Vital Surveillances

eALT-F: A New Non-Invasive Staging Method to Identify Medium to High-Risk Patients with HCC from Ultra-High HBV Viral Load Population — China, 2010–2023

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ABSTRACT

Background: The objective of this study was to examine the clinical characteristics of individuals with ultra-high hepatitis B virus (HBV) viral load and develop a novel staging method for chronic hepatitis B (CHB) that can more effectively identify patients with medium to high hepatocellular carcinoma (HCC) risk.

Methods: A total of 2,118 patients with HBV DNA >1×10^7 IU/mL who visited Peking University People's Hospital between January 2010 and March 2023 were enrolled retrospectively. Clinical data from the first visit were obtained and analyzed. The traditional phases and new 'eALT-F' stages were compared to evaluate the risk of HCC.

Results: In the overall patients, more than one-third of the patients were under 30 years old. Additionally, a small proportion of older people (>60 years) also had ultra-high HBV viral load (4.3%). 9.1% and 6.7% of individuals with ultra-high HBV viral load showed FIB-4>3.25 and aMAP≥50, respectively. In the traditional stages of CHB, which are based on HBeAg and alanine aminotransferase (ALT) [the upper limit of normal (ULN) ALT level at 40 IU/L for both men and women], regardless of phase, a certain proportion of patients were at risk of developing HCC (4.1%, 6.4%, 25.0%, and 20.3%). However, in the new 'eALT-F' stages, which are based on HBeAg, ALT (the ULN of ALT level at 30 IU/L for men and 19 IU/L for women), and/or FIB-4 levels (>1.45), aMAP≥ 50 was only observed in chronic hepatitis patients with positive or negative HBeAg (6.4% and 22.1%, respectively).

Conclusions: The 'eALT-F' staging method, based on HBeAg, ALT (males: the ULN of ALT was 30 IU/L, females: 19 IU/L) and/or FIB-4 levels, was more effective in identifying medium to high-risk patients with HCC from patients with ultra-high HBV viral load than the traditional staging methods.

INTRODUCTION

Chronic hepatitis B virus (HBV) infection remains a major public health concern worldwide. According to the World Health Organization (WHO), there are approximately 296 million individuals with chronic HBV infection globally, resulting in liver-related diseases such as cirrhosis, hepatocellular carcinoma (HCC), and liver failure, which lead to the deaths of an estimated 820,000 patients annually (*1*). Despite the successful popularization of the hepatitis B vaccine, there is still a prevalence of 5%–6% of individuals with positive HBsAg in the general population in China (*1*). Therefore, chronic HBV infection poses a serious socio-economic burden. Achieving the WHO's objective of eliminating viral hepatitis by 2030 remains a challenging responsibility, involving inhibiting HBV transmission and treating or even curing individuals with chronic HBV infection.

Based on markers of HBV infection, such as HBsAg, HBeAg, HBV DNA level, alanine aminotransferase (ALT) level, and liver pathological features, the natural history of chronic HBV infection can be categorized into four classical phases, including HBeAg-positive chronic HBV infection (immune-tolerant phase, IT phase), HBeAg-positive chronic hepatitis B (immune activation phase), HBeAg-negative chronic HBV infection (low replication phase), and HBeAg-negative chronic hepatitis B (reactivation phase) (*2*). Individuals in the HBeAg-positive chronic HBV infection phase are often accompanied by higher levels of HBV DNA. Previous studies demonstrated that an elevated HBV viral load was associated with an increased risk of HCC occurrence (*3*–*4*). Additionally, a higher HBV viral load has been identified as an independent risk factor for HCC recurrence, specifically after liver resection, transplantation, or radiofrequency ablation (*5*–*6*). However, there is still a lack of evidence-based medical guidelines regarding the treatment of patients with ultra-high HBV viral load, particularly those in the IT phase (*7*). Therefore, it is crucial to investigate the

clinical features of individuals with ultra-high HBV viral load and identify those at risk of developing HCC.

