Original articles

Liver fibrosis despite normal aminotransferases – Implications for Hepatitis B management and treatment eligibility in Vietnam: A cross-sectional study

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Received: 01/10/2025; **Accepted:** 27/07/2026; **Published:** 25/08/2026
DOI: 10.34071/jmp.2026.4.723

Abstract

Background: Chronic hepatitis B (CHB) is a major public health challenge in Vietnam. Many patients have normal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, yet clinically relevant fibrosis may progress silently. This study assessed fibrosis prevalence using transient elastography (FibroScan®) and identified factors associated with significant fibrosis (≥ F2) in CHB patients with normal aminotransferases.

Methods: We conducted a cross-sectional study among CHB patients aged ≥ 18 years at the Gastroenterology Clinic of 115 People's Hospital, Ho Chi Minh City, from April 2024 to March 2025. Eligible patients were treatment-naïve with normal ALT and AST (Vietnam Ministry of Health 2019 definition). Clinical, laboratory, and virological data were collected, and liver stiffness was measured by transient elastography. Logistic regression was used to assess predictors of fibrosis.

Results: Among 220 patients, 86.4% had no or mild fibrosis (F0 - F1), 12.3% had significant fibrosis (F2), and 1.3% had advanced fibrosis (F3); none had cirrhosis (F4). In multivariable analysis, older age (OR 1.06; 95% CI 1.02 - 1.11) and lower platelet count (OR 0.98; 95% CI 0.98 - 0.99) were independent predictors of significant fibrosis. According to the 2019 Vietnam Ministry of Health guidelines, 23.2% of patients with normal aminotransferases met indications for antiviral therapy, whereas application of the 2024 WHO criteria increased eligibility to 34.1%.

Conclusions: A substantial proportion of CHB patients with normal aminotransferases had significant fibrosis, underscoring the limitations of ALT-based monitoring. Incorporating non-invasive fibrosis assessment into HBV programs could support earlier treatment and accelerate elimination efforts.

Keywords: *Chronic hepatitis B; liver fibrosis; transient elastography; FibroScan®; aminotransferases; Vietnam.*

1. INTRODUCTION

Chronic hepatitis B virus (HBV) infection remains a pressing global public health challenge, driving substantial morbidity and mortality through chronic liver disease, cirrhosis, and hepatocellular carcinoma. In 2019, approximately 295.9 million people—3.8% of the global population—were living with chronic HBV, resulting in more than 820,000 deaths, yet only about 6.6 million were receiving antiviral therapy [1]. The World Health Organization (WHO) Global Hepatitis Report 2024 highlights persistent obstacles in achieving elimination goals, particularly in low- and middle-income countries where access to diagnosis and treatment remains limited [2]. These gaps represent a major barrier to achieving the United Nations Sustainable Development Goal (SDG) of ending viral hepatitis as a public health threat by 2030.

Vietnam continues to face one of the highest HBV burdens in the Western Pacific region. A recent community-based seroprevalence survey reported HBsAg prevalence at 7.5% and evidence of past HBV exposure in nearly 50% of the population [3]. Such high prevalence not only places millions of individuals

Key Messages

Over one in eight Vietnamese CHB patients with normal ALT had significant fibrosis.

ALT-based monitoring alone may be insufficient to identify all treatment-eligible patients, highlighting the need for additional risk stratification tools.

WHO 2024 guidelines expand eligibility: 34% qualified vs. 23% under Vietnam 2019 criteria.

Integrating non-invasive fibrosis assessment into national HBV programs can accelerate elimination progress.

at risk for cirrhosis and liver cancer but also poses significant strain on the health system. HBV's natural course is complex—progressing through immune tolerance, immune clearance, inactive carrier, and reactivation phases—and patients in so-called "low-risk" phases may still progress silently to advanced liver disease[4]. Studies have shown that even among patients with normal aminotransferases, up to one quarter may already have moderate-to-severe histologic disease [5, 6]. From a public health perspective, these findings suggest that reliance on liver enzyme testing alone risks missing a substantial proportion of patients in need of earlier intervention.

