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Observational Study

Lowering the threshold of alanine aminotransferase for enhanced identification of significant hepatic injury in chronic hepatitis B patients

Hong-Sheng Yu, Hao Jiang, Ming-Kai Li, Bi-Lan Yang, Abdukyamu Smayi, Jian-Ning Chen, Bin Wu, Yi-Dong Yang

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Abstract

BACKGROUND

The clinical and histological features of chronic hepatitis B (CHB) patients who fall into the "grey zone (GZ)" and do not fit into conventional natural phases are unclear.

AIM

To explore the impact of varying the threshold of alanine aminotransferase (ALT) levels in identifying significant liver injury among GZ patients.

METHODS

This retrospective analysis involved a cohort of 1617 adult patients diagnosed with CHB who underwent liver biopsy. The clinical phases of CHB patients were determined based on the European Association for the Study of the Liver 2017 Clinical Practice Guidelines. GZ CHB patients were classified into four groups: GZ-A (HBeAg positive, normal ALT levels, and HBV DNA $\leq 10^7$ IU/mL), GZ-B (HBeAg positive, elevated ALT levels, and HBV DNA $< 10^4$ or $> 10^7$ IU/mL), GZ-C (HBeAg negative, normal ALT levels, and HBV DNA ≥ 2000 IU/mL), and GZ-D (HBeAg negative, elevated ALT levels, and HBV DNA ≤ 2000 IU/mL). Significant hepatic injury (SHI) was defined as the presence of notable liver inflammation (\geq

G2) and/or significant fibrosis (\geq S2).

RESULTS

The results showed that 50.22% of patients were classified as GZ, and 63.7% of GZ patients developed SHI. The study also found that lowering the ALT treatment thresholds to the American Association for the Study of Liver Diseases 2018 treatment criteria (35 U/L for men and 25 U/L for women) can more accurately identify patients with significant liver damage in the GZ phases. In total, the proportion of patients with ALT \leq 40 U/L who required antiviral therapy was 64.86% [(221 + 294)/794]. When we lowered the ALT treatment threshold to the new criteria (30 U/L for men and 19 U/L for women), the same outcome was revealed, and the proportion of patients with ALT \leq 40 U/L who required antiviral therapy was 75.44% [(401 + 198)/794]. Additionally, the proportion of SHI was 49.1% in patients under 30 years old and increased to 55.3% in patients over 30 years old ($P = 0.136$).

CONCLUSION

These findings suggest the importance of redefining the natural phases of CHB and using new ALT treatment thresholds for better diagnosis and management of CHB patients in the GZ phases.

Key Words: Chronic hepatitis B; Grey zone; Indeterminate phase; Alanine aminotransferase; Antiviral therapy

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Core Tip: In clinical practice, 27.8%-55% of chronic hepatitis B patients fall into the “grey zone” or “indeterminate phase” that does not meet the diagnostic criteria of the traditional stages. Additionally, there is still debate regarding how best to treat these grey zone (GZ) patients and the advantages of antiviral therapy. Hence, we evaluated the clinical and histological characteristics, and additionally explored the impact of adjusting the threshold of alanine aminotransferase (ALT) in identifying significant liver injury among GZ patients. Based on these data, lowering ALT thresholds can more accurately identify patients with significant hepatic injury at an earlier stage and reduce the need for unnecessary liver biopsies.

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INTRODUCTION

Hepatitis B poses a significant global public health challenge, as evidenced by the estimated 316 million individuals worldwide who were afflicted with the hepatitis B virus (HBV) in 2019. The impact of HBV-related diseases is substantial, as they result in approximately 555000 fatalities globally, which constitutes 48.8% of all hepatitis-related deaths. Notably, hepatitis B stands as the primary cause of mortality in cases of liver cancer and ranks as the third leading cause of death in cirrhosis cases[1]. The progression of chronic hepatitis B (CHB) is a multifaceted interplay involving viral, host, and environmental factors. HBV interacts with the immune system of the host, and the infection status undergoes continuous changes as the disease progresses[2,3]. According to the European Association for the Study of the Liver (EASL) 2017 Clinical Practice Guidelines, CHB can be categorized into five phases: HBeAg-positive chronic HBV infection, HBeAg-positive CHB, HBeAg-negative chronic HBV infection, HBeAg-negative CHB and HBsAg-negative phase[4]. Antiviral treatment is recommended for patients with HBeAg-positive and HBeAg-negative CHB, while regular monitoring is suggested in HBeAg-positive and HBeAg-negative chronic HBV infection phases[4-6].

Nevertheless, in clinical practice, a considerable proportion of CHB patients (27.8%-55%) fall into the “grey zone (GZ)” or “indeterminate phase” that does not meet the diagnostic criteria for the five stages previously indicated[7-9]. Additionally, there is still debate regarding how best to treat these GZ patients and the advantages of antiviral therapy. A study from the United States showed the incidence of hepatocellular carcinoma (HCC) is higher in GZ patients than in HBeAg-negative chronic HBV infection patients (2.67% *vs* 0.61%)[7]. Furthermore, Huang *et al*[10] demonstrated a significant decrease in the risk of HCC among GZ patients who underwent antiviral therapy[10]. In contrast, another study found that none of the patients progressed to advanced fibrosis or cirrhosis, and only a small proportion (6.3%) of GZ patients transitioned to HBeAg-negative CHB, necessitating the use of antiviral therapy[11].

There is a crucial indication for receiving antiviral therapy when patients with CHB have significant liver fibrosis and/or inflammation, which are risk factors for HCC and liver-related mortality[4-6]. However, few studies have explored liver histological injury in the GZ phase[12]. Therefore, assessing the clinical and histological features may provide useful recommendations for managing the GZ phase. Moreover, an issue that complicates the management of CHB is the disagreement regarding the appropriate treatment threshold for alanine aminotransferase (ALT) levels. The American Association for the Study of Liver Diseases (AASLD) guidelines suggest that the upper normal limit (ULN) for ALT

should be 35 U/L for men and 25 U/L for women, while the EASL guidelines consider 40 U/L as the ULN[4,5]. In China, a recent publication titled "Expert opinion on expanding anti-HBV treatment for chronic hepatitis B" proposed a lower ALT threshold (30 U/L for males and 19 U/L for females) as initiating antiviral therapy in CHB patients[13]. However, the efficacy of reducing ALT thresholds in accurately identifying patients with significant liver damage at an earlier stage and mitigating the necessity for superfluous liver biopsy remains uncertain.

Therefore, using a retrospective cohort of treatment-naïve CHB patients who underwent liver biopsy, we evaluated the clinical and histological characteristics, and additionally explored the impact of adjusting the threshold of ALT in identifying significant liver injury among GZ patients.

