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ORIGINAL RESEARCH

Non-Invasive Monitoring of the Impact of Low-Level Viremia on Liver Fibrosis in Treated Chronic Hepatitis B Patients

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Background: Chronic hepatitis B (CHB) presents a global health challenge due to its potential to cause severe liver conditions such as hepatocellular carcinoma (HCC) and cirrhosis. Prior research has established a correlation between CHB infection with low-level viremia (LLV) and liver disease progression, such as increased HCC incidence. This study aims to investigate whether LLV during treatment with nucleos(t)ide analogs (NAs) contributes to the accelerated progression of liver fibrosis (LF).

Methods: This retrospective cohort study at Jinhua Central Hospital focused on CHB patients undergone NA monotherapy for over 96 weeks. Patients were categorized into maintained virological response (MVR) and LLV groups based on hepatitis B virus (HBV) DNA levels. The study assessed LF using various markers and methods, including chitinase 3-like 1 protein (CHI3L1), aspartate aminotransferase-to-platelet ratio index (APRI), fibrosis-4 (FIB-4) score, and transient elastography.

Results: Analysis was conducted on 92 CHB patients, categorized into LLV (n=42) and MVR (n=50) groups, following the exclusion of 101 patients for various reasons. Significant findings included lower baseline HBV DNA in MVR (<20 IU/mL) compared to LLV (67.8 IU/mL, P<0.001) and different AST/ALT ratios (LLV: 1.1, MVR: 1.36, P=0.011). LF was assessed using CHI3L1, FIB-4, and APRI, with LLV showing a higher baseline CHI3L1 (LLV:83.3 ng/mL vs MVR: 54.5 ng/mL, P=0.016) and scores compared to MVR, indicative of fibrosis. CHI3L1 levels in LLV were higher at baseline and weeks 48, 72, and 96 than MVR, with significance at baseline (P=0.038) and week 48 (P=0.034). Liver stiffness measurement (LSM) showed a time-dependent decline in both groups but no significant intergroup differences.

Conclusion: Non-invasive monitoring of CHB patients who have received treatment indicates that LLV contributes to the progression of LF, necessitating proactive adjustment of antiviral treatment strategies.

Keywords: chronic hepatitis B, low-level viremia, liver fibrosis, non-invasive methods, treatment strategies

Introduction

Chronic Hepatitis B (CHB) presents a global health challenge, contributing significantly to global morbidity and mortality rates.[1] The major concern regarding CHB is its potential progression to severe liver conditions such as hepatocellular carcinoma (HCC) and cirrhosis.[2]

Nucleic acid testing technology advancements, particularly high-sensitivity hepatitis B virus (HBV)-DNA testing techniques, have achieved a detection limit of 10 IU/mL.[3] This advancement raises the possibility that some patients, previously categorized as having achieved a complete virological response, might be false negatives. Moreover, these technological improvements facilitate the identification of more patients exhibiting low-level viremia (LLV) following treatment with nucleos(t)ide analogs (NAs).[4]

Currently, there is no international consensus on defining LLV; definitions vary across different guidelines and among researchers. Both domestic and international treatment guidelines and consensus statements suggest that patients experiencing LLV (< 2000 IU/mL) during monotherapy with tenofovir or entecavir should continue their monotherapy,

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regardless of alanine aminotransferase (ALT) levels. However, it is important to note that the evidence supporting this recommendation is low.[5–7]

Furthermore, there is a lack of comprehensive clinical data to determine whether the occurrence of LLV during CHB monotherapy with entecavir or tenofovir is a benign outcome. Therefore, this study aims to determine if the presence of LLV during treatment with NAs contributes to the accelerated progression of liver fibrosis (LF). It evaluates the impact of persistent LLV on LF by monitoring dynamic changes in fibrosis markers such as serum chitinase 3-like 1 protein (CHI3L1), aspartate aminotransferase-to-platelet ratio index (APRI), and fibrosis-4 (FIB-4), providing evidence-based medical grounds for further diagnostic and treatment strategy adjustments.

Patients and Methods

Study Design, Setting, and Patients

This retrospective cohort study was conducted with CHB patients treated at Jinhua Central Hospital. A total of 193 patients who received monotherapy with NAs between January 2019 and September 2023 were selected for the study. Eligible patients had undergone NA monotherapy for over 96 weeks, including cases with maintained virologic response (MVR) and LLV. The study involved dynamic monitoring of various biomarkers, including HBV DNA, CHI3L1, platelet count, and liver function tests. Additionally, liver stiffness measurements (LSMs) were conducted using transient elastography (FibroScan®).

The study included 92 patients based on the following inclusion criteria: 1) Adults aged ≥18 years; 2) Diagnosis of CHB, including both HBeAg negative and positive patients; 3) Presence of LLV, with hepatitis B viral levels maintained between 20 and 2000 IU/mL after 96 weeks of treatment; 4) Absence of cirrhosis or malignancy, including HCC, at baseline; 5) No coinfection with human immunodeficiency virus or hepatitis C virus; 6) Undergoing monotherapy with either tenofovir (300mg) or entecavir (0.5mg).