Effective antiviral therapy is available and proven to reduce the risk of cirrhosis and hepatocellular carcinoma[4]. However, guidelines from AASLD, EASL, APASL, and Vietnam's Ministry of Health emphasize that treatment eligibility should not be based solely on ALT or HBV DNA, but rather should incorporate fibrosis stage, age, family history, and other clinical factors [7, 8]. In practice, many health facilities—especially at the district and provincial levels—continue to depend primarily on liver enzyme monitoring, reflecting limitations in health system resources and diagnostic infrastructure. Wider adoption of non-invasive tools such as transient elastography (FibroScan®) could help bridge this gap, providing an accurate and accessible method for fibrosis staging that can be integrated into public health programs [9].

Despite Vietnam's high HBV prevalence and recent progress in vaccination and surveillance, limited data exist on the burden of fibrosis among patients with persistently normal aminotransferases. This knowledge gap has important public health implications because without accurate detection of silent fibrosis, opportunities for early treatment and prevention of cirrhosis may be missed. Addressing this challenge is critical to advancing HBV micro-elimination strategies and achieving equitable health outcomes. Accordingly, this study aims to *1) assess the distribution of fibrosis stages using transient elastography among chronic HBV patients with normal aminotransferases; 2) identify factors associated with significant fibrosis (≥ F2); and 3) examine associations between liver stiffness and clinical or laboratory markers such as age, platelet count, and HBV DNA levels.*

2. METHODS

2.1. Study Population and Setting

The study included adults aged ≥18 years with chronic hepatitis B virus (HBV) infection, normal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and no history of antiviral therapy. The sampling frame was patients meeting these criteria who attended the Gastroenterology Clinic of 115 People's Hospital, Ho Chi Minh City, between April 2024 and March 2025. Eligible participants were enrolled consecutively.

Chronic HBV infection was defined as persistent positivity for hepatitis B surface antigen (HBsAg) and/or detectable HBV DNA for ≥ 6 months, or positivity for HBsAg with negativity for anti-HBc IgM. Normal aminotransferase levels were defined as AST, ALT < 25 IU/L for women and < 35 IU/L for men[10]. Serum ALT and AST levels were measured at the time of study enrollment and FibroScan assessment. Classification of patients according to aminotransferase status was based on these baseline measurements, as longitudinal aminotransferase data were not consistently available. Participants were required to be treatment-naïve, not receiving medications known to lower aminotransferase levels, and to have complete laboratory and imaging results (blood count, ALT, AST, HBV DNA, HBeAg, anti-HCV, abdominal ultrasound, and FibroScan®). Written informed consent was obtained from all participants.

Exclusion criteria were alternative causes of liver fibrosis, including anti-HCV positivity, hepatic steatosis on ultrasound, or significant alcohol use (≥ 20 g/day or ≥ 140 g/week for men; ≥ 10 g/day or ≥ 70 g/week for women for at least two consecutive years) [11]. Patients were also excluded if they had autoimmune hepatitis (e.g., fatigue, anorexia, myalgia, arthralgia), hemochromatosis (skin hyperpigmentation or hepatosplenomegaly)[12], Wilson's disease (tremors, movement disorders, or Kayser–Fleischer rings) [13], or if they were pregnant or breastfeeding.

2.2. Study Design and Sample Size

We conducted a cross-sectional study. The required sample size was calculated using the single-proportion formula with a 95% confidence level (Z = 1.96), a precision of 6%, and an estimated prevalence of significant fibrosis (≥F2) of 28.7% based on a previous study in Spain[5]. The minimum required sample size was 219 participants. A consecutive sampling method was used until the target was achieved.