This study analyzed data from all patients with an HBV DNA level greater than 1×10^7 IU/mL at Peking University People's Hospital between January 2010 and March 2023. Demographic information, liver function parameters, and markers related to HBV infection were collected to investigate the clinical characteristics of individuals with an ultra-high HBV viral load, identify medium to high-risk populations for developing HCC, and provide new indications for antiviral treatment.

METHODS

This retrospective cross-sectional study was conducted at Peking University People's Hospital. Chronic HBV infection was defined as the persistent presence of serum HBsAg for more than 6 months. CHB patients meeting the following criteria were included in the study: HBsAg positive for >6 months; HBV DNA >1x10^7 IU/mL; no prior or current antiviral treatment; no concomitant cirrhosis and HCC; and no missing data on HBeAg. Patients with other concurrent viral hepatitis or chronic liver diseases, including primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), alcoholic liver disease (ALD), and nonalcoholic fatty liver disease (NAFLD), et al., were excluded from this study. The research protocol was approved by the Ethics Committee of Peking University People's Hospital (2023PHB053-001) and was conducted in accordance with the principles outlined in the 1975 Declaration of Helsinki and its 1983 revision.

HBV serological and virological markers including HBsAg, HBeAg, and HBV DNA levels were assessed. Liver function indexes include ALT, aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), and albumin (ALB). Hematological index includes platelet (PLT) count. FIB-4 [Age (year) × AST (U/L) / (PLT (×10^9/L) × ALT (U/L)$^{1/2}$] was calculated to evaluate the extent of liver fibrosis, whose score ≥3.25 could diagnose liver fibrosis and Metavir score ≥F3, while FIB-4 <1.45 could exclude Metavir score ≥F3. aMAP[({0.06 × age (year) + 0.89 × sex (Male: 1, Female: 0) + 0.48 [$\log_{10}$BIL (μmol/L) × 0.66 + (ALB (g/L) × −0.085)] − 0.01 × PLT (10^3/mm^3)} + 7.4) / 14.77 × 100] was calculated to predict HCC occurrence, whose score ≥50 indicates a medium to high risk of HCC.

The gold standard for staging chronic HBV infection relies on liver pathology; however, obtaining this in clinical practice is challenging. Therefore, in our study, we developed a new staging method based on HBeAg status, ALT level, and/or FIB-4 (eALT-F) to assess the risk of HCC in patients with an ultra-high viral HBV load.

The Kolmogorov-Smirnov test was utilized to assess the normality of the data. The baseline characteristics of the enrolled patients were described as follows: normally distributed data (e.g. age, HBV DNA, ALB, ALP, PLT, and aMAP) were presented as mean±standard deviation (SD), while non-normally distributed continuous data (e.g. HBsAg, HBeAg, ALT, AST, GGT, TBIL, and FIB-4) were reported as median [interquartile range (IQR)]. Categorical variables (e.g. gender, age grouping, ALT level grouping, FIB-4 grouping, and aMAP grouping) were presented as numbers (%). We used chi-square tests for categorical variables, Mann-Whitney tests for non-normally distributed continuous variables, and independent sample T tests for normally distributed continuous variables to detect significant differences between groups. All significance tests were two-tailed, with *P*-value <0.05 indicating statistical significance. Statistical analysis was performed using the R software package (http://www.R-project.org, version 4.1.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical Characteristics of Patients with Ultra-High HBV Viral Load

A total of 2,118 individuals with HBV DNA>1×10^7 IU/mL detected for the first visit from January 2010 to March 2023 at Peking University People's Hospital were enrolled in this study. Patients meeting the following criteria were excluded: prior or current antiviral therapy (*n*=94); cirrhosis and HCC (*n*=51); missing data for HBeAg (*n*=425); and coexistence of hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV) (*n*=11); alcohol consumption >20 g/day (ALD) (*n*=7) and NAFLD (*n*=19). Finally, 1,511 CHB patients who had not undergone antiviral treatment with HBV DNA >1×10^7 IU/mL have been enrolled in our study (Figure 1). The baseline features of CHB patients with

