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TREAT-B has Good Accuracy in Selecting HBV Infected Patients for Treatment in Sudan

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Non-invasive and invasive diagnostic methods, which are not readily available in Sudan, are used to guide HBV treatment. Africa adopted the TREAT-B as a straightforward score in 2018 to identify patients in need of anti-HBV treatment.
Objective: To compare the diagnostic accuracy of the TREAT-B score to the standard scores EASL and AASLD in HBV patients.
Methods: At Ibn Sina Specialized Hospital, 108 HBV patients were enrolled in an analytical cross-

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sectional study (January- October 2019). Data was collected using an interviewer-administered questionnaire and analyzed using SPSS.
Results: Eight patients (7.4%) were eligible for therapy under the AASLD recommendations, 18 patients (16.7%) were suitable under the EASL guidelines, and twenty-seven patients (25%) were eligible under the TREAT-B guidelines. According to the Wald statistic, the AUROC of TREAT-B (0.883; 95% CI 0.790-0.976; Sen. 85.3%; Sp. 70.3%) was substantially higher than the AUROC of the AASLD criteria (0.722; 95% CI 0. 0.566-0.878; Sen. 74.4%; Sp. 69.8%); and lower than the AUROC of the EASL criteria (0.952; 95% CI 0.790-0.976.
Conclusion: The TREAT-B score was effective at identifying HBV-infected patients who should receive antiviral treatment.

Keywords: Hepatitis B; treatment; sensitivity and specificity; diagnostic; antiviral therapy.

ABBREVIATIONS

AASLD : American Association of the study of liver disease
AFP : Alpha-fetoprotein
ALT : Alanine aminotransferase
APASL : Asian Pacific Association for the Study of the Liver
AST : Aspartate aminotransferase
AUROC : Area under the receiver operating characteristic curve
CKD : Chronic kidney disease
DM : Diabetes mellitus
EASL : European Association of the study of liver disease
HBV : Hepatitis-B Virus
HBeAg : Hepatitis B e Antigen
HCC : Hepatocellular carcinoma
HCV : Hepatitis C Virus
HTN : Hypertension
INR : International normalized ratio
LMICs : Low-income and middle-income countries
PPF : Periportal fibrosis
PROLIFICA : Prevention of Liver Fibrosis and Cancer in Africa
TREAT-B : Treatment Eligibility in Africa for the Hepatitis B Virus
WHO : World Health Organization.

1. INTRODUCTION

Many people worldwide are affected by viral hepatitis. As the seventh leading cause of death in the world, it ranks higher than any of the major illnesses, including HIV, tuberculosis (TB), and malaria. Most viral hepatitis-related deaths in 2013 were expected to occur in low- and middle-income countries (LMICs), with hepatitis B infection (HBV) accounting for nearly half of those deaths, which can lead to cirrhosis and hepatocellular cancer (HCC) [1].

Sudan has a high prevalence of hepatitis B surface antigen (HBsAg), with more than 8% of the population infected [2]. Some African countries demonstrated HBsAg seroprevalence rates of (15.6%) in Burundi and (7%) in Ethiopia [3-4]. These rates were comparable to Sudan, where hepatitis B surface antigen (HBsAg) seroprevalence ranged from 6.8% in central Sudan to 26% in southern Sudan [5-6]. Exposure to infected body fluids (saliva, blood, and seminal fluid), sexual transmission with multiple partners, sharing sharp objects (needles, tattooing, piercing, razors) and during medical, surgical, and dental procedures and vertical transmission are all risk factors for HBV infection in Sudan [7]. The World Health Organization's (WHO) current objectives are to expand HBV treatment from 8% to 80% among eligible candidates, decrease HBV incidence by 90%, and reduce HBV death by 65% [8-9]. In outreach and LMIC settings, HBV infection is screened with HBsAg. Finding those in need of assistance remains a challenge [10-11].

