0.75)	0.03
Sensitivity (%)	69.8%	58.7%	
Specificity (%)	70.4%	77.4%	
Positive predictive value (%)	48.4%	50.7%	
Negative predictive value (%)	85.5%	82.6%	

AUROC, area under the receiver operating characteristic curve; WHO, World Health Organization. * p value was obtained using the Wald test.

using a simpler molecular assay (e.g., loop-mediated isothermal amplification (LAMP))¹² or inexpensive serological test (e.g., hepatitis B core-related antigen (HBcrAg)).¹³ Further evaluation of simple, affordable, and reliable diagnostic algorithms, including TREAT-B, is crucial to reach the global elimination goal.

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Conflict of interest

YS has served as consultant of Gilead Sciences. The other authors declare no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

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Another clinical unmet need in liver patients: Multidrug resistant bacteria in decompensated cirrhosis

To the Editors:

We read with interest the article by Fernández *et al.* regarding the epidemiology, risk factors and impact of bacterial infections in cirrhotic patients in Europe.¹ While most of the previous studies came from single centers, this study addresses an emerging and threatening health issue in series of patients from different geographic areas. The prevalence of multidrug-resistant (MDR) bacteria in culture-positive infections was 29.2% and was significantly higher in Northern and Western Europe than Southern Europe. In a recent published study by Piano *et al.*,² the estimated global prevalence of MDR bacteria was 34% in patients with a positive culture, with a reported prevalence of 29% in Europe, despite relevant variability among European countries. Nevertheless, this issue may be underestimated.

Taking this into account, we retrospectively analyzed all bacterial infections with confirmed microbiological isolation in patients with decompensated liver cirrhosis that were admitted, between January 2009 and May 2016, to a non-transplant tertiary reference center from Porto, the largest city of northern Portugal. Three hundred and eight infections with positive cultures were identified, corresponding to 218 admissions, in a total of 161 patients. The median age of the patients was 63 years (interquartile range 55–71) and 67% of them were men. Alcohol-related liver disease (72%) and hepatitis C virus infection (10%) were the major causes of cirrhosis. The median model for end-stage liver disease score on admission was 20

(interquartile range 12–25). Among the infections evaluated, 87% were nosocomial and 13% community-acquired. Urinary tract infection (57%), bacteremia (12%) and spontaneous bacterial peritonitis (SBP; 8%) were the most common types of infection in patients with microbiological isolation. In 27% of patients, there were at least 2 concomitant bacterial infections. Gram-negative bacteria and gram-positive bacteria each accounted for 50% of positive cultures. MDR bacteria were isolated in 51% of cases (n = 158), the most common being extended spectrum β-lactamase producing *Enterobacteriaceae* (n = 39), *Enterococcus Faecium* (n = 34), *Enterococcus Faecalis* (n = 16), *Pseudomonas Aeruginosa* (n = 6) and *Methicillin-resistant Staphylococcus aureus* (n = 4). Overall, 19 cases of extensively drug-resistant (XDR) bacteria (6.2%) were isolated and there was 1 reported case of pandrug-resistant (PDR) bacteria. This was a patient admitted with SBP, and a positive culture for *Enterobacter cloacae* resistant to all available antimicrobial agents. The patient was under large-spectrum antibiotic therapy with ertapenem, but died 4 days after admission.

We aimed to identify risk factors for MDR infection (Table 1). In our cohort, in contrast to the study by Fernández *et al.*, the multivariate analysis showed that prophylaxis for SBP was associated with MDR bacterial infection. Other factors independently associated with MDR bacterial infections replicated those previously described, including hospitalization in an intensive/intermediate care unit in the previous month and

Table 1. Predictors of development of MDR infection.

	Unadjusted OR (95% CI)	p value	Covariate-adjusted OR (95% CI)	p value
Age	0.98 (0.96–0.99)	0.018	0.99 (0.97–1.01)	0.248
Immunosuppressants	2.84 (1.36–5.92)	0.005	1.84 (0.79–4.28)	0.159
Antibiotic prophylaxis for SBP	3.01 (1.69–5.36)	<0.001	2.25 (1.14–4.47)	0.020
Ascites on admission	1.79 (1.11–2.90)	0.018	1.27 (0.73–2.32)	0.398
MELD score on admission	1.03 (1.01–1.06)	0.016	1.01 (0.98–1.04)	0.508
Hospitalization in the previous 3 months	2.73 (1.70–4.39)	<0.001	1.58 (0.89–2.79)	0.118
Hospitalization in an intermediate/intensive care unit in the previous month	3.19 (1.78–5.74)	<0.001	2.50 (1.31–4.77)	0.005
Antibiotic therapy in the previous 6 months	3.50 (2.18–5.61)	<0.001	1.88 (1.06–3.32)	0.030

MDR, multidrug resistant; MELD, model for end-stage liver disease; OR, odds ratio; SBP, spontaneous bacterial peritonitis. Predictors of MDR infection were determined by binary logistic regression (SPSS®v.24.0 data)