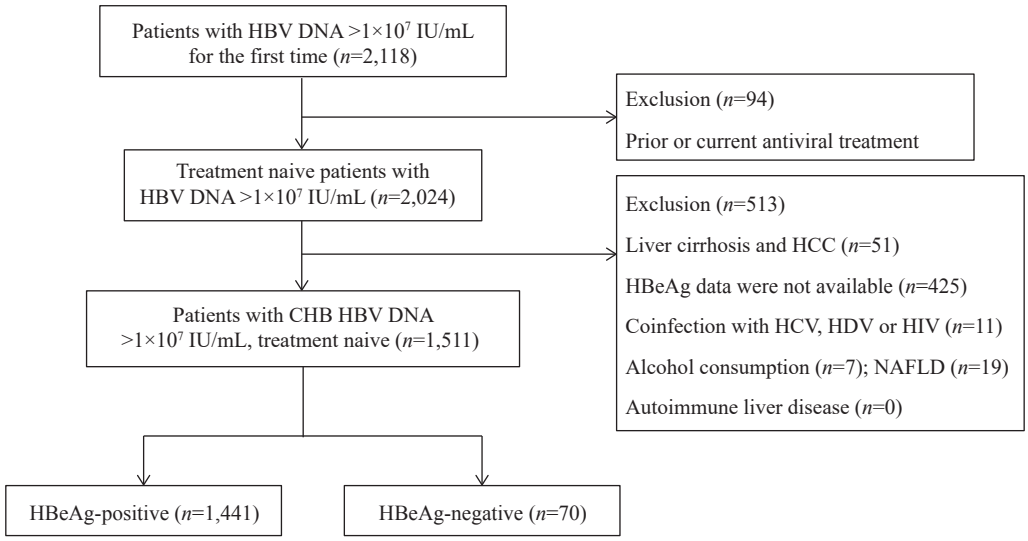

FIGURE 1. The Flow chart of selecting patients with ultra-high HBV viral load.
Abbreviation: HBV=hepatitis B virus; CHB=chronic hepatitis B; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; HDV=hepatitis D virus; HIV=human immunodeficiency virus; NAFLD=nonalcoholic fatty liver disease.

ultra-high HBV viral load are presented in Table 1. Except for younger patients, there were still a small proportion of older people (>60 years old) who showed ultra-high HBV viral load (4.3%). The median HBV DNA level was higher than 8.0 $\log_{10}$ IU/mL. Approximately, 2/3 of patients have ALT levels above the detection threshold (40 IU/L). There were 102 (9.1%) and 73 (6.7%) patients with FIB-4>3.25 and aMAP≥50, respectively.

Inadequacy of Traditional HBV Natural History Phases for Managing High-Risk HCC Populations

According to the status of HBeAg and ALT-level in the 2017 ESAL CHB guideline, 1,448 ultra-high HBV viral load patients were divided into four traditional phases: HBeAg positive-chronic infection, with positive HBeAg and ALT level<40 IU/L (*n*=528), HBeAg positive-chronic hepatitis, with positive HBeAg and ALT level >40 IU/L (*n*=833), HBeAg negative-chronic infection, with negative HBeAg and ALT level <40 IU/L (*n*=14) and HBeAg negative-chronic hepatitis, with negative HBeAg and ALT level >40 IU/L (*n*=73). Patients in the stage of HBeAg positive-chronic infection showed higher HBV DNA levels compared to the other groups (*P*<0.001). However, regardless of the phase, there is a certain proportion of patients at risk of developing HCC, even in the HBeAg negative-chronic infection phase (Table 2, Figure 2A). Therefore, this traditional staging method is not suitable for managing the HCC risk population.