MATERIALS AND METHODS

Methods

Patient selection: Between January 2008 and December 2020, a total of 1617 consecutive adult patients (age, ≥ 18 years) diagnosed with CHB (hepatitis B surface antigen positive > 6 mo) who had undergone liver biopsy at the Third Affiliated Hospital of Sun Yat-Sen University were included in this retrospective analysis. The exclusion criteria were as follows: (1) Viral coinfection (hepatitis C virus, hepatitis D virus, or HIV); (2) Alcohol abuse (≥ 30 g of alcohol per day for men, ≥ 20 g of alcohol per day for women), nonalcoholic fatty liver disease (diagnosed by liver biopsy) and autoimmune liver disease; (3) Decompensated cirrhosis, HCC, and nonliver cancer; (4) Liver transplantation; and (5) Prior or current antiviral treatment (Supplementary Figure 1). The study was approved by the Ethics Committee of The Third Affiliated Hospital of Sun Yat-sen University. Written informed consent was obtained from each participant prior to the liver biopsy.

Definitions: The clinical phases of patients with CHB were determined in accordance with the EASL 2017 clinical practice guidelines, taking into consideration the highest HBV-DNA levels and ALT levels observed in at least two determinations within the 12 mo preceding enrolment (Supplementary Table 1)[4]. Patients who did not meet the criteria for any of the five phases were classified as GZ, with subcategories including GZ-A (HBeAg positive, normal ALT levels, and HBV DNA $\leq 10^7$ IU/mL), GZ-B (HBeAg positive, elevated ALT levels, and HBV DNA $< 10^4$ or $> 10^7$ IU/mL), GZ-C (HBeAg negative, normal ALT levels, and HBV DNA ≥ 2000 IU/mL), and GZ-D (HBeAg negative, elevated ALT levels, and HBV DNA ≤ 2000 IU/mL)[9,12]. We used ALT and gamma-glutamyl transpeptidase (GGT) levels of 40 U/L and 60 U/L as the ULN, respectively[4]. The calculations were formulated as follows: Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) = $[\text{AST (U/L)}/\text{ULN}]/[\text{PLT (10}^9/\text{L)}] \times 100$; fibrosis score based on four factors (FIB-4) = $[\text{age (years)} \times \text{AST (U/L)}]/[\text{PLT (10}^9/\text{L)} \times \sqrt{\text{ALT (U/L)}}]$; GGT-to-platelet ratio (GPR) = $[\text{GGT (U/L)}/\text{ULN}]/[\text{PLT (10}^9/\text{L)}] \times 100$.

Histological assessment: Ultrasonography-guided percutaneous liver biopsy was conducted using a 16-gauge disposable needle. The minimum sample length required was 15 mm, with a minimum inclusion of 6 portal tracts. Inflammation grade (G0-G4) and fibrosis stage (S0-S4) were estimated according to Scheuer's classification[14]. In accordance with the pathological staging system, significant liver inflammation and significant fibrosis were defined as $\geq G2$ and $\geq S2$, respectively. Significant hepatic injury (SHI) was defined as $\geq G2$ and/or $\geq S2$ [12,15]. The biopsy samples were subjected to blind and independent observation and interpretation by two proficient pathologists. In cases where discordance arose between the two pathologists, a third pathologist, Jianning Chen, was consulted for additional evaluation, leading to a consensus being achieved through subsequent discussion.

Statistical analysis

SPSS version 25.0 software (SPSS Inc., Chicago, IL, United States) was used for statistical analyses. Continuous variables are expressed as the median and interquartile range, and categorical data are expressed as counts and percentages. Kruskal-Wallis tests and Pearson's chi-squared tests were applied to compare variables that were significantly different between groups. The independent predictors of SHI were determined by univariate and multiple logistic regression analyses. Areas under the receiver operating characteristic curve (AUROC) were calculated to investigate the diagnostic performance of the noninvasive scores and were compared by the DeLong test. All *P* values were two-sided, and *P* < 0.05 was deemed statistically significant.

RESULTS

Distribution, clinical characteristics, and liver histological features of patients in different immune states

The baseline characteristics of the 1617 treatment-naïve patients are presented in Table 1. Based on the defined criteria, 161 (9.96%) patients were classified as having HBeAg-positive chronic HBV infection, 203 (12.55%) patients were categorized as HBeAg-positive CHB, 171 (10.58%) patients were identified as having HBeAg-negative chronic HBV infection, and 270 (16.70%) patients were classified as HBeAg-negative CHB. Interestingly, 812 (50.22%) patients did not meet the criteria for any of the aforementioned phases and were therefore designated as GZ. Notably, there were significant variations in clinical characteristics across the different phases. The average age of patients with GZ was 36.0 years, with 74.1% being male. These patients had a mean HBV DNA level of 5.24 Log₁₀ IU/mL and an intermediate ALT level of 37.0 U/L.

Table 1 Baseline characteristics of chronic hepatitis B patients among different immune phases