2.3. Data Collection and Measures

Data were collected using structured case report forms, including demographics (age, sex, anthropometrics), clinical history (hypertension, diabetes, dyslipidemia, family history of HBV or

hepatocellular carcinoma), duration of HBV infection, and alcohol use. Laboratory assessments included complete blood count, ALT, AST, HBeAg, HBV DNA, and anti-HCV. Abdominal ultrasound was performed in all participants.

Liver fibrosis was assessed using transient elastography (FibroScan®, Echosens, Paris, France) performed by a single experienced radiologist using the M probe. Measurements were obtained from the right lobe through the intercostal space. Each patient underwent at least 10 valid measurements; results were considered reliable if the success rate exceeded 60% and the interquartile range (IQR) was < 30% of the median liver stiffness measurement (LSM). Fibrosis stages were classified according to the 2019 Vietnam Ministry of Health guidelines: F0 - F1 (<7.0 kPa), F2 (7.0 - < 9.5 kPa), F3 (9.5 - < 11.0 kPa), and F4 (≥11.0 kPa) [10].

2.4. Statistical Analysis

Data were entered into Microsoft Excel 2019 and analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on distribution. Categorical variables were reported as frequencies and percentages. Comparisons between groups were conducted using Student's *t* test or Mann–Whitney U test for continuous variables and chi-square test for categorical variables. Factors associated with significant fibrosis (≥ F2) were examined using univariable and multivariable logistic regression. Variables with $p < 0.10$ in univariable analyses were entered into the multivariable model. Statistical significance was set at $p < 0.05$. Variables were selected for inclusion in the multivariable logistic regression model based on clinical relevance, prior evidence from the literature, and their association with the outcome in univariable analyses. Potential confounders considered in regression analysis included age, sex, body mass index (BMI), diabetes, hypertension, platelet count, and HBV DNA level. Missing data were minimal (<5% for all variables). Patients with missing values were excluded from regression analyses but included in descriptive statistics.

2.5. Ethical Considerations

The study adhered to the principles of the Declaration of Helsinki. As an observational, non-interventional study, no additional risks were posed to participants. All patients were informed of the study objectives and procedures and provided written informed consent prior to enrollment. Personal identifiers were removed, and data were coded to maintain confidentiality throughout the study. Ethical approval was obtained from the Institutional Review Board of 115 People's Hospital, Ho Chi Minh City.

3. RESULTS

3.1. Characteristics of the patients enrolled in the study

Between April 2024 and March 2025, a total of 220 patients with chronic hepatitis B infection and normal ALT and AST levels were enrolled. The baseline characteristics are summarized in Table 1.

Table 1. Baseline clinical, laboratory, and virological characteristics of patients with chronic hepatitis B (n = 220)

Characteristics	Values
Demographics	
Age (years), mean ± SD	41.95 ± 11.29
Age groups, n (%)	
< 30 years	29 (13.2%)
30 - 44 years	118 (53.6%)
45 - 60 years	60 (27.3%)
> 60 years	13 (5.9%)
Sex Female, n (%)	131 (59.5%)
Clinical characteristics	
Duration of HBV infection, n (%)	
6 months - 5 years	24 (10.9%)
5 - 10 years	75 (34.1%)
> 10 years	121 (55.0%)