Identifying HCC Risk in High HBV Load Patients via 'eALT-F' Staging

To better manage patients with ultra-high HBV viral load at risk of developing HCC, we endeavored to develop a novel staging method. By combining the 2016 American Association for the Study of Liver Diseases (AASLD) CHB guidelines with the aMAP score (*8*–*9*), a total of 1,092 patients were reclassified into four new phases, referred to as the 'eALT-F' stages: 1) HBeAg positive-chronic infection (*n*=142), characterized by positive HBeAg, normal ALT levels [the upper limit of normal (ULN) for ALT was 30 IU/L for males and 19 IU/L for females], and FIB-4 <1.45; 2) HBeAg positive-chronic hepatitis (*n*=869), characterized by positive HBeAg, elevated ALT levels, and/or FIB-4 ≥1.45; 3) HBeAg negative-chronic infection (*n*=4), characterized by negative HBeAg, normal ALT levels, and FIB-4 <1.45; and 4) HBeAg negative-chronic hepatitis (*n*=77), characterized by negative HBeAg, elevated ALT levels, and/or FIB-4 ≥ 1.45 (Table 3). According to the 'eALT-F' staging method, all patients at risk of HCC (aMAP score ≥50) were classified as having chronic hepatitis, regardless of HBeAg status (*n*=56 or 17, Figure 2B). In addition, individuals with an ultra-high viral HBV load who had ALT levels lower than 30 IU/L for males or 19 IU/L for females, and FIB4 <1.45, could be reliably identified as having no risk of developing HCC (aMAP

TABLE 1. Baseline characteristics of CHB patients with HBV DNA >1×10^7 IU/mL, treatment naive.

Index	Total (*n*=1,511)	HBeAg-positive (*n*=1,441)	HBeAg-negative (*n*=70)	*P*
Age (years)	34.6±11.5	34.2±11.3	44.1±11.0	<0.001
<30	606 (40.1)	602 (41.8)	4 (5.7)	<0.001
30–60	840 (55.6)	780 (54.1)	60 (85.7)	
≥60	65 (4.3)	59 (4.1)	6 (8.6)	
Male (%)	942 (62.3)	889 (61.7)	53 (75.7)	0.018
HBV DNA (log_{10} IU/mL)	8.0±0.5	8.0±0.5	7.6±0.4	<0.001
HBsAg (COI)	34,132.8 (11,512.7, 61,309.7)	36,254.6 (13,788.6, 62,189.2)	5,537.1 (2,933.6, 9,656.2)	<0.001
HBeAg (COI)	1,376.2 (924.2, 1581.3)	1,399.1 (1,044.1, 1,591.7)	0.3 (0.3, 0.4)	<0.001
ALT (U/L)	85.0±35.8	84.5±35.9	94.8±32.2	<0.001
<40	542 (37.4)	532 (38.6)	10 (14.3)	<0.001
40–80	363 (25.1)	354 (25.7)	9 (12.9)	
≥80	543 (37.5)	492 (35.7)	51 (72.9)	
AST (U/L)	38.0 (24.0, 80.0)	36.0 (24.0, 74.0)	109.5 (59.5, 208.5)	<0.001
GGT (U/L)	27.0 (17.0, 50.0)	25.0 (16.0, 49.0)	45.5 (33.5, 86.0)	<0.001
ALP (U/L)	85.0±35.8	84.5±35.9	94.8±32.2	0.021
ALB (g/L)	44.5±4.2	44.6±4.0	42.8±6.1	<0.001
TBIL (μmol/L)	15.2 (11.8, 20.3)	15.0 (11.7, 20.2)	17.1 (13.1, 23.1)	0.002
PLT (×10^9/L)	211.1±62.3	212.8±61.5	184.1±69.5	<0.001
FIB-4	0.9 (0.6, 1.6)	0.8 (0.6, 1.5)	2.1 (1.2, 4.1)	<0.001
<1.45	803 (71.8)	779 (74)	24 (36.4)	<0.001
1.45–3.25	214 (19.1)	194 (18.4)	20 (30.3)	
>3.25	102 (9.1)	80 (7.6)	22 (33.3)	<0.001
aMAP	37.8±7.3	37.5±7.1	43.3±8.1	<0.001
<50	1,019 (93.3)	969 (94.4)	50 (76.9)	<0.001
≥50	73 (6.7)	58 (5.6)	15 (23.1)	