Clinical characteristics	HBeAg-positive chronic infection (n = 161)	HBeAg-positive chronic hepatitis (n = 203)	HBeAg-negative chronic infection (n = 171)	HBeAg-negative chronic hepatitis (n = 270)	Grey zone (n = 812)	P value
Age (year)	31.0 (26.0-36.0)	33.0 (27.0-39.0)	37.0 (32.0-42.0)	39.0 (33.0-45.0)	36.0 (30.0-42.0)	< 0.001
Male (%)	97 (60.2)	168 (82.8)	133 (77.8)	221 (81.9)	602 (74.1)	< 0.001
BMI (kg/m ²)	21.3 (19.1-23.0)	22.5 (20.3-24.9)	22.6 (20.3-24.5)	22.8 (20.4-25.1)	22.0 (20.0-24.4)	< 0.001
Diabetes (%)	0 (0)	3 (1.5)	4 (2.4)	10 (3.7)	14 (1.7)	0.071
HBV DNA (log ₁₀ IU/mL)	8.12 (7.60-8.23)	6.17 (5.38-6.61)	2.52 (2.00-2.89)	5.47 (4.50-6.31)	5.24 (3.92-7.50)	< 0.001
PLT (10 ⁹ /L)	211.0 (179.5-238.0)	185.0 (144.0-217.0)	191.0 (156.0-230.0)	185.0 (154.8-219.3)	199.0 (160.0-234.0)	< 0.001
ALT (U/L)	27.0 (21.0-33.0)	69.0 (51.0-111.0)	25.0 (19.0-31.0)	61.5 (50.0-100.3)	37.0 (27.0-59.0)	< 0.001
AST (U/L)	24.0 (21.0-31.0)	48.0 (36.0-73.0)	24.0 (20.0-29.0)	44.0 (33.0-66.0)	31.0 (24.0-45.0)	< 0.001
GGT (U/L)	18.0 (14.0-30.0)	51.0 (30.0-93.0)	25.0 (17.0-36.0)	40.0 (27.8-80.5)	29.0 (20.0-50.0)	< 0.001
Tbil (μmol/L)	12.7 (9.3-17.6)	14.1 (11.0-19.5)	12.6 (9.9-16.5)	14.4 (10.3-21.6)	13.0 (9.6-18.0)	< 0.001
ALB (g/L)	45.2 (43.3-47.6)	44.1 (41.0-46.2)	45.8 (43.7-48.0)	44.5 (41.2-46.9)	44.9 (42.3-47.0)	< 0.001
AFP (ng/mL)	2.4 (1.7-3.5)	5.1 (3.1-14.6)	2.3 (1.6-3.8)	3.8 (2.5-8.0)	3.1 (2.1-5.3)	< 0.001
PT (s)	13.4 (13.0-13.8)	13.4 (12.8-14.1)	13.4 (12.9-14.0)	13.5 (12.9-14.1)	13.4 (12.9-14.0)	0.073
APRI	0.29 (0.24-0.39)	0.69 (0.47-1.12)	0.32 (0.24-0.43)	0.63 (0.42-0.99)	0.40 (0.28-1.27)	< 0.001
FIB-4	0.72- (0.55-1.08)	1.05 (0.71-1.55)	0.92 (0.71-1.33)	1.18 (0.77-1.81)	0.93 (0.67-1.40)	< 0.001
GPR	0.23 (0.16-0.30)	0.71 (0.39-1.44)	0.32 (0.22-0.52)	0.56 (0.34-1.23)	0.37 (0.23-0.68)	< 0.001
Inflammation						< 0.001
G0-1	103 (64.0%)	35 (17.2%)	94 (55.0%)	76 (28.1%)	351 (43.2%)	
≥ G2	58 (36.0%)	168 (82.8%)	77 (45.0%)	194 (71.9%)	461 (56.8%)	
Fibrosis						< 0.001
S0-1	119 (73.9%)	64 (31.5%)	95 (55.6%)	98 (36.3%)	378 (46.6%)	
≥ S2	42 (26.1%)	139 (68.5%)	76 (44.4%)	172 (63.7%)	434 (53.4%)	
SHI						< 0.001
No	95 (59.0%)	32 (15.8%)	80 (46.8%)	63 (23.3%)	295 (36.3%)	
Yes	66 (41.0%)	171 (84.2%)	91 (53.2%)	207 (76.7%)	517 (63.7%)	

PLT: Platelet; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; GGT: Gamma-glutamyl transpeptidase; Tbil: Total bilirubin; ALB: Albumin; AFP: α -fetoprotein; PT: Prothrombin time; APRI: Aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis score based on four factors; GPR: Gamma-glutamyl transpeptidase-to-platelet ratio; SHI: Significant hepatic injury.

The clinical and liver histological characteristics are presented in [Table 1](#) and [Figure 1](#). In the GZ group, the proportion of significant liver inflammation (\geq G2) was 56.8%, and the proportion of significant fibrosis (\geq S2) was 53.4%. Among GZ patients, 63.7% had SHI. Higher proportions of SHI were observed in HBeAg-positive (84.2%) and HBeAg-negative (76.7%) CHB patients. However, HBeAg-positive (41.0%) and HBeAg-negative chronic HBV infection (53.2%) had lower but still relatively high proportions of SHI.

Distribution, clinical characteristics, and liver histological characteristics of patients in different GZs

The clinical characteristics of 812 GZ patients are shown in [Supplementary Table 2](#). Among these patients, the proportion of GZ-C was the highest (41.1%), followed by GZ-B (34.6%), GZ-A (15.8%), and GZ-D (8.5%). Notably, patients in the GZ-A (35.0 years) and GZ-B (31.0 years) subgroups were younger than those in the GZ-C (40.0 years) and GZ-D (36.0 years) subgroups. Furthermore, higher HBV DNA levels were observed in GZ-B (7.86 Log₁₀ IU/mL), followed by GZ-A (5.39 Log₁₀ IU/mL), GZ-C (4.40 Log₁₀ IU/mL), and GZ-D (2.40 Log₁₀ IU/mL).

As shown in [Supplementary Figure 2](#), HBeAg-positive GZ patients exhibited a significantly higher rate of significant liver inflammation (\geq G2) (66.1% *vs* 47.4%, $P < 0.001$) and SHI (70.4% *vs* 56.8%, $P < 0.001$) than HBeAg-negative GZ patients. However, there was no statistically significant difference in fibrosis stages between HBeAg-positive and HBeAg-