Past medical history, n (%)	
None	140 (63.6%)
Family history of HCC/cirrhosis/HBV	86 (39.1%)
Hypertension	26 (11.8%)
Hyperlipidemia	17 (7.7%)
Diabetes mellitus	13 (5.9%)
Other comorbidities (e.g., gastritis, varices)	45 (20.5%)
BMI (kg/m²), median (IQR)	21.60 (20.0 - 23.5)
WHO BMI Classification, n (%)	
Normal (18.5 - 22.9)	145 (65.9%)
Overweight (23 - 24.9)	54 (24.5%)
Obese (25 - 29.9)	21 (9.5%)
Laboratory and imaging characteristics	
Platelet counts (K/µL), median (IQR)	236 (200 - 283)
AST (U/L), median (IQR)	21.28 (18.42 - 24.00)
ALT (U/L), mean ± SD	20.74 ± 5.78
HBeAg, n (%)	56 (25.5%)
HBV DNA levels, n (%)	
Undetectable	99 (45.0%)
< 2000 IU/ml	56 (25.5%)
2,000 – 20,000 IU/ml	33 (15.0%)
> 20,000 IU/ml	32 (14.5%)
Abdominal sonography, n (%)	
None detected	108 (49.1%)
Others (kidney stone, liver cyst, liver hemangioma, uterine fibroids)	104 (47.3%)
Coarse liver echotexture and/or cirrhosis	7 (3.2%)
Liver stiffness by FibroScan (kPa), median (IQR)	5.50 (4.80 - 6.30)
Fibrosis stage by FibroScan, n (%)	
F0 - F1	190 (86.4%)
F2	27 (12.3%)
F3	3 (1.3%)
F4	0 (0.0%)

The mean age was 41.9 ± 11.3 years, with most participants aged 30 - 60 years (81%). Females accounted for 59.5% of the study population. More than half of patients (55.0%) reported HBV infection for over 10 years. At the time of enrollment, most were asymptomatic, with 58.2% having no clinical symptoms and 65.9% showing no abnormal physical findings. The median body mass index (BMI) was 21.6 kg/m². According to WHO criteria, 65.9% had a normal BMI, with women tending to have lower BMI than men. The median platelet count was 236 × 10^3/µL, and 95% of patients had values ≥ 150 × 10^3/µL. Mean ALT and AST levels were within the normal range (ALT: 20.7 ± 5.8 U/L; AST: 21.3 U/L). The majority of patients were HBeAg negative (74.5%), and 45.0% had undetectable HBV DNA. Abdominal ultrasound revealed abnormalities in 50.5% of cases, though most were extrahepatic; only a small proportion showed changes suggestive of cirrhosis.

3.2. Liver Fibrosis by Transient Elastography

Table 2. Comparison of baseline characteristics according to fibrosis status in patients with chronic hepatitis B (F0 - F1 vs. ≥ F2)

Characteristics	Fibrosis staging		P values
	F0 - F1(n = 190)	≥ F2 (n = 30)	
Sex, n (%)			0.122[a]
Female	117 (61.60%)	14 (46.70%)	
Male	73 (38.40%)	16 (53.30%)	
Age (years), mean ± SD	40.84 ± 10.89	48.93 ± 11.46	**<0.001**[d]
Age groups, n (%)			**0.001**[b]
< 30 years	28 (14.70%)	1 (3.30%)	
30 - 44 years	107 (56.30%)	11 (36.70%)	
45 - 60 years	48 (25.30%)	12 (40.00%)	
> 60 years	7 (3.70%)	6 (20.00%)	
Duration of HBV infection, n (%)		0.847[b]	
6 months - 5 years	22 (11.60%)	2 (6.70%)	
5 - 10 years	64 (33.70%)	11 (36.70%)	
> 10 years	104 (54.70%)	17 (56.70%)	
BMI (kg/m²), median (IQR)	21.55 (19.98 – 23.33)	22.55 (20.90 - 23.83)	0.173[c]
WHO BMI Classification, n (%)			**0.035**[b]
Normal (18.5 - 22.9)	131 (68.90%)	14 (46.70%)	
Overweight (23 - 24.9)	41 (21.60%)	13 (43.30%)	
Obese (25 - 29.9)	18 (9.50%)	3 (10.00%)	
Platelet counts (K/µL), median (IQR)	241 (203 - 287)	208 (144 - 249)	**< 0.001**[c]
Classification of platelet counts, n (%)			**< 0.001**[b]
≥ 150,000/µL	188 (98.90%)	21 (70.00%)	
< 150,000/µL	2 (1.10%)	9 (30.00%)	
AST (U/L), median (IQR)	21.32 (18.40 - 24.00)	21.00 (19.09 - 24.24)	0.830[c]
ALT (U/L), mean ± SD	20.55 ± 5.79	21.96 ± 5.66	0.214[d]
HBeAg, n (%)			**0.004**[a]
Positive	42 (22.10%)	14 (46.70%)	
Negative	148 (77.90%)	16 (53.30%)	
HBV DNA levels, n (%)			**< 0.001**[a]
< 2000 IU/mL	149 (78.40%)	6 (20.00%)	
≥ 2000 IU/mL	41 (21.60%)	24 (80.00%)	