Abbreviation: CHB=chronic hepatitis B; HBV=hepatitis B virus; HBsAg=HBV surface antigen; HBeAg=HBV e antigen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyl transpeptidase; ALP=alkaline phosphatase; ALB=Albumin; TBIL=total bilirubin; PLT=platelet count; FIB-4=Fibrosis 4 score.

score <50, *n*=142 or 4). The area under the receiver operating characteristic (AUROC) curve for the novel 'eALT-F' method was 0.977 (0.968–0.986), with a sensitivity of 0.959 (0.913–1.000), specificity of 0.910 (0.913–0.927), positive predictive value of 0.432 (0.356–0.508), and negative predictive value of 0.997 (0.993–1.000).

DISCUSSION

This study was based on HBV DNA >10^7 IU/mL as the threshold for ultra-high viral load according to the 2017 EASL CHB Guideline and the 2021 US hepatitis B Management Algorithm Update (*2*,*9*). Ultra-high viral load implies active HBV replication, strong infectivity, poor treatment response, and a certain relationship with the occurrence of end-stage liver diseases, including cirrhosis and HCC, et al (*10*). The conventional natural history staging for chronic HBV infection comprises four phases: IT, immune activation phase with positive HBeAg, low replication phase, and reactivation phase with negative HBeAg phases, with levels of HBV DNA >10^7 IU/mL, 10^4–10^7 IU/mL, <2,000 IU/mL, and >2,000 IU/mL, respectively (*9*). Based on this, HBV DNA >10^7 IU/mL should belong to the IT stage, and chronic HBV infection in the IT period is considered not to require active antiviral therapy due to the absence or mild inflammation of liver cells, slow progression of the disease, low risk of liver cirrhosis and HCC, and poor treatment response (*11*). However, there have been reports indicating a positive association between baseline HBV DNA levels and the risk of HCC, as well as the need for antiviral treatment in the IT phase (*12*).

TABLE 2. Clinical characteristics of patients in four traditional natural history stages of CHB.

Index	HBeAg-positive (*n*=1,361)		HBeAg-negative (*n*=87)		*P*
	Chronic infection (*n*=528)	Chronic hepatitis (*n*=833)	Chronic infection (*n*=14)	Chronic hepatitis (*n*=73)	
Age (years)	33.4±11.5	34.3±10.9	46.2±12.2	44.1±10.9	<0.001
<30	244 (46.2)	329 (39.5)	2 (14.3)	3 (4.1)	<0.001
30–60	261 (49.4)	472 (56.7)	10 (71.4)	64 (87.7)	
≥60	23 (4.4)	32 (3.8)	2 (14.3)	6 (8.2)	
Male (%)	245 (46.4)	598 (71.8)	11 (78.6)	53 (72.6)	<0.001
HBV DNA (log_{10} IU/mL)	8.1±0.5	7.9±0.5	7.9±0.6	7.6±0.4	<0.001
HBsAg (COI)	54,200.7 (34,117.8, 77,197.1)	25,149.3 (9,330.6, 50,020.3)	3,034.8 (2,488.9, 6,499.4)	5,254.5 (2,589.5, 9,656.2)	<0.001
HBeAg (COI)	1,498.8 (1353.7, 1634.2)	1,273.4 (799.0, 1539.2)	0.3 (0.3, 0.4)	0.3 (0.3, 0.4)	<0.001
ALT (U/L)	25.0 (19.0, 31.0)	95.0 (58.0, 190.0)	30.0 (25.8, 35.8)	167.0 (99.0, 360.0)	<0.001
AST (U/L)	23.0 (20.0, 26.0)	60.0 (39.0, 110.0)	31.0 (21.2, 48.0)	120.0 (70.0, 218.0)	<0.001
GGT (U/L)	16.0 (13.0, 22.0)	38.0 (23.0, 68.0)	26.0 (22.0, 55.0)	46.0 (35.0, 76.0)	<0.001
ALP (U/L)	77.3±35.9	89.3±35.5	90.4±31.6	90.9±31.5	<0.001
ALB (g/L)	45.2±3.7	44.2±4.3	43.8±5.0	43.1±5.9	<0.001
TBIL (μmol/L)	13.6 (10.9, 17.7)	16.1 (12.4, 21.7)	14.3 (11.9, 24.8)	18.4 (13.3, 22.8)	<0.001
PLT ($\times 10^9$/L)	225.3±62.2	206.6±60.1	174.1±70.0	187.5±65.0	<0.001
FIB4	0.7 (0.5, 0.9)	1.0 (0.7, 1.8)	1.2 (0.9, 2.3)	2.1 (1.3, 4.0)	<0.001
<1.45	332 (88.8)	441 (66.5)	8 (66.7)	22 (31.4)	<0.001
1.45–3.25	32 (8.6)	156 (23.5)	1 (8.3)	25 (35.7)	
>3.25	10 (2.7)	66 (10)	3 (25)	23 (32.9)	
aMAP	35.6±6.9	38.4±6.9	44.5±9.5	42.9±7.4	<0.001
<50	354 (95.9)	601 (93.6)	9 (75)	55 (79.7)	<0.001
≥50	15 (4.1)	41 (6.4)	3 (25)	14 (20.3)	