Most patients with positive HBsAg do not have liver-related mortality, and if it is necessary, treatment will be continued for a longer period. Therefore, patients should be selected based on worldwide recommendations that consider three factors: viral replication (HBV DNA levels), inflammation (liver enzymes), and assessment of liver stiffness to assess fibrosis by liver biopsy and transient elastography [12-13]. The main goal of treatment is to increase survival and quality of life by halting the growth of the disease and, as a result, the emergence of HCC [14].

The American Association for the Study of the Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), the Asian Pacific Association for the Study of the Liver (APASL), and three Italian scientific societies have all recommended different

treatment regimens for chronic hepatitis B. However, the primary distinction between these recommendations is the use of a different treatment threshold for HBV-DNA and ALT levels [15]. Shimakawa conducted study in The Gambia, a nation in West Africa, in 2018. To select individuals for HBV treatment, he developed TREAT-B, a straightforward score based on HBeAg and ALT. The final TREAT-B score is determined by adding the HBeAg score (negative 0 points or positive 1 point) with the ALT score (20 IU/L 0 points), 20-39 (1 point), 40-79 (2 points), or 80 (3 points). The TREAT-B findings ranged from 0 (HBeAg-negative with an ALT of 20 IU/L) to 4 (HBeAg-positive with an ALT of 80 IU/L) [16]. However, the recommendation of using international guidelines has limitations due to the requirement of special tests that are costly and unavailable in most hospitals. Therefore, this study aimed to compare the diagnostic accuracy of the TREAT-B score to the standard scores EASL and AASLD in HBV patients among Sudanese patients.

2. MATERIALS AND METHODS

Study settings: This is a hospital-based cross-sectional analytical study. The research was carried out from January to October 2019 at Ibn-Sina Specialized Hospital, a tertiary referral hospital in Khartoum that serves patients from all over the country and neighboring countries. Since 2001, it has provided medical and surgical facilities, including a specialized hepatology unit, and its outpatient clinic serves 100 patients per week.

Selection of study participants: In this study, 108 HBV-infected individuals who were 18 years of age or older and who visited the hepatology clinic in accordance with EASL recommendations were enrolled. Patients with established liver cirrhosis, HCC, coinfection with HCV, HIV and pregnant ladies were excluded. The sample size was calculated using the epi info software, and a convenience nonprobability sampling method was used for recruitment.

Data collection procedure: An Interviewer-administered questionnaire was used for data collection, which consisted of demographic and clinical characteristics; existing laboratory and imaging records. The questionnaire includes the following variables: age, gender, residence, occupation, clinical symptoms, and comorbidity. Laboratory investigations: include (AST, ALT, HBeAg, viral DNA levels, AFP, INR), and radiological tests (abdominal ultrasound and transient elastography). We compare the performance of (the TREAT-B) score for selecting patients for antiviral treatment in comparison with EASL and AASLD guidelines.

Statistical analysis: Data were analyzed using Statistical Package for Social Studies Program (SPSS, V. 21.0. IBM; Chicago). Data were summarized using percentages, means, and standard deviation. The Chi-square test used as a significance test to determine deviations in differences between the expected and observed between TREAT B and AASLD, while receiver operating curve analysis (ROC) was used to detect the area under the curve (AUC), sensitivity, and specificity. The P. value was considered significant at level 0.05.

3. RESULTS

A total of 108 HBV patients were enrolled. Table 1 shows the socio-demographic, clinical characteristics, laboratory investigations, and radiological findings.

Age, Gender, and Occupation: Males made up 77 (71%). The most common age groups were between 20-39 years of age (57.4%). Most individuals were laborers, 46 (42.6%), followed by students who were 29 (26.8%) (Table 1).

Clinical Findings and laboratory Investigations: There were no symptoms reported by 96 patients (88.9%). CKD 11 (10.2%) was the most common comorbidity. The liver enzyme analysis revealed that 50 (46.3%) of the participants had ALT levels less than 20 IU/L, and the majority of 90 (83.3%) had AST levels less than 40 IU/L. HBeAg was found to be positive in 20 cases (18%). HBV DNA levels ranged from 20 to 2000 in 43 (39.8%). However, 100 patients (92.6%) had platelet counts greater than 150000 microliters. Most of patients (103 (95.4%) had normal liver ultrasounds (Table 1).