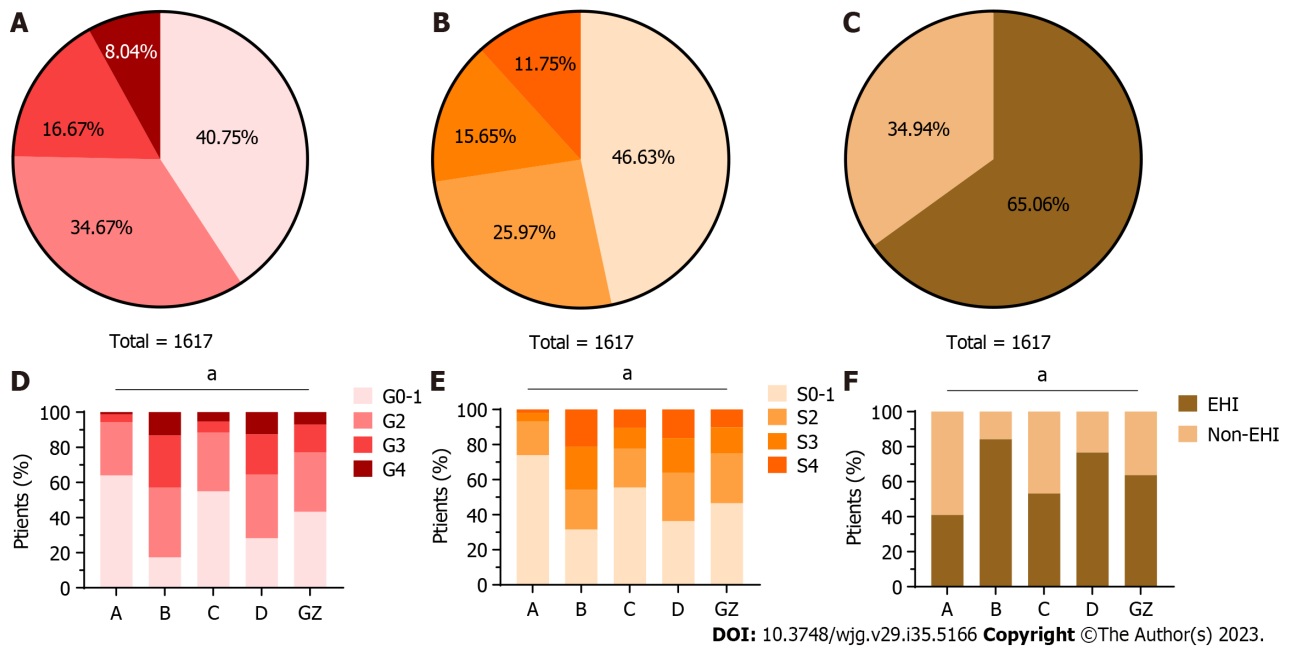


Figure 1 Distribution and liver histological features of chronic hepatitis B patients in different immune states. A and D: Proportions of liver inflammation grades in different immune status groups; B and E: Proportions of fibrosis stages in different immune status groups; C and F: Proportions of significant hepatic injury in different immune status groups. A: HBeAg-positive chronic hepatitis B virus (HBV) infection; B: HBeAg-positive chronic hepatitis B; C: HBeAg-negative chronic HBV infection; D: HBeAg-negative chronic hepatitis B; GZ: Grey zone; EHI: Evidenced hepatic injury. ^a $P < 0.001$.

negative GZ patients (55.8% *vs* 51.2%, $P = 0.186$). The distributions of liver inflammation grades, fibrosis stages, and SHI are shown in [Supplementary Table 2](#) and [Supplementary Figure 2](#). The highest prevalence of significant liver inflammation ($\geq G2$) was observed in GZ-B (66.5%), while GZ-D (62.3%) had the highest proportion of significant fibrosis ($\geq S2$). In terms of SHI, the highest proportion was found in patients from GZ-B (70.5%), followed by GZ-A (70.3%), GA-D (69.6%), and GZ-C (54.2%).

Diagnostic performance of APRI, FIB-4, and GPR to detect SHI in patients with GZ

SHI was observed in 517 (63.7%) GZ patients. Of those, 288 were HBeAg-positive GZ patients, and 229 were HBeAg-negative GZ patients. In the HBeAg-positive cohort, univariate analysis indicated that PLT, ALT, AST, GGT, total bilirubin (Tbil), albumin (ALB), and prothrombin time (PT) were associated with SHI. However, multiple logistic regression analysis indicated that only PLT, AST, GGT, and ALB remained significantly associated with SHI. For the HBeAg-negative cohort, female sex, HBV-DNA, ALT, AST, GGT, Tbil, and PT were associated with higher SHI, whereas PLT and ALB were negatively associated with this event by univariate analysis. By multiple logistic regression analysis, female sex, HBV-DNA, GGT, and PLT were associated with SHI ([Supplementary Table 3](#) and [Figure 2](#)).

Further investigation was conducted to assess the diagnostic efficacy of established scoring systems such as APRI, FIB-4, and GPR in predicting SHI ([Figure 2](#)). The AUROCs for these three tests showed no significant difference in the HBeAg-positive GZ ($P > 0.05$). However, in HBeAg-negative GZ, APRI demonstrated superior performance compared to FIB-4 ($P < 0.001$) and was comparable to GPR ($P = 0.30$).

Effect of lowering the treatment threshold of ALT on identifying SHI

To examine the significance of lowering the treatment threshold for ALT, a total of 794 patients with normal ALT levels ($ULN \leq 40$ U/L) were chosen for further investigation. The distribution of their immune states was as follows: 161 (20.28%) patients had HBeAg-positive chronic HBV infection, 128 (16.12%) patients fell within GZ-A, 171 (21.54%) patients had HBeAg-negative chronic HBV infection, and 334 (42.07%) patients were categorized under GZ-C.

Based on the AASLD 2018 criteria of the ALT antiviral treatment threshold (35 U/L for males and 25 U/L for females), we subsequently evaluated the ratio of SHI in different groups. Among the 794 chronic HBV infections, more than one-quarter of them (221/794, 27.8%) were above the AASLD criteria ([Figure 3A](#)). Of these 221 individuals, 29.2% (47/161) with HBeAg-positive chronic HBV infection, 36.7% (47/128) with GZ-A, 21.1% (36/171) with HBeAg-negative chronic HBV infection, and 27.2% (91/334) with GZ-C were above this ALT threshold ([Figure 3B](#)). It is worth noting that 54.8% (121/221) of patients had significant liver inflammation ($\geq G2$), which was significantly higher than that of patients below the ALT threshold (43.1%, 247/573) ($P = 0.003$) ([Figure 3C](#)). In addition, the proportion of SHI in the high ALT group was significantly higher than that in the low ALT group (60.6% *vs* 51.3%, $P = 0.018$). In total, the proportion of patients with ALT ≤ 40 U/L who required antiviral therapy was 64.86% [(221 + 294)/794] according to the AASLD 2018 Clinical Practice Guidelines.

Obviously, the SHI value in patients with HBeAg-positive chronic HBV infection below the new ALT threshold was substantially lower than that of GZ-A patients above the ALT threshold (36.8% *vs* 57.4%, $P = 0.016$). The former was in the

