Original Research Article

TREAT-B has good accuracy to select HBV infected patients for treatment in Sudan

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-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 performed well in terms of identifying HBV-infected patients who should get 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.

Introduction

Hepatitis caused by viruses affects many people globally. It ranks higher than any of the main illnesses including the human immunodeficiency virus (HIV), TB, and malaria as the seventh leading cause of mortality in the world. The majority of viral hepatitis-related deaths in 2013 were anticipated to occur in low- and middle-income countries (LMICs), and almost half of those deaths were anticipated to be caused by hepatitis B infection (HBV), which can lead to cirrhosis and hepatocellular cancer (HCC). (1)

Sudan has a high prevalence of hepatitis B surface antigen (HBsAg), with a prevalence of more than 8%. (2) Some African countries (3) demonstrated HBsAg seroprevalence rates of (15.6%) in Burundi (4) and (7%) in Ethiopia. These rates were similar to Sudan (5), in which hepatitis B surface antigen (HBsAg) seroprevalence, extending as low as (6.8%) in central Sudan (6) to as high as (26%) in southern Sudan. Risk factors for HBV infection in Sudan include 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. (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)

HBV infection is screened with HBsAg in outreach and LMIC settings. Finding those who need care is still a problem, though. (10-11)

The majority of patients with positive HBsAg do not develop liver-related mortality, and if treatment is indicated it will be for longer period of time. So, selection of patients for potential benefit of treatment should be according to international guidelines which depend on three factors: viral replication (HBV DNA levels), inflammation (liver enzymes) and liver stiffness measurement to evaluate 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).

For the treatment of chronic hepatitis B, different guidelines have been recommended by 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. However, the basic difference among these guidelines is the adoption of a different threshold of HBV-DNA and ALT levels for treatment (15).

In 2018, Shimakawa conducted research in The Gambia, a country in West Africa. He created TREAT-B, an unique basic score devoid of HBV DNA and based purely on ALT level and

HBeAg sero-status, using the PROLIFICA data. The total TREAT-B score is calculated by combining 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). TREAT-B values ranged from 0 (HBeAg-negative with ALT of 20 IU/L) to 4 (HBeAg-positive with ALT of 80 IU/L). It was found that TREAT-B had high diagnostic accuracy for the selection of treatment entitled patients (area under the receiver operating characteristic curve (AUROC) 0.85; sensitivity 84.5%; specificity 77.3%), and that is based on the reference tests used in the European Association for the Study of the Liver (EASL) guidelines, which was carried out in the validation dataset from other African populations (16).

Material and Methods

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.

The ethics committees of the Sudanese Medical Specialization Board (S.M.S.B.) and Ibn Sina hospital approved the study, ensuring adherence to the World Medical Association Declaration of Helsinki. Following an explanation of the study, each participant signed an informed consent form. The participants received guarantees of anonymity and confidentiality, and those who opted out would not have their present or future treatment impacted.

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.

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 (TREAT-B) score for selecting patients for antiviral treatment in comparison with EASL and AASLD guidelines.

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

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 were found to be 77 (71%) while 31(29%) were females. The commonest age groups were between 20-39 years of age (57.4%). The majority of individuals were found to be laborers 46 (42.6%) followed by students which were 29 (26.8%), housewives 19 (17.6%), employees 12 (11.1%), and 2 (1.9%) were not working(table1).

Clinical Findings

Majority of patients 96 (88.9%) were found to be asymptomatic and 12 (11.1%) were symptomatic. The 11 (10.2%) showed CKD as comorbidity, while the remaining DM, PPF, and HTN were found to be 6 (5.6%), 5 (4.6%), and 1 (0.9%) respectively.

Laboratory Investigations

In the liver enzymology, 50 (46.3%) had ALT levels below 20 IU/L, and the majority 90 (83.3%) had AST level below 40 IU/L. HBeAg was found to be negative 88 (82%) and positive 20 (18%). HBV DNA level was 20 to 2000 in 43 (39.8%). However, 100 (92.6%) of patients had platelet count of more than 150000 microliters while 8 (7.8%) had platelet count less than 150000 microliters. Most of the patients had normal liver ultrasound 103 (95.4%) with the remaining 4 (3.7%) had coarse, and 1 (0.9%)had fatty(table1) .