Abbreviation: CHB=chronic hepatitis B; HBV=hepatitis B virus; HBsAg=HBV surface antigen; HBeAg=HBV e antigen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyl transpeptidase; ALP=alkaline phosphatase; ALB=Albumin; TBIL=total bilirubin; PLT=platelet count; FIB-4=Fibrosis 4 score.

Previously, the traditional natural history phases have played a significant role in managing chronic HBV infection. However, as our understanding of HBV infection deepens and antiviral therapy develops, its limitations have become increasingly apparent: 1) Although it is based on immunological characteristics, there is no corresponding immunological evidence or indicators to define it. Some studies have even found that children and adolescent IT patients do not exhibit the immune tolerant T lymphocyte characteristics (*13*). 2) The current staging cannot include all chronic HBV carriers, leading to several 'gray areas' (*14*). 3) The value of guiding treatment and predicting prognosis is decreasing, and with the emergence of new anti-HBV drugs and the expansion of anti-HBV indications, this value will further decrease (*9*). Professor Zhuang mentioned that a considerable number of patients in the 'IT period' have obvious liver cell inflammation, necrosis, and pathological changes of liver fibrosis (*15*). In this case, these patients should not be categorized into the IT period and should not be treated as 'gray areas'. They should be classified as CHB with positive or negative HBeAg.

As current treatment strategies for chronic HBV infection focus on 'treat more' as opposed to 'treat all,' it is recommended that only HBeAg status, degree of liver inflammation, and non-invasive liver fibrosis scores be employed as the basis for staging chronic HBV-infected patients. The commonly used substitute indicator for liver inflammation in clinical practice is ALT. A study showed that even according to the AASLD regulation of 35 IU/mL for men and 25 IU/mL for women, 28.7% of HBV-infected individuals without significant fibrosis and with normal ALT still have significant inflammation (*16*). Therefore, the ULN of the new staging method for ALT was selected from the relatively recognized domestic and international 30 IU/mL for males and 19