Treat-B score comparison result: As shown in Fig. 1, the eligibility for HBV treatment by different guidelines (AASLD, EASL, and TREAT-B); 8(7.4%) patients were eligible for treatment according to AASLD, 18(16.7%) to EASL, and 27(25%) patients to TREAT-B score.

Table 1. Socio-demographic and clinical characteristics

Variable	Subgroups	Frequency	Percentages
Gender	male	77	71%
	female	31	29%
Age(year)	<20	6	5.6%
	20-39	62	57.4%
	40-59	31	28.7%
	>60	9	8.3%
Occupation	Laborers	46	42.6%
	Students	29	26.9%
	Housewives	19	17.6%
	Employee	12	11.1%
	Not working	2	1.9%
Clinical symptoms	symptomatic	12	11.1%
	Asymptomatic	96	88.9%
Comorbidity	CKD	11	10.2%
	DM	6	5.6%
	PPF	5	4.6%
	HTN	1	0.9%
Platelet count (per microliter)	>150,000	100	92.6%
	<150,000	8	7.8%
The liver enzyme (ALT) IU/L	<20	50	46.3%
	20-39	41	38%
	40-79	11	10.2%
	>80	6	5.6%
The liver enzyme (AST) IU/L	<40	90	83.3%
	>0	18	16.7%
Liver ultrasound	Normal	103	95.4%
	Coarse	4	3.7%
	fatty	1	0.9%
Spleen ultrasound	Normal	104	96.3%
	Enlarge	4	3.7%
HBeAg	Positive	20	18.5%
	Negative	88	81.5%
HBV DNA Level	<20	26	24%
	20-2000	43	39.8%
	2001-20000	20	18.6%
	>20000	19	17.6%

Table 2 and Fig. 2 revealed the performance of TREAT-B and AASLD criteria to treatment eligibility. As determined by the EASL guidelines, the AUROC of TREAT-B (0.883; 95% CI 0.790 – 0.976) was significantly higher than that of the AASLD criteria (0.722; 95% CI 0. 0.566 – 0.878 using the Wald statistic ($p = 0.03$), and lower than AUROC of EASL criteria (0.952; 95% CI 0.790 – 0.976) using the Wald statistic ($p = 0.000$).

The sensitivity and specificity were 85.3% and 70.3% for TREAT-B, 74.4% and 69.8% for AASLD criteria and 97.5% and 85.7% for EASL criteria as shown in (Table 2).

4. DISCUSSION

By utilizing a straightforward score based on HBeAg and ALT for choosing patients for HBV therapy (TREAT-B) score, this study examines and confirms a diagnostic prediction score for treatment eligibility in people with HBV infection.

In this study, there were males (71%) predominance compared to female (29%) patients (M: F= 3.7:1). According to Sara E. et al. study, a similar finding showed the prevalence of HBV higher in males (64%) than females (36%). In addition, studies of El-Zayadi et al. and Osman et al. in Egypt showed similar findings in which males are more exposed to HBV risk factors than females [17-19].

Most of our study participants (57.4%) were between the ages of 20 and 39. These findings were in line with those of a study by Hatim M. et al., who revealed that among 404 patients who

underwent screening with a mean age of 35 years, exposure to HBV infection increased from 47.5% in those 20 to 39 years of age to 80% in those 39 years of age. Tajeldin M et al. in Eastern Sudan, on the other hand, discovered that the average age group among 31 HBV patients was 27.2±11.4 years. Meanwhile, Osman et al. study's in Egypt found that the average age was 45±8 years [20-23].