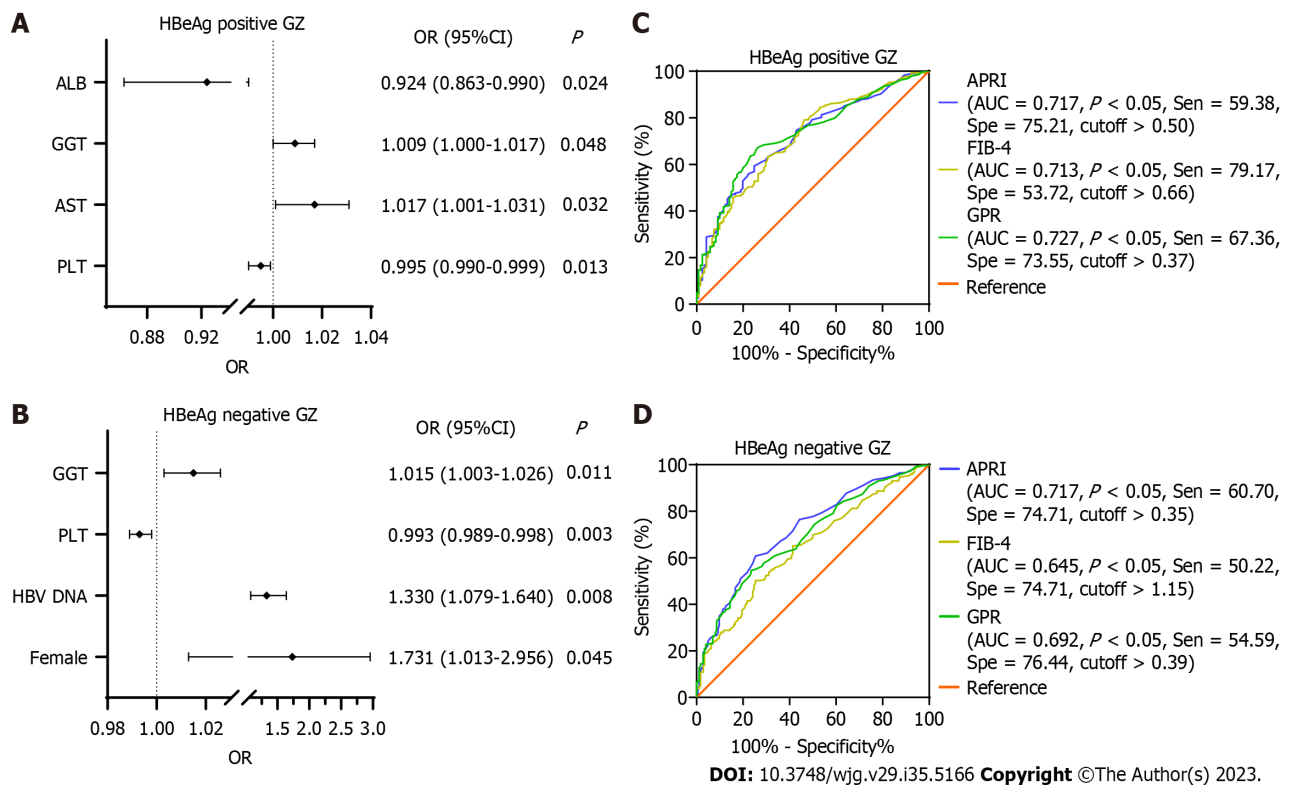


Figure 2 Multiple logistic regression analysis. A: Multiple logistic regression analysis of clinical parameters of chronic hepatitis B patients in HBeAg-positive grey zones associated with significant hepatic injury; B: Multiple logistic regression analysis of clinical parameters of chronic hepatitis B patients in HBeAg-negative grey zones associated with significant hepatic injury; C: Receiver operating characteristic (ROC) curves of aspartate aminotransferase-to-platelet ratio index (APRI), fibrosis score based on four factors (FIB-4), and gamma-glutamyl transpeptidase-to-platelet ratio (GPR) in the prediction of significant hepatic injury (SHI) in HBeAg-positive grey zones; D: ROC curves of APRI, FIB-4, and GPR in the prediction of SHI in HBeAg-negative grey zones. PLT: Platelet; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; ALB: Albumin; APRI: Aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis score based on four factors; GPR: Gamma-glutamyl transpeptidase-to-platelet ratio.

“truly” HBeAg-positive chronic HBV infection group due to high HBV DNA levels and low ALT levels. Similarly, GZ-C patients had a significantly higher SHI ratio than the “truly” HBeAg-negative chronic HBV infection patients (62.6% *vs* 48.1%, $P = 0.032$) (Figure 3D).

According to the new recommendations for the treatment threshold of ALT (30 U/L for males and 19 U/L for females), we investigated the rate of SHI in different groups separately. Among the 794 chronic HBV infections, nearly half of them (393/794, 49.5%) were below the new criteria (Figure 4A). Among these 393 patients, 46.0% (74/161) with HBeAg-positive chronic HBV infection, 36.7% (47/128) with GZ-A, 64.9% (111/171) with HBeAg-negative chronic HBV infection and 48.2% (161/334) with GZ-C were below this ALT threshold (Figure 4B). Notably, the proportions of significant liver inflammation (\geq G2) and SHI in patients above the ALT threshold were significantly higher than those in patients below the ALT threshold (50.9% *vs* 41.7%, $P = 0.01$; 57.4% *vs* 50.4%, $P = 0.049$) (Figure 4C). In total, the proportion of patients with ALT \leq 40 U/L who required antiviral therapy was 75.44% [(401 + 198)/794] according to the “expert opinion on expanding anti-HBV treatment for chronic hepatitis B” in China.

The SHI values in patients with HBeAg-positive chronic HBV infection below the new ALT threshold was 36.4%. However, higher SHI values of 67.9% were seen in the GZ-A patients above the new ALT threshold, and the difference was statistically significant ($P < 0.001$). However, there was no significant difference in the proportion of SHI between patients with HBeAg-negative chronic HBV infection below the new ALT threshold and GZ-C patients above the new ALT threshold (45.0% *vs* 54.9%, $P = 0.105$) (Figure 4D).

An age > 30 years may not be a limitation for initiating antiviral therapy

The median age was 31, 35, 37, and 40 years for HBeAg-positive chronic HBV infection, GZ-A, HBeAg-negative chronic HBV infection, and GZ-C patients, respectively. There was an increasing trend of age in these states (Figure 5A). Among 794 patients, 76.7% (609/794) were > 30 years old, and almost 70% were HBeAg-negative patients, including 77.8% with HBeAg-negative chronic HBV infection and 88.3% with GZ-C (Figure 5B). The ratio of SHI in patients \leq 30 years old was 49.1%, and it increased to 55.3% for those patients > 30 years old. However, there was no significant difference ($P = 0.136$). A similar result was observed in all states regardless of whether they were older or younger than 30 years old ($P > 0.05$) (Figure 5C).