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%

Treat-B score comparison result

As shown in figure (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 Ineligibility was encountered in 87(80.6%) patients according to AASLD, 86(79.6%) patients to EASL, and 81(75%) patients to TREAT-B score. Further assessment was needed according to AASLD and EASL guidelines in 13(12%) and 4(3.7%) patients respectively.

In the comparison of the eligibility to HBV treatment regarding the different guidelines (AASLD, EASL, and TREAT-B), eligibility for the treatment did not differ significantly between the guideline (P= 0.387). Moreover, ineligibility to the treatment did not differ significantly between the guideline (P= 0.557) (figure 2)

Table 2 and Figure 3 showed 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 (table2).

Figure 1: the eligibility to HBV treatment by different guidelines (AASLD, EASL, and TREAT-B) among HBV patients (N= 108)

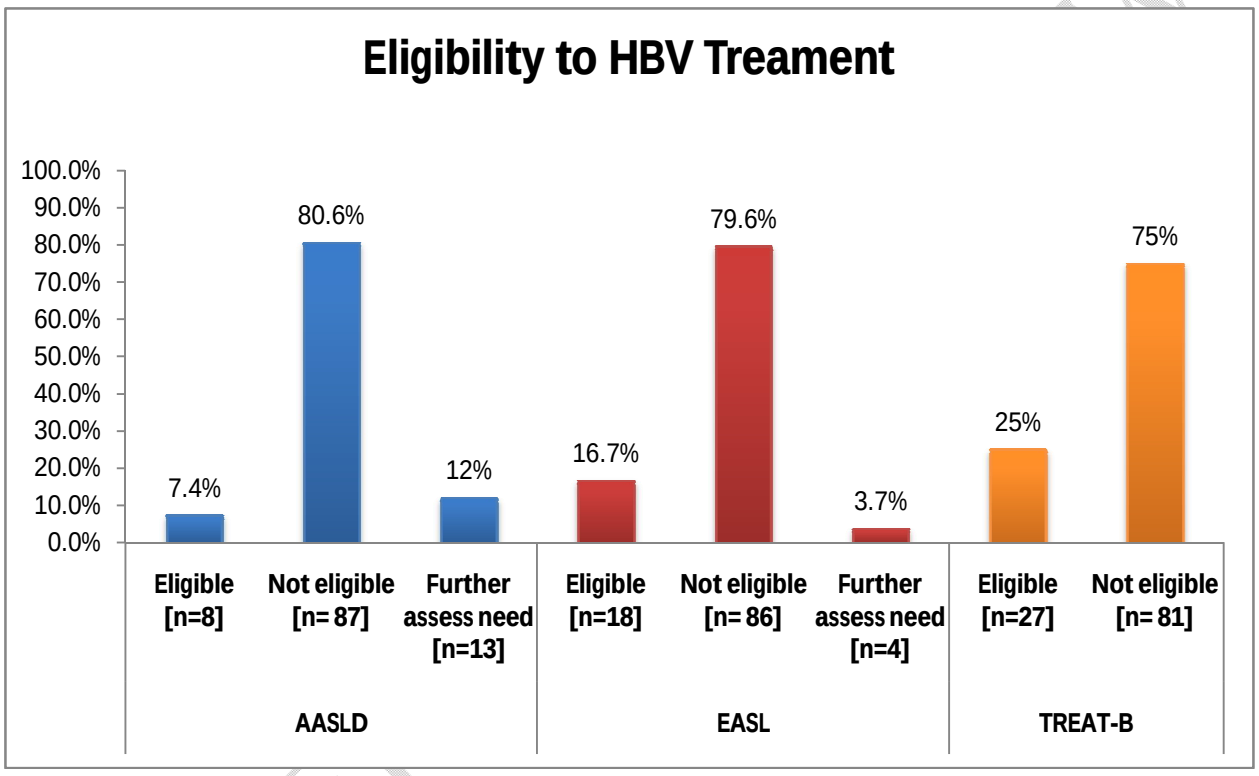


Figure 2: the comparison of the eligibility to HBV treatment according to the different guidelines (AASLD, EASL, and TREAT-B) among HBV patients (N= 108)