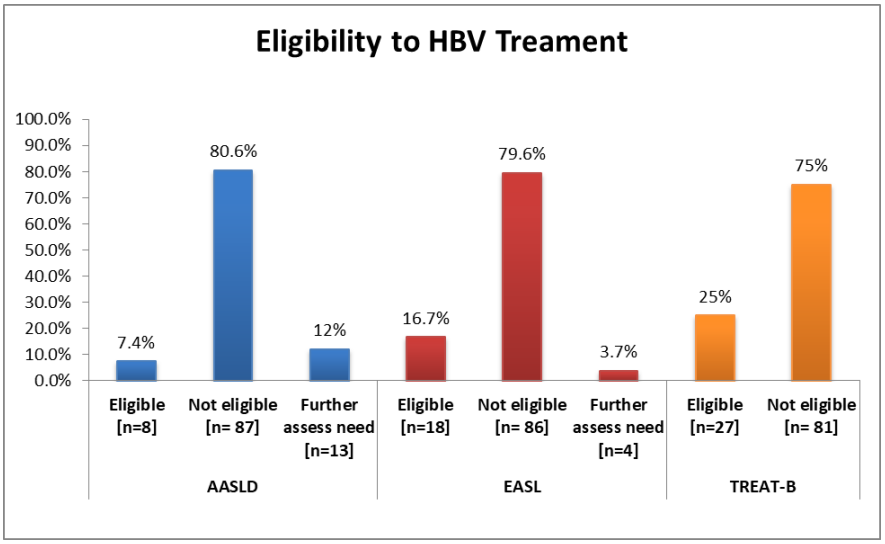

Fig. 1. The eligibility to HBV treatment by different guidelines (AASLD, EASL, and TREAT-B) among HBV patients (N= 108)

Table 2. Area under the curve (AUC), sensitivity and specificity of TREAT-B criteria comparing to AASLD and EASL criteria

	AASLD	EASL	TREAT-B
AUC (95% CI)	0.722 (0.566 – 0.878)	0.952 (0.909 – 0.991)	0.883 (0.790 – 0.976)
Sensitivity (%)	74.4	97.5	85.3
Specificity (%)	69.8	85.7	70.3
P. value	0.003	0.000	0.000

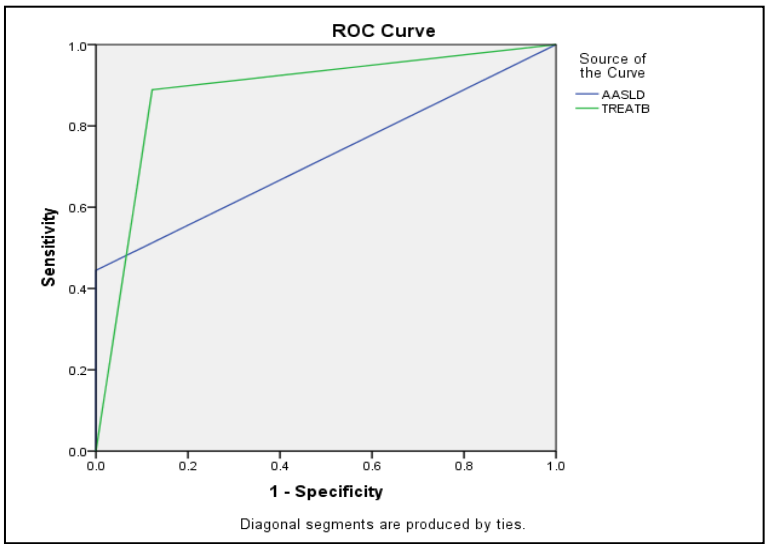

Fig. 2. The performance of TREAT-B and AASLD criteria to treatment eligibility based on the EASL guidelines

This study found that 18% of the cases had HBeAg positivity, which was comparable to a Sudanese study by Mukhlid Y et al. in Khartoum, which revealed that 12.1% of HBV patients had HBeAg positivity. Our HBeAg rate, however, was higher than that reported by Mohamed A. et al. in Gezira state, where the prevalence of HBeAg was 8.7%. In the meantime, 9.6% of HBeAg was detected, according to Monika S et al. in the USA [24-26]. This demonstrates that HBeAg and HBV patients are related.