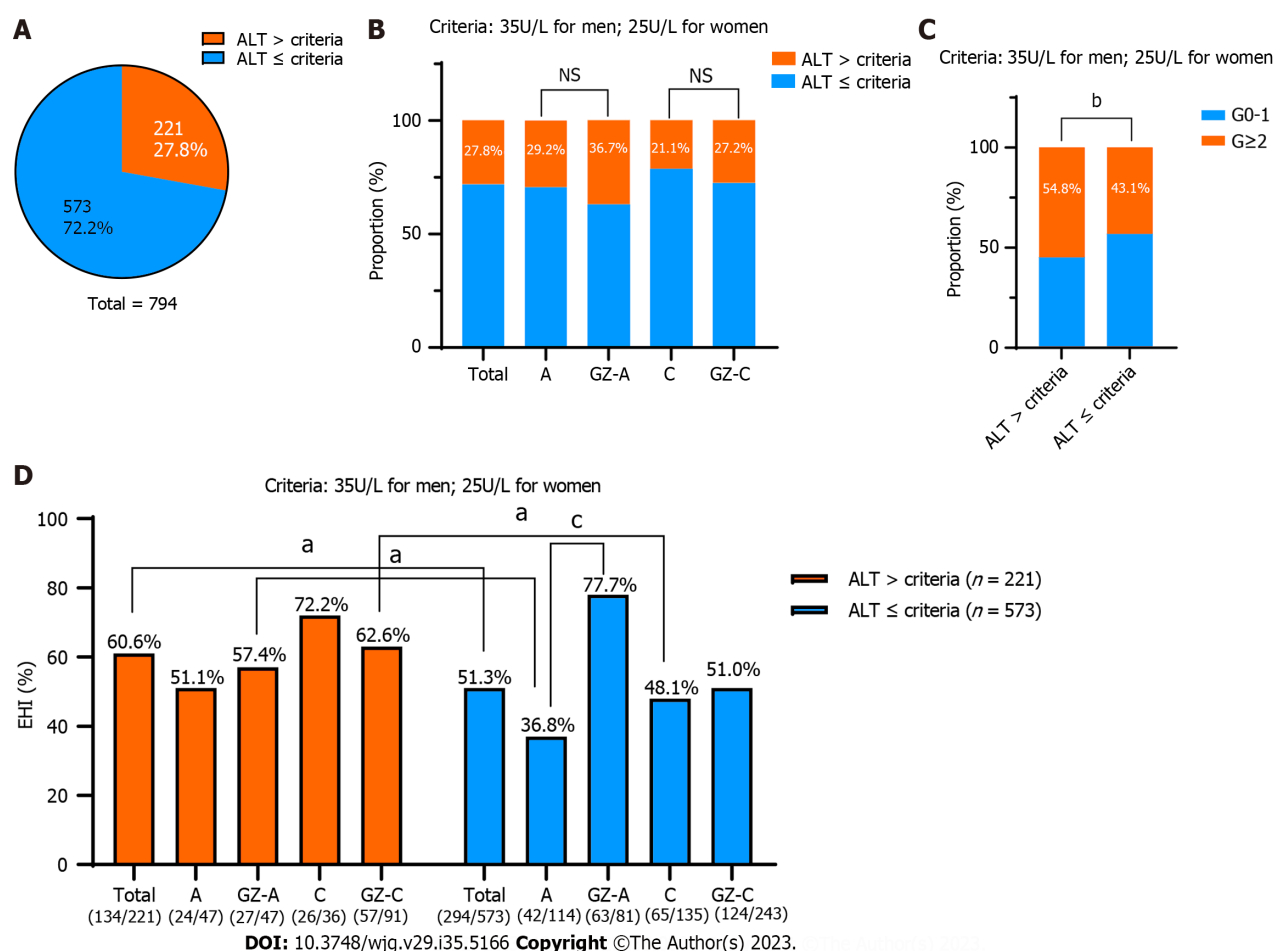


Figure 3 The alanine aminotransferase treatment threshold was lowered to the American Association for the Study of Liver Diseases 2018 treatment criteria (35 U/L for males and 25 U/L for females). A: Among the 794 chronic hepatitis B virus infections, 27.8% (221/794) of patients were above the American Association for the Study of Liver Diseases criteria; B: Comparison of the proportions of patients exceeding the alanine aminotransferase (ALT) threshold in different groups; C: A total of 43.1% (247/573) of patients below the ALT threshold had significant liver inflammation (\geq G2); D: The proportion of significant hepatic injury (SHI) in patients below the ALT threshold was 51.3%. Comparison of the proportions of SHI in each group. ALT: Alanine aminotransferase; NS: Not significant. ^a $P < 0.05$, ^b $P < 0.01$, ^c $P < 0.001$.

DISCUSSION

This retrospective cohort study examined a group of CHB patients who underwent liver biopsy at the Third Affiliated Hospital of Sun Yat-Sen University. The study showed that 50.22% of the patients with HBV infection fell into the GZ category, with 56.8% and 53.4% having significant liver inflammation (\geq G2) and fibrosis (\geq S2), respectively. More than half of the patients (63.7%) in the GZ category exhibited SHI, which was less than the proportion observed in HBeAg-positive and HBeAg-negative chronic hepatitis patients but more severe than those in the HBeAg-positive and HBeAg-negative chronic infection categories. While current guidelines do not require urgent antiviral therapy for GZ patients[4-6], the study findings indicated that HBeAg-positive and HBeAg-negative chronic HBV infections had relatively high proportions of SHI. The proportions were higher than those of a meta-analysis, which indicated the prevalence of significant fibrosis for chronic HBV infection as 16.9% (95%CI: 7.8-26.1) for HBeAg-positive and 24.8% (95%CI: 4.5-45.1) for HBeAg-negative chronic HBV infection[16]. This may be because the population included in the study is Asian and the genotypes are mainly B and C. Therefore, noninvasive methods, including liver biopsy, should be considered to evaluate liver inflammation and fibrosis in these individuals[17-19].

To better direct clinical diagnosis and treatment strategies, we analysed the risk factors for SHI in GZ patients. In the HBeAg-positive cohort, multiple logistic regression analysis indicated that PLT, AST, GGT, and ALB were associated with SHI. For the HBeAg-negative cohort, female sex, HBV-DNA, GGT, and PLT were associated with SHI by multiple logistic regression analysis. Based on these risk factors, we compared the diagnostic performance of APRI, FIB-4, and GPR in predicting SHI. The AUROCs of APRI, FIB-4, and GPR were 0.717, 0.713, and 0.727, respectively, in the HBeAg-positive GZ phases and 0.717, 0.645, and 0.692, respectively, in the HBeAg-negative GZ phases. Previous studies have shown that GPR provided a significantly higher AUROC than APRI and FIB-4, implying the superiority of GPR in predicting significant liver fibrosis and cirrhosis. For diagnosing significant fibrosis, the AUROCs of GPR were 0.66-0.86 and the cut-off was 0.32-0.43[20-22]. Thus, for simplicity of use in clinical practice, we advised utilizing a GPR cut-off of 0.37 as the optimal cut-off for predicting SHI in GZ patients. Treatment should be individualized for GZ patients, especially those who are over 40 years of old, HBeAg positive, and exhibit high ALT and HBV DNA levels. The state of