Exclusion criteria were: 1) Patients with less than 1 year of follow-up; 2) Patients experiencing an increase in HBV DNA levels to ≥2000 IU/mL during follow-up or who had a reduction to <2000 IU/mL followed by an increase, indicative of resistance; 3) Presence of coexisting conditions such as hepatitis C, autoimmune liver disease, fatty liver, or other liver diseases; 4) History of alcohol abuse; 5) Poor treatment adherence, characterized by irregular medication intake or failure to maintain outpatient follow-up.

A detailed analysis was then performed on the 92 eligible adults with CHB who had been under tenofovir/entecavir monotherapy for over a year (Figure 1). The study was performed in accordance with the ethics principles of Declaration of Helsinki and good clinical practice guidelines. The study protocol was approved by the Ethics Review Committee of Jinhua Central Hospital (Ethics approval number: 2023–173) and the informed patient consent requirement was waived due to the retrospective nature of the study.

Study Variables and Definitions

A comprehensive review of patient data was conducted to determine patient eligibility for the study. This review included assessments of age, gender, medical history, and regular hematological chemistry indices. The hematological chemistry indices assessed were aspartate aminotransferase (AST), serum platelet count (PLT), ALT, HBV DNA levels, and CHI3L1. LSMs obtained through liver elastography (FibroScan®) were also incorporated into the analysis. During the follow-up period of each patient, HBV DNA levels were systematically collected and analyzed, typically monitored at intervals of three to six months. Quantitative analysis of serum HBV DNA was performed using real-time polymerase chain reaction (PCR) with a lower limit of detection (LLOD) of 20 IU/mL.

Patients were categorized into two groups based on their HBV DNA levels during follow-up: the MVR group and the LLV group. MVR was defined as patients who, following the achievement of a complete virologic response (CVR, indicated by HBV DNA levels below 20 IU/mL), maintained undetectable HBV DNA throughout the entire follow-up period. In this study, 50 patients were identified as having achieved MVR status. Patients who exhibited persistent or intermittent detectable HBV DNA levels of less than 2000 IU/mL were classified as LLV group, comprising 42 patients.

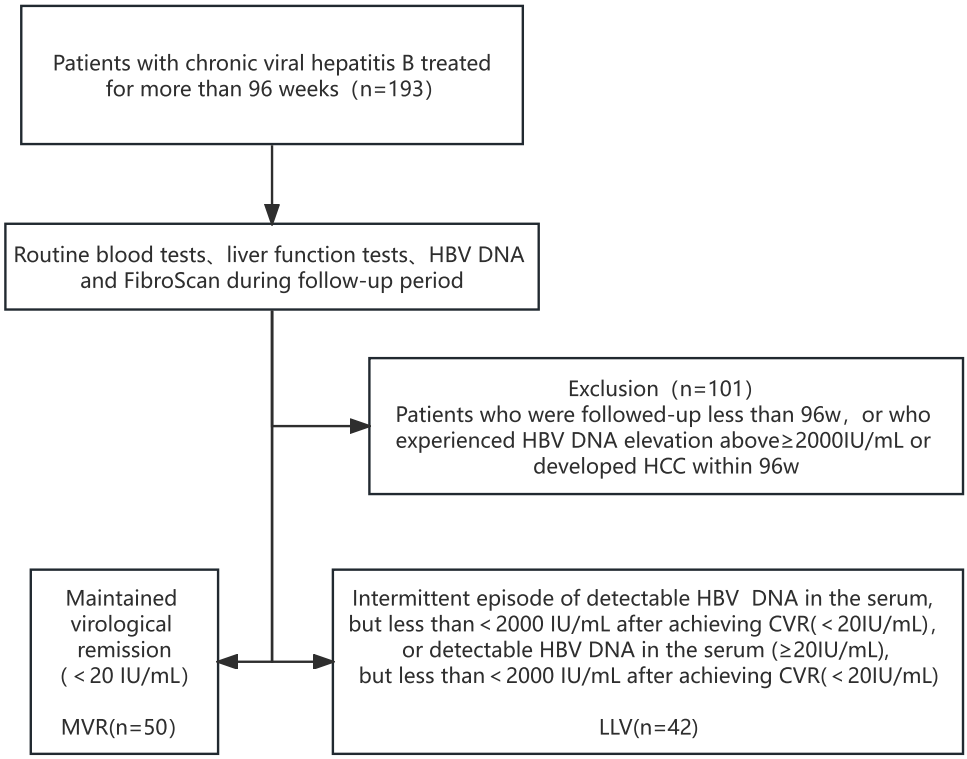

Figure 1 Patient flowchart. A total of 92 adult chronic hepatitis B patients treated with nucleos(t)ide analogs monotherapy for more than 96 weeks were analyzed.

Statistical Analyses

To compare baseline characteristics between the LLV and the MVR groups, numerical variables were first subjected to a normality distribution test. In cases where both groups satisfied a normal distribution, the mean (standard deviation) was used for statistical description, and *t*-tests were applied for intergroup comparisons. For data not conforming to a normal distribution, the median (P25, P75) was employed for description, and non-parametric tests were used for intergroup comparisons. Categorical data were described using frequencies or proportions, with chi-square tests or Fisher's exact tests used for intergroup comparisons. Intergroup significance was evaluated using one-way ANOVA analysis, with a P-value < 0.05 considered statistically significant.