In the performance of TREAT-B criteria in the diagnosis of eligibility to HBV treatment among our study patients, 25%, 16.7%, and 7.4% of the cases were eligible to viral treatment regarding TREAT-B, EASL, and AASLD criteria respectively, with no significant differences between the three criteria (P> 0.05), which supports using the Treat-B score in recruiting HBV patients for treatment as it doesn't require HBV DNA level which is expensive and widely unavailable.

The AUROC of TREAT-B (0.883; 95% CI 0.790 - 0.976) in the TREAT-B performance determination based on the EASL guidelines, indicates the TREAT-B score as an excellent tool to determine treatment eligibility among our cases. Our findings were strikingly similar to those of Shimakawa Y et al. from The Gambia, who reported an AUROC of 0.88 (95% CI 0.83-0.93) (16). Also, Shimakawa Y et al., in Burkina Faso reported the AUROC of TREAT-B was (0.84; 95% CI 0.80–0.88). Johannessen and coworkers demonstrated that in Ethiopia, the AUROC of TREAT-B was (0.73; 95% CI 0.68-0.78). In a study by Kyoko Y et al. on the use of the TREAT-B score in patients with HBV infection from Africa and non-Africa, they found that the AUROC of the TREAT-B criteria for all HBV cases was 0.84 (0.80-0.88), for patients from Africa it was 0.90 (0.84-0.96), and for non-African patients, it was 0.82. (0.77–0.87) [27-29].

The AUROC of TREAT-B (0.883; 95% CI 0.790–0.976) was considerably better than AASLD criteria (AUROC= 0.722; 95% CI 0. 0.566–0.878) in the diagnosis of eligibility to the viral treatment among our study participants, which is one of the study's most important findings.

As a result, TREAT- B is the best criterion for HBV eligibility treatment. Due to limited healthcare resources in Sudan, HBV DNA and transient elastography are both expensive and unaffordable. In Africa, HBV-related HCC was found in adults younger than 40 years old, most of whom were between the ages of 32.5 and 37.5 [30]. Thus, ensuring early treatment for those patients with active HBV and high enzymes will reduce morbidity and mortality.

According to the 2017 EASL guidelines on the management of chronic hepatitis B infection, it is based on the levels of severity of HBsAg, HBeAg, HBV DNA viral load, ALT levels, and Liver disease where the focus of chronicity predominantly depends on DNA viral load, which is unaffordable to LMICs whereas TREAT B is a simplified scoring system preferably based on the HBeAg which predicts the chronicity of the Liver pathology [31]. EASL will undoubtedly remain the gold standard reference guidelines and has a higher AUC than TREAT B, but the former is a more convenient guideline based on the country's socioeconomic status.

One of the limitations of this study was that the participants were chosen from outpatient clinics. Another limitation in using Treat-B score, is an absence of HBV DNA level, which confirms HBV activity leading to high liver enzymes and ignoring other causes of elevated enzymes such as autoimmune diseases and other co-infections. As a result of its feasibility, a randomized sample could be more representative, and individuals would be randomly selected to avoid bias. However, the study design allowed researchers to learn about the diagnostic accuracy of the TREAT-B score in identifying patients for antiviral treatment compared to the EASL and AASLD scores. The validity of TREAT-B could be confirmed with a broader and multicenter sample. TREAT-B is dependable, valuable, affordable, and simple to apply in Sudan.

5. CONCLUSION

According to the current study's findings, chronic HBV was more prevalent among Sudanese men and younger patients. The TREAT-B score performed well in terms of identifying HBV-infected patients who should get antiviral treatment. As a result, we suggest utilizing (TREAT-B) as a straightforward measure for determining treatment eligibility for HBV infection in Sudan.

ETHICAL APPROVAL AND CONSENT

The Sudanese Medical Specialization Board (S.M.S.B.) and Ibn Sina hospital ethics committees approved the study, ensuring

compliance with the World Medical Association Declaration of Helsinki. Each participant signed an informed consent form after an explanation of the study. Participants received guarantees of anonymity and confidentiality, and those who opted out would not have their present or future treatment impacted.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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