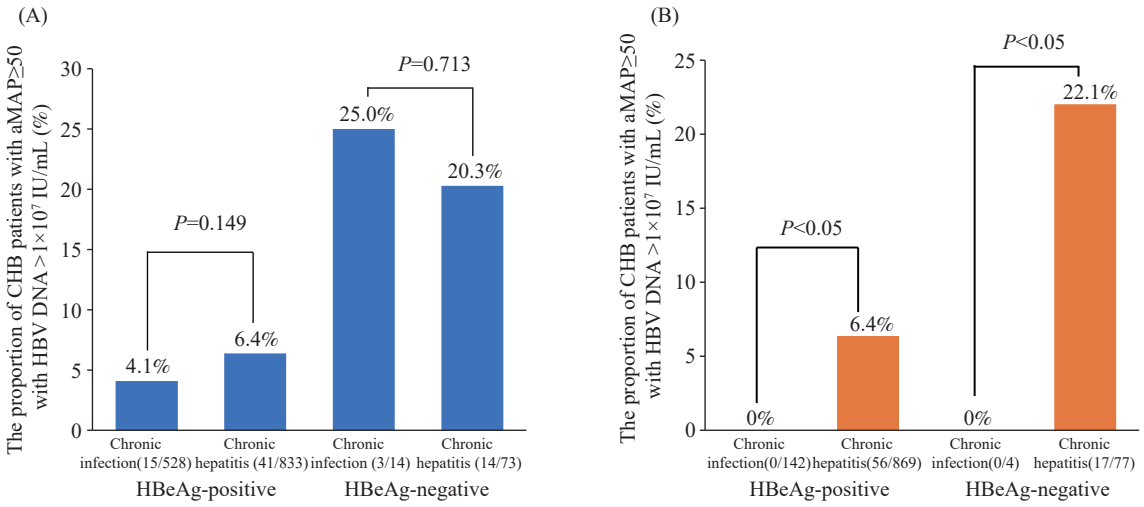

FIGURE 2. The proportion of CHB patients with aMAP≥50 in (A) traditional natural history stages and (B) 'eALT-F' stages of CHB.

Notes: in panel A, significant differences in the proportion of aMAP≥50 was not observed among the patients in four traditional natural history stages of CHB; In panel B, significant differences in the proportion of aMAP≥50 was observed among the patients in four 'eALT-F' stages of CHB.

Abbreviation: CHB=chronic hepatitis B; HBeAg=HBV e antigen; HBV=Hepatitis B virus.

IU/mL for females (*17*). There are various non-invasive alternative indicators for liver fibrosis, among which FIB-4 is easy to use and widely recognized for its evaluation efficacy (*18*). FIB-4, in addition to evaluating the degree of liver fibrosis, is also useful in predicting HCC risk and even liver disease-related death (*19*). Kim et al. retrospectively analyzed 413 cases of HBV infection during the IT phase, and stratification analysis revealed that patients with FIB-4 >1.45 had a significantly higher 5-year cumulative incidence of HCC compared to those with FIB-4 <1.45 (*20*). Following 'eALT-F,' the new staging method, in our study, those with HBeAg-positive chronic infection and chronic hepatitis account for 13.0% and 79.6%, respectively, and those with HBeAg-negative chronic infection and chronic hepatitis account for 0.4% and 7.0%, respectively.

The objective of CHB treatment is to minimize the occurrence of end-stage liver disease, particularly HCC, which is a slow process. To achieve this, we utilized the widely recommended HCC risk score-aMAP to assess the risk of HCC in individuals infected with chronic HBV and guide the selection of antiviral treatment indications (*11*). The aMAP score, which was developed and externally validated by Chinese pathologists and their collaborators, encompasses age, male gender, albumin, bilirubin, and platelet data. An aMAP score of ≥50 indicates a medium to high risk of HCC. A recent study demonstrated that the aMAP score has substantial value in evaluating advanced liver fibrosis and cirrhosis in patients with CHB (*21*). Our study reveals that according to the 2017 EASL guideline, among individuals with ultra-high HBV viral load and an aMAP score of ≥50, 24.7% (18/73) of patients in both HBeAg-positive and -negative chronic infected stages do not require antiviral treatment. This suggests that these patients, who should receive antiviral treatment, have not been treated. According to the new 'eALT-F' staging method, the aMAP scores in all HBeAg-positive and -negative chronic carriers with ultra-high viral load were lower than 50. This indicates that the new staging effectively excludes and identifies medium-high risk patients with HCC occurrence.