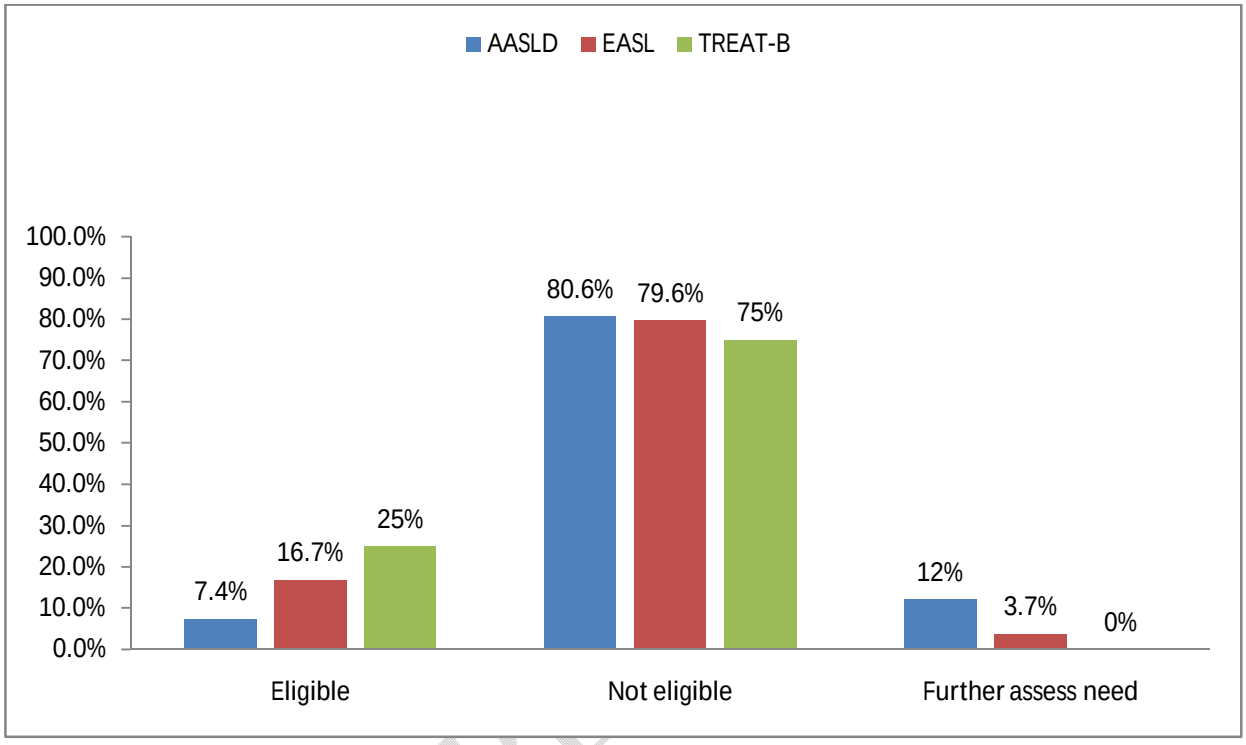
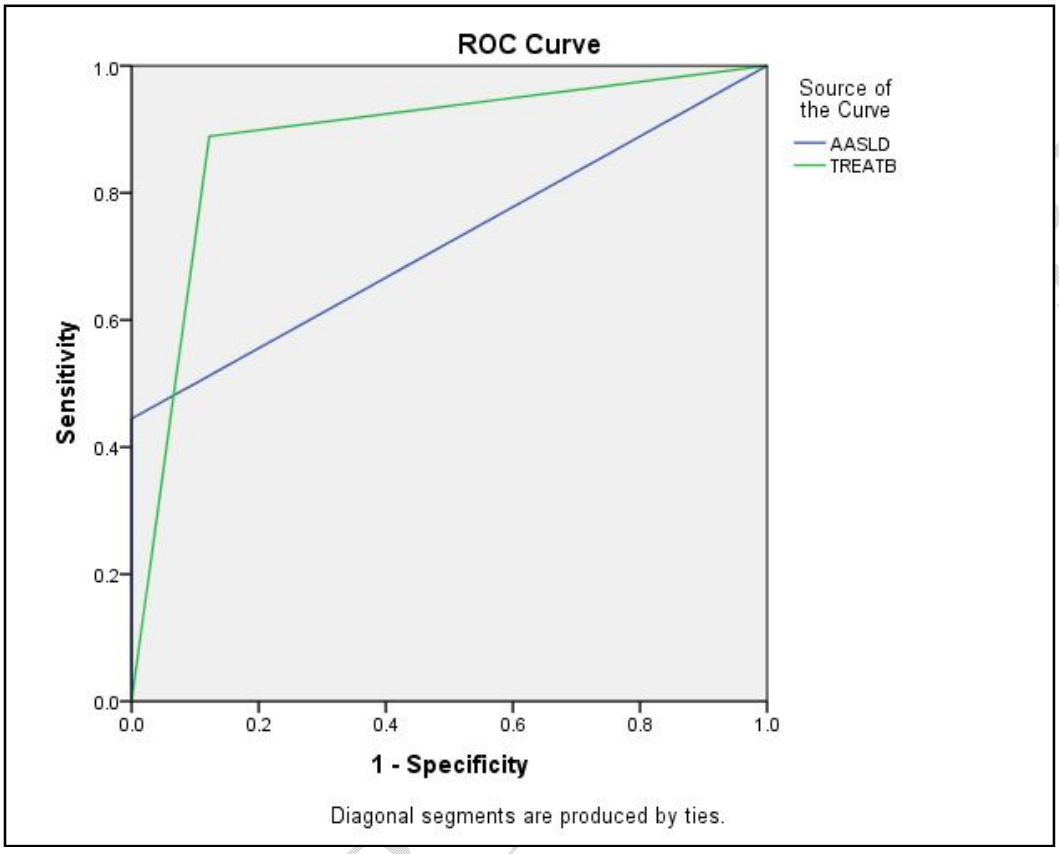