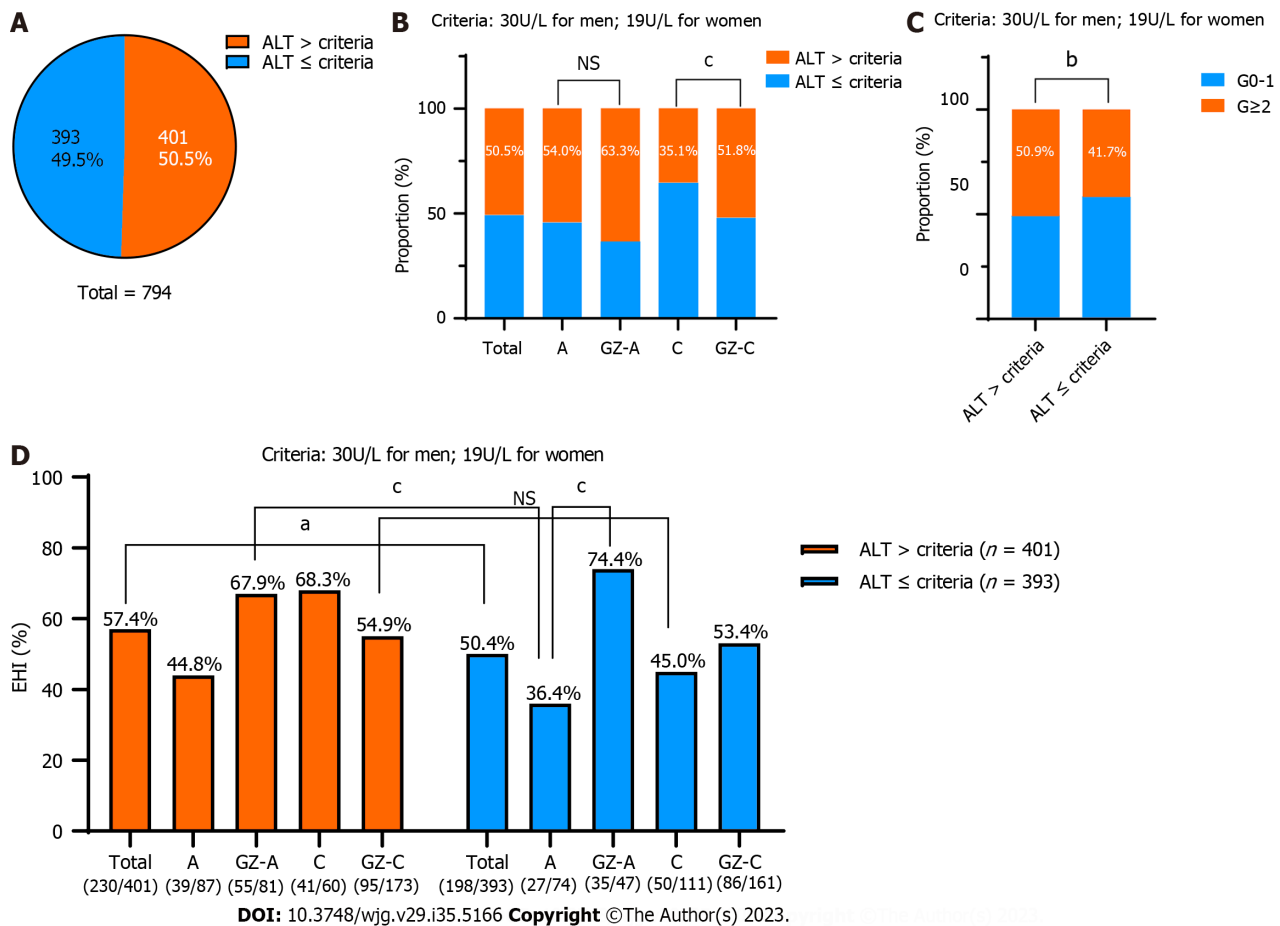


Figure 4 Lowering the alanine aminotransferase treatment threshold to new criteria (30 U/L for men and 19 U/L for women). A: Among the 794 chronic hepatitis B virus infections, 50.5% (401/794) of patients were above the new criteria; B: Comparison of the proportions of patients exceeding the alanine aminotransferase (ALT) threshold in different groups; C: A total of 41.7% (164/393) of patients below the ALT threshold had significant liver inflammation (\geq G2); D: The proportion of significant hepatic injury (SHI) in patients below the ALT threshold was 50.4%. Comparison of the proportions of SHI in each group. NS: Not significant. ^a $P < 0.05$, ^b $P < 0.01$, ^c $P < 0.001$.

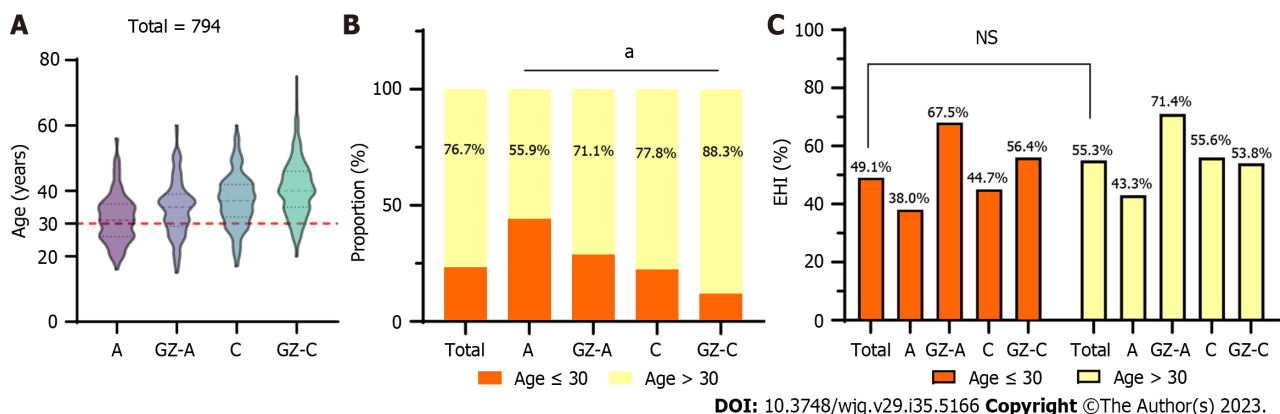


Figure 5 Comparison in different groups. A: Comparison of age in different groups; B: Comparison of the proportions of patients older than 30 years in different groups; C: The proportion of significant hepatic injury (SHI) in patients \leq 30 years of age was 49.1%. Comparison of the proportions of SHI in each group. NS: Not significant. ^a $P < 0.05$.

the GZ is not constant but should be dynamic. Periodic monitoring is particularly important.

The main purpose of this study was to investigate the effect of lowering the treatment threshold of ALT according to different clinical guidelines in identifying SHI patients with CHB virus infection in the GZ. A total of 794 patients with normal ALT levels ($\text{ULN} \leq 40 \text{ U/L}$) were selected for further investigation; of these patients, 53.90% (428/794) necessitated antiviral therapy. The proportion of patients with $\text{ALT} \leq 40 \text{ U/L}$ who required antiviral therapy was 64.86% [(221 + 294)/794] according to the AASLD 2018 Clinical Practice Guidelines. Furthermore, the proportion of patients with

ALT ≤ 40 U/L who required antiviral therapy was 75.44% [(401 + 198)/794] according to the “expert opinion on expanding anti-HBV treatment for chronic hepatitis B” in China.