[a]Chi-square test; [b]Fisher's exact test; [c]Mann–Whitney test (non-normally distributed data); [d]Independent-samples t-test (normal distribution)

The median liver stiffness measurement was 5.5 kPa (IQR 4.8 - 6.3), ranging from 2.9 to 10.7 kPa (Table 2). Based on fibrosis staging criteria, 86.4% of patients were classified as F0 - F1, 12.3% as F2 (significant fibrosis), and 1.3% as F3 (advanced fibrosis). No patients had cirrhosis (F4). Overall, 13.6% of participants had significant fibrosis or worse (≥ F2) despite having persistently normal aminotransferase levels.

Compared with patients without fibrosis or with only mild fibrosis (F0 - F1), those with significant fibrosis (≥ F2) were older (mean age 48.9 ± 11.5 vs. 40.8 ± 10.9 years, $p < 0.001$). The prevalence of overweight or obesity was also higher in this group (53.3% vs. 31.1%, $p = 0.035$). Median platelet count was lower among patients with ≥ F2 fibrosis ($208 \times 10^3/\mu L$ vs. $241 \times 10^3/\mu L$, $p < 0.001$), and 30% had thrombocytopenia ($< 150 \times 10^3/\mu L$).

In terms of virological markers, the proportion of HBeAg positivity was greater in the significant fibrosis group (46.7% vs. 22.1%, $p = 0.004$). Likewise, a higher proportion had HBV DNA levels ≥ 2000 IU/mL (80.0% vs. 21.6%, $p < 0.001$). No significant differences were observed in ALT or AST levels between the two groups.

3.3. Factors Associated with Significant Liver Fibrosis

Table 3. Logistic regression analysis of factors associated with significant fibrosis (≥ F2)

Predictors	OR	95% Confidence Interval	P values	Adjusted OR	95% Confidence Interval	P values
Age	1.06	1.03 - 1.10	**< 0.001**[a]	1.06	1.02 - 1.11	**0.002**[b]
BMI	1.14	0.97 - 1.35	0.110[a]	—	—	
Platelet counts (K/µL)	0.98	0.97 - 0.99	**< 0.001**[a]	0.98	0.98 – 0.99	**< 0.001**[b]

[a] Univariable logistic regression; [b] Multivariable logistic regression

In univariable logistic regression, older age (OR: 1.06; 95% CI: 1.03 - 1.10) and lower platelet count (OR: 0.98; 95% CI: 0.97 - 0.99) were significantly associated with fibrosis ≥ F2. In multivariable analysis, age and platelet count remained independent predictors of fibrosis ≥ F2 (Table 3)

3.4. Correlation Between Liver Stiffness and Clinical or Laboratory Parameters

Table 4. Correlation of liver stiffness (kPa) with clinical and laboratory characteristics

Characteristics	r coefficients	p values
Age	0.268	**<0.001**
BMI	0.195	**0.004**
Platelet counts (K/µL)	-0.202	**0.003**
HBV DNA levels (IU/mL)	0.296	**<0.001**

The correlations between liver stiffness measurements (kPa) and selected clinical and laboratory variables are presented in Table 4. Liver stiffness showed weak but statistically significant positive correlations with age ($r = 0.268$, $p < 0.001$), body mass index (BMI) ($r = 0.195$, $p = 0.004$), and HBV DNA levels ($r = 0.296$, $p < 0.001$). Conversely, platelet count demonstrated a weak negative correlation with liver stiffness ($r = –0.202$, $p = 0.003$). Although these associations were statistically significant, all correlation coefficients were below 0.3, indicating only weak relationships between liver stiffness and the examined variables.