Table 2: area under the curve (AUC), sensitivity and specificity of TREAT-B criteria comparing to AASLD and EASL criteria

	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

Figure 3: The performance of TREAT-B and AASLD criteria to treatment eligibility based on the EASL guidelines



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)(18)(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 year (20) (21) (22) (23).

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) (25) (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 unavilable.

The AUROC of TREAT-B (0.883; 95% CI 0.790 - 0.976) in the TREAT-B performance determination based on the EASL guidelines, indicating 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) (28) (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.

Hence, TREAT- B is the most suitable criteria for HBV eligibility treatment in Sudan due to limited healthcare resources, as HBV DNA and transient elastography are costly and unaffordable. In Africa, HBV-related HCC was found in adults younger than 40 years of age predominately between 32.5 to 37.5 years (30).Thus, ensuring early treatment for those patients with active HBV and high enzymes will reduce morbidity and mortality.
However,

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. Therefore, a randomized sample would have been more representative as its feasibility and individuals would be chosen randomly to avoid bias. However, the study design made it possible to obtain information about the diagnostic accuracy of TREAT-B score for selecting patients for antiviral treatment in comparison with EASL and AASLD scores. A larger and multicenter sample can take place to confirm the validity of TREAT-B. TREAT-B is reliable, valuable, cost-effective and easy to use in Sudan.

Conclusion

The current study concludes that chronic HBV was more common in Sudanese males and younger patients. TREAT-B score showed good performance for selecting HBV-infected patients for antiviral therapy, with AUROC (0.883), sensitivity (85.3%), and specificity (70.3%). As a result, we recommend using (TREAT-B) as a simple score for HBV infection treatment eligibility in Sudan.

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