The current criteria for determining “normal” ALT levels were established based on populations that encompassed individuals with subclinical liver disease. Prati *et al*[23] propose that it is prudent to reconsider the established thresholds for ALT levels in patients diagnosed with chronic HCV infection or nonalcoholic fatty liver disease[23]. Previous studies have shown that even if the ALT level is within the normal range, the ALT level correlates with the degree of liver inflammation and fibrosis. Sonneveld *et al*[24] showed that 52% of 168 patients without liver fibrosis and 82% of 66 patients with significant liver fibrosis with normal ALT levels had mild and moderate inflammation[24]. More importantly, even if the ALT level is within the normal range, higher ALT levels have a higher incidence of decompensated cirrhosis and HCC. Compared to patients with ALT levels $< 0.5 \times \text{ULN}$ (53 U/L and 31 U/L for males and females, respectively), patients with ALT levels of $0.5\text{--}1 \times \text{ULN}$ had an increased risk for the development of complications including ascites, spontaneous bacterial peritonitis, oesophageal varices, encephalopathy and HCC[25]. Similarly, REVEAL-HBV research demonstrated that compared to ALT < 15 U/L, patients with ALT 15–44 U/L had an increased risk of cirrhosis (aHR = 1.97, 95% CI: 1.56–2.48) and HCC (aHR = 2.45, 95% CI: 1.74–2.48)[26]. Therefore, lowering the ALT threshold in CHB patients is conducive to early initiation of antiviral therapy, which in turn reduces the incidence of cirrhosis and HCC, especially in the GZ phases.

Current studies and guidelines recommend that age > 30 years old is an independent risk factor for disease progression and can be an indication for initiating antiviral therapy. A linear correlation between age and the mortality risk of primary liver cancer, chronic liver disease and cirrhosis, and viral hepatitis was found in those whose ages ranged from 15 years to 74 years[27]. Among 794 individuals in our study with normal ALT levels ($\text{ULN} \leq 40$ U/L), 23.3% of the patients were under 30 years old. The ratio of SHI in patients ≤ 30 years old was 49.1%, and it increased to 55.3% for those patients > 30 years old. However, the difference was not significant. Huang *et al*[7] showed that among patients who remained indeterminate, an age ≥ 40 years (aHR = 9.06) and ≥ 45 years (aHR = 18.40) were independently associated with HCC development[7]. This suggested that setting 30 years old as a threshold is not suitable for GZ patients. We noticed that a large proportion of CHB patients ≤ 30 years old with normal ALT levels still had inflammation and fibrosis. This finding was consistent with a previous study that noted that among 432 CHB patients with normal or mildly elevated ALT who underwent liver biopsy, the inflammation and fibrosis scores increased with age. Of these patients < 30 years old, $G \geq 2$ accounted for approximately 50%, and $S \geq 2$ accounted for approximately 40%[28]. Hence, age may not be a limitation for initiating antiviral therapy in patients with CHB who have normal ALT levels. Instead, more individualized attention should be given to the patient's liver inflammation and fibrosis, with the aim of reducing misdiagnosis and underdiagnosis. Additionally, patients with hepatitis B who need treatment and are at risk of disease progression should be placed on antiviral therapy in a timely manner.

Nevertheless, our study has several limitations. First, selection bias could not be ruled out because this was a retrospective and cross-sectional study. Second, the proportion of patients with SHI in this cohort may be higher than the natural population because the patients were sourced from tertiary care hospitals rather than the community, and there may be a bias in the enrolled patients. Third, because the follow-up of patients after liver biopsy was insufficient, the phase transition, benefits of antiviral therapy, and prognosis of GZ patients could not be assessed. Fourth, the study was unable to obtain information on the genotypes of all hepatitis B patients, and the limited data suggest a predominance of genotype B (65%) and genotype C (33%).

CONCLUSION

In conclusion, this study showed that 50.22% of CHB patients were in the GZ, and over half of GZ patients (63.7%) had SHI. Lowering ALT thresholds can more accurately identify patients with significant liver damage at an earlier stage and reduce the need for some unnecessary liver biopsies. Furthermore, age may not be a limitation for initiating antiviral therapy in patients with CHB who have normal ALT levels. This may have significance for refining the natural history of CHB and providing supporting evidence of lowering the antiviral therapy threshold for ALT.

ARTICLE HIGHLIGHTS

Research background

In clinical practice, a considerable proportion of chronic hepatitis B (CHB) patients (27.8%–55%) fall into the “grey zone (GZ)” or “indeterminate phase”. Additionally, there is still debate regarding how best to treat these GZ patients and the advantages of antiviral therapy. Moreover, an issue that complicates the management of CHB is the disagreement regarding the appropriate treatment threshold for alanine aminotransferase (ALT) levels.

Research motivation

To explore the impact of varying the threshold of ALT levels in identifying significant hepatic injury (SHI) among GZ patients.

Research objectives

Our research evaluated the clinical and histological characteristics and additionally explored the impact of adjusting the threshold of ALT in identifying significant liver injury among GZ patients.

Research methods

This retrospective analysis involved a cohort of 1617 adult patients diagnosed with CHB who underwent liver biopsy. Significant hepatic injury was defined as the presence of notable liver inflammation (\geq G2) and/or significant fibrosis (\geq S2). Kruskal-Wallis tests and Pearson's chi-squared tests were applied to compare variables that were significantly different between groups.

Research results

The study showed that 50.22% of the patients with HBV infection fell into the GZ category, and more than half of the patients (63.7%) in the GZ category exhibited SHI. The areas under the receiver operating characteristic curves of Aspartate aminotransferase-to-platelet ratio index, fibrosis score based on four factors, and gamma-glutamyl transpeptidase-to-platelet ratio in predicting SHI were 0.717, 0.713, and 0.727, respectively, in the HBeAg-positive GZ phases and 0.717, 0.645, and 0.692, respectively, in the HBeAg-negative GZ phases. Lowering the ALT treatment thresholds to the American Association for the Study of Liver Diseases 2018 treatment criteria can more accurately identify patients with significant liver damage in the GZ phases. When we lowered the ALT treatment threshold to the new criteria, the same outcome was revealed.

Research conclusions

This study showed that 50.22% of CHB patients were in the GZ, and over half of GZ patients (63.7%) had SHI. Lowering ALT thresholds can more accurately identify patients with significant liver damage at an earlier stage and reduce the need for some unnecessary liver biopsies. Furthermore, age may not be a limitation for initiating antiviral therapy in patients with CHB who have normal ALT levels.

Research perspectives

Further investigation is needed to determine the assessment and treatment strategy for CHB patients in the GZ phases.

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FOOTNOTES

Author contributions: Yu HS and Jiang H have contributed equally to this work; Yu HS and Jiang H designed the study, performed the statistical analysis, and drafted the manuscript; Li MK, Yang BL, Smayl A and Chen JN collected the clinical data and then reviewed the data; Wu B and Yang YD revised the manuscript; Yang YD and Wu B were responsible for the study conception, design, data, analysis; All authors have read and approved the manuscript.

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