3.5. Proportion of Patients Meeting Antiviral Treatment Criteria

Table 5. Proportion of patients eligible for antiviral therapy according to WHO (2024) and Vietnam Ministry of Health (2019) guidelines

Treatment eligibility	Vietnam Ministry of Health 2019	WHO 2024
Fibrosis ≥ F2, HBV DNA ≥ 2,000 IU/mL, and HBeAg (-)	13 (5.91%)	—
Fibrosis ≥ F2, HBV DNA ≥ 20,000 IU/mL, and HBeAg (+)	6 (2.72%)	—
Family history of HCC and/or cirrhosis	32 (14.55%)	32 (14.55%)
Fibrosis ≥ F2	—	30 (13.64%)
Concurrent Diabetes mellitus	—	13 (5.91%)
Total eligible	51 (23.2%)	75 (34.1%)

The proportion of patients eligible for antiviral therapy according to two current guideline systems is presented in Table 5. Based on the 2019 Vietnam Ministry of Health (MOH) guidelines, 23.2% of patients (51/220) met treatment indications. Specifically, 5.9% had significant fibrosis (≥ F2) with HBV DNA ≥ 2000 IU/mL and were HBeAg-negative; 2.7% had significant fibrosis with HBV DNA ≥ 20,000 IU/mL and were HBeAg-positive; and 14.6% had a family history of hepatocellular carcinoma or cirrhosis.

Using the updated World Health Organization (WHO) 2024 guidelines, the proportion of eligible patients increased to 34.1% (75/220). Among

these, 13.6% had significant fibrosis (≥ F2), 5.9% had diabetes mellitus, and 14.6% reported a family history of liver disease.

4. DISCUSSION

In this cross-sectional study, we found that while the majority had minimal fibrosis (F0–F1, 86.4%), a clinically significant proportion already showed evidence of significant (F2, 12.3%) or advanced (F3, 1.3%) fibrosis, despite the absence of elevated liver enzymes. Several factors differed significantly between patients with and without significant fibrosis, including age, body mass index (BMI), HBeAg status, platelet count, and HBV DNA levels. Liver stiffness was positively correlated with age, BMI, and HBV DNA, and negatively correlated with platelet count. Importantly, age emerged as an independent predictor of fibrosis ≥ F2 (OR 1.06; 95% CI 1.02 - 1.11), underscoring that the risk of liver damage increases progressively with advancing age, even among asymptomatic individuals with normal aminotransferases. From a public health perspective, these findings highlight the limitations of relying solely on ALT for patient monitoring and treatment eligibility, and strengthen the case for incorporating non-invasive fibrosis assessment into HBV control programs to prevent missed opportunities for early intervention.