In summary, patients with CHB who have an ultra-high viral load, elevated ALT levels (the ALT was 30 IU/L for males and 19 IU/L for females), and/or FIB-4 ≥1.45 should receive active antiviral treatment. For individuals with simple chronic infection and normal ALT levels and FIB-4 <1.45, further observation can be conducted and evaluated every six months. Once the values go beyond this range, timely antiviral treatment should be initiated. The decision to initiate antiviral treatment for HBV-infected individuals with an ultra-high viral load is not only based on indications, but also on the risk of HCC, specifically the aMAP score and its changing trend.

Conflicts of interest: No conflicts of interest.

TABLE 3. Clinical characteristics of patients in four 'eALT-F' stages of CHB.

Index	HBeAg-positive (*n*=1,011)		HBeAg-negative (*n*=81)		*P*
	Chronic infection (*n*=142)	Chronic hepatitis (*n*=869)	Chronic infection (*n*=4)	Chronic hepatitis (*n*=77)	
Age (years)	31.9±7.9	35.7±11.6	40.2±12.1	44.4±11.3	<0.001
<30	63 (44.4)	307 (35.3)	1 (25)	4 (5.2)	<0.001
30–60	79 (55.6)	516 (59.4)	3 (75)	65 (84.4)	
≥60	0 (0)	46 (5.3)	0 (0)	8 (10.4)	
Male (%)	83 (58.5)	543 (62.5)	3 (75)	56 (72.7)	0.179
HBV DNA (log_{10} IU/mL)	8.1±0.5	8.0±0.5	7.6±0.5	7.7±0.5	<0.001
HBsAg (COI)	59,710.6 (40,016.6, 80,457.6)	28,824.2 (10,367.2, 55,875.4)	2,679.6 (2,634.8, 4,125.7)	5,297.2 (2,712.3, 10,018.8)	<0.001
HBeAg (COI)	1,544.0 (1,411.3, 1,682.9)	1,340.3 (881.2, 1,565.0)	0.3 (0.3, 0.4)	0.3 (0.3, 0.4)	<0.001
ALT (U/L)	19.0 (15.0, 24.0)	70.0 (38.0, 155.0)	24.5 (20.0, 28.0)	136.0 (77.0, 331.0)	<0.001
AST (U/L)	21.0 (18.0, 23.0)	46.0 (28.0, 92.0)	21.0 (19.2, 24.2)	115.0 (64.0, 218.0)	<0.001
GGT (U/L)	16.0 (13.0, 21.0)	30.0 (19.5, 57.0)	29.5 (23.8, 36.0)	46.0 (33.0, 85.0)	<0.001
ALP (U/L)	78.8±29.2	86.3±34.1	85.0±11.2	92.2±32.4	0.029
Albumin (g/L)	45.9±3.2	44.1±4.4	45.4±2.9	43.0±5.9	<0.001
TBIL (μmol/L)	14.4 (11.0, 18.6)	15.4 (12.0, 20.8)	13.1 (11.4, 22.3)	17.9 (13.1, 22.5)	0.002
PLT ($\times 10^9$/L)	233.3±51.5	209.6±62.7	222.0±79.7	183.3±65.1	<0.001
FIB4	0.7 (0.5, 0.8)	0.9 (0.6, 1.7)	1.0 (0.8, 1.1)	2.1 (1.3, 4.0)	<0.001
<1.45	142 (100)	608 (70)	4 (100)	26 (33.8)	<0.001
1.45–3.25	0 (0)	185 (21.3)	0 (0)	25 (32.5)	
>3.25	0 (0)	76 (8.7)	0 (0)	26 (33.8)	
aMAP	34.5±5.1	37.9±7.2	39.1±6.0	43.3±7.8	<0.001
<50	142 (100)	813 (93.6)	4 (100)	60 (77.9)	<0.001
≥50	0 (0)	56 (6.4)	0 (0)	17 (22.1)	

Abbreviation: CHB=chronic hepatitis B; HBV=hepatitis B virus; HBsAg=HBV surface antigen; HBeAg=HBV e antigen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyl transpeptidase; ALP=alkaline phosphatase; ALB=Albumin; TBIL=total bilirubin; PLT=platelet count; FIB-4=Fibrosis 4 score.

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