In this study, the median liver stiffness among chronic hepatitis B (CHB) patients with normal aminotransferases was 5.5 kPa, comparable to findings from Vietnam (5.3 kPa) [14] and lower than values reported in Spain (6.3 ± 5.8 kPa) [5]. The lower stiffness in our cohort may reflect exclusion of patients with hepatic steatosis or significant alcohol use—both known contributors to increased stiffness [11]. Although most patients (86.4%) were classified as F0 - F1, a notable 13.6% had significant or advanced fibrosis (≥ F2). This aligns with prior biopsy-based studies showing that 20 - 30% of CHB patients with persistently normal ALT still had histological fibrosis ≥ F2 [15]. Kumar et al. reported a higher prevalence (56.6%) in India, which may be attributable to older ALT cutoffs (40 U/L) and reliance on biopsy rather than transient elastography [16]. San Juan López et al. also observed higher rates, likely influenced by different fibrosis cutoffs (≥ 7.9 kPa) and higher obesity prevalence (62% vs. 9.5% in our study) [5]. These findings highlight that even patients with normal ALT may harbor progressive disease, underscoring the need for comprehensive fibrosis assessment in CHB management. However, FibroScan cutoff values for fibrosis staging in chronic hepatitis B are not fully standardized, and alternative thresholds have been proposed in international studies and guidelines. Variations in study populations, histological reference standards, disease activity, and methodological approaches may contribute to differences in the reported optimal liver stiffness thresholds. Accordingly, the estimated prevalence of significant fibrosis in our cohort may be influenced by the cutoff values applied. The use of higher thresholds for F2 would be expected to decrease the proportion of patients classified as having significant fibrosis, whereas lower thresholds would increase prevalence estimates. Therefore, direct comparisons of fibrosis prevalence across studies should be interpreted with caution when different liver stiffness criteria are used. Nevertheless, the principal finding that a subset of patients with normal aminotransferase levels harbor clinically significant fibrosis is unlikely to be materially altered by modest variations in FibroScan thresholds.

We identified older age and lower platelet count as independent predictors of significant fibrosis. Each additional year of age increased the risk of fibrosis by 6%, consistent with prior evidence that host factors such as age, sex, and family history shape fibrosis progression [17, 18]. Similar findings have been reported in China and Korea, where older patients showed more advanced histological changes despite normal ALT [19, 20]. BMI was also higher in patients with fibrosis ≥ F2. This association is consistent with evidence linking metabolic syndrome and obesity with fibrosis progression in CHB [21-23]. Metabolic cofactors may act synergistically with HBV to accelerate fibrogenesis, even in the absence of elevated liver enzymes.

Platelet count was inversely correlated with liver stiffness ($r = –0.202$, $p = 0.003$). This supports its role as a surrogate marker of fibrosis, explained by reduced thrombopoietin synthesis, hypersplenism, or portal hypertension [24-26]. Thrombocytopenia has been widely validated as a component of non-invasive fibrosis indices such as APRI and FIB-4, which remain particularly valuable in low-resource settings [27, 28]. Notably, ALT and AST levels did not differ significantly between fibrosis groups, supporting the argument that aminotransferases are unreliable markers of disease severity [29, 30]. Recent data confirm that a substantial proportion of CHB patients with normal ALT exhibit moderate-to-severe histological activity, reinforcing calls to broaden treatment eligibility beyond ALT thresholds [31, 32].

Applying the 2019 Vietnam Ministry of Health (MOH) guidelines, only 23.2% of patients met treatment criteria, whereas the proportion increased to 34.1% under the 2024 WHO guidelines. Notably, application of the WHO 2024 criteria resulted in a 34.1% relative increase in treatment eligibility (10.9% absolute increase), highlighting the potential impact of the revised guidelines on expanding access to antiviral therapy among patients with chronic hepatitis B. This finding suggests that adoption of the updated WHO criteria may substantially increase the number of patients with chronic hepatitis B identified as candidates for antiviral therapy. Such an expansion has important public health implications, particularly in resource-limited settings where treatment access, healthcare capacity, and long-term monitoring strategies must be considered. This reflects a paradigm shift in HBV management, where non-invasive fibrosis assessment and broader clinical criteria identify more patients at risk of progression [2, 7]. Recent studies confirm that earlier antiviral therapy reduces the risk of cirrhosis and hepatocellular carcinoma, even in patients with normal ALT [8, 31]. From a public health perspective, these findings underscore the importance of integrating transient elastography into national HBV programs. FibroScan® offers a scalable and reproducible alternative to biopsy [9,33], and when combined with simple markers like platelet count, can enable effective stratification in resource-limited settings [27]. Wider adoption could prevent missed treatment opportunities and accelerate progress toward HBV elimination goals by 2030 [2]. However, expanding treatment eligibility would also increase demands on healthcare systems, including costs related to antiviral therapy, patient monitoring, and long-term follow-up. Therefore, decisions regarding the adoption of expanded treatment criteria should consider not only their potential clinical benefits but also their affordability, feasibility, and cost-effectiveness within the local healthcare context. Future studies evaluating the cost-effectiveness of expanded treatment strategies and broader use of non-invasive fibrosis assessment in resource-limited settings are needed to inform national HBV elimination policies.

This study has several limitations. First, it was conducted among outpatients at a single tertiary hospital in Ho Chi Minh City, which may limit the generalizability of findings to all chronic hepatitis B patients in Vietnam. Hospitalized patients, who often have more severe or complex disease, were not represented and may have a different fibrosis burden. However, outpatients constitute the majority of individuals living with chronic HBV in the community, and their clinical profile may be more comparable to the general population, particularly for public health surveillance and programmatic planning. Future studies with larger, multicenter cohorts will be important to confirm and extend these findings.

Second, liver fibrosis was assessed exclusively with transient elastography (FibroScan®). Although FibroScan is a reliable, non-invasive method that is highly suitable for large-scale screening and public health programs, it cannot fully replace liver biopsy, the histological gold standard. Biopsy, however, is invasive, carries procedural risks, and is not realistic for routine practice or population-level studies. As such, the reliance on FibroScan may have underestimated the true prevalence of fibrosis in this cohort. However, its accuracy is lower for intermediate fibrosis stages, particularly F2, where overlap in liver stiffness values between adjacent fibrosis stages may result in misclassification. Consequently, some patients categorized as having significant fibrosis may have been overestimated, whereas others with true significant fibrosis may have been underestimated. Several factors may influence liver stiffness measurements independently of fibrosis severity, including hepatic inflammation, steatosis, cholestasis, hepatic congestion, and technical variability. Although our study excluded patients with conditions known to markedly affect liver stiffness measurements, residual measurement error cannot be completely excluded. Therefore, the reported prevalence of significant fibrosis should be interpreted with caution.The liver stiffness cutoffs applied in this study were selected from previously published studies and international clinical practice recommendations for chronic hepatitis B. However, because optimal FibroScan thresholds may vary according to patient characteristics, disease phase, and ethnicity, further studies incorporating liver biopsy are needed to validate the most appropriate cutoff values for Vietnamese patients with chronic hepatitis B, particularly those with normal aminotransferase levels.

Third, the limitation of this study is that aminotransferase status was determined using a single measurement obtained at the time of enrollment. Because serial ALT and AST measurements were not available, some patients with fluctuating hepatitis activity may have been misclassified, potentially affecting the estimated prevalence of significant fibrosis among patients

with normal aminotransferase levels.

5. CONCLUSION

A notable proportion of patients with chronic hepatitis B and normal ALT levels had significant fibrosis despite apparently normal biochemical profiles. This finding highlights the limitations of ALT-based monitoring and supports the integration of non-invasive fibrosis assessment into routine HBV care in Vietnam to improve early detection of patients at risk of progressive liver disease.

Acknowledgements

The authors thank the clinical staff of the Gastroenterology Clinic, 115 People's Hospital, Ho Chi Minh City, for their support in patient recruitment and data collection. We also acknowledge the patients who generously participated in this study.

Author Contributions

Truong Thi Ai Phuong: Conceptualization, Methodology, Data Curation, Formal Analysis, Writing – Original Draft.

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Pham Quang Thien Phu: Methodology, Investigation, Data Collection, Project Administration.

Tran Vy Thao: Writing – Original Draft, Writing – Review & Editing, Visualization.

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Tran Kinh Thanh: Conceptualization, Methodology, Supervision, Formal Analysis, Writing – Review & Editing, Project Administration.

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Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of 115 People's Hospital, Ho Chi Minh City (Approval No. [insert number]). Written informed consent was obtained from all participants prior to enrollment.

Data Availability

The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

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The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

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