Data processing and analysis were conducted using SPSS Version 26.0 (IBM Corp., NY, USA), and data visualization was performed using GraphPad Prism 8 (Dotmatics, Boston, Massachusetts, USA).

Results

Patient Characteristic

After excluding 101 cases due to incomplete data, follow-up time less than 96 weeks, viral loads exceeding 2000 IU/mL, or progression to HCC, the study included 92 subjects comprising 42 patients in the LLV group and 50 in the MVR group. The mean age in the LLV group was 43.8±10.5 years, with 31 male patients (73.8%), while the MVR group had a mean age of 58.8±14.2 years, with 27 male patients (54.0%) (Table 1). Patients in both groups were treated with monotherapy, either entecavir (0.5 mg) or tenofovir (300 mg). In the LLV group, 23 patients (54.8%) received entecavir, compared to 26 patients (52.0%) in the MVR group (P-value > 0.05).

All patients underwent high-sensitivity HBV DNA testing, with a <20 IU/mL detection limit. At baseline, the mean HBV DNA level in the LLV group was 67.8 IU/mL (range: 30.1 to 260.5 IU/mL), while the MVR group had undetectable levels (P<0.001). The serum AST/ALT ratio in the LLV group was 1.1 ± 0.5, compared to 1.36 ± 0.4 in the MVR group (P=0.011). Platelet counts were 169.7 ± 57.9 x 10^9/L in the LLV group and 177.2 ± 91.8 x 10^9/L in the MVR group, with no significant statistical difference. Ferritin levels were measured at 107.4 ng/mL (range: 18.9 to 778.9

Table 1 Baseline Characteristics of the Study Population

	LLV (n=42)	MVR (n=50)	p
Age, years	43.8±10.5	58.8±14.2	0.000
Male, %	31 (73.8%)	27 (54.0%)	0.050
HBVDNA, IU/mL	67.8 (30.1, 260.5)	0.0 (0.0,0.0)	0.000
CHI3L1, ng/mL	83.3 (42.9, 216.0)	54.5 (36.3, 118.0)	0.016
AST/ALT	1.1±0.5	1.36±0.4	0.011
Platelet, 109/L	169.7±57.9	177.2±91.8	0.649
Ferritin, ng/mL	107.4 (18.9, 778.9)	192.2 (128.3, 576.1)	0.344
LSM, kPa	10.3±2.9	9.3±3.3	0.015
FIB-4	3.05 (2.05, 5.20)	1.45 (0.89, 2.11)	0.000
APRI	0.63 (0.45, 1.05)	0.48 (0.33, 0.68)	0.021

Notes: Calculation formula: age (years) × AST (IU/L) / [platelet count (×109/L) ×], the larger the FIB-4 value suggests the more serious degree of liver fibrosis; FIB-4 ≥ 3.25 diagnosis of liver fibrosis and liver inflammation grading Metavir score ≥ F3, FIB-4 < 1.45 exclude Metavir score ≥ F3; APRI=(AST/ULN)×100/PLT (109/L).
Abbreviations: LSM, liver stiffness measurement; FIB-4, Indicator for assessing the degree of liver-related hepatic fibrosis.

ng/mL) in the LLV group and 192.2 ng/mL (range: 128.3 to 576.1 ng/mL) in the MVR group, also demonstrating no significant statistical difference.

The study employed various non-invasive methods to compare and analyze the degree of LF, including serum CHI3L1 measurement, FIB-4 score, APRI score, and transient elastography. Results at baseline showed that the CHI3L1 level in the LLV group was 83.3 ng/mL (range: 42.9 to 216.0 ng/mL), compared to 54.5 ng/mL (range: 36.3 to 118.0 ng/mL) in the MVR group (P=0.016). In the scoring models, the FIB-4 score in the LLV group was 3.05 (range: 2.05 to 5.20), compared to 1.45 (range: 0.89 to 2.11) in the MVR group (P<0.001). The APRI score in the LLV group was 0.63 (range: 0.45 to 1.05), whereas in the MVR group, it was 0.48 (range: 0.33 to 0.68) (P=0.021) (Table 1).

The Progression of Liver Fibrosis Following Nucleos(t)ide Analog Therapy

During the follow-up period, 50 patients achieved MVR. To assess and compare the dynamic changes in LF levels from baseline to week 96, various non-invasive methods were employed for both LLV and MVR patients. The specific results are detailed in Figure 2, which includes data for the two groups: the LLV group (depicted in red) and the MVR group (depicted in black). Each chart in the figure is annotated with significance levels, where asterisks indicate the levels of statistical significance (*P < 0.05, **P < 0.01, ***P < 0.001) and "ns" denotes no statistically significant difference.

Chart A displays the trend of CHI3L1 levels in both the LLV and MVR groups. The LLV group showed a slow decline from baseline and then remained relatively stable, whereas no significant downward trend was observed in the MVR group. The results indicate that the CHI3L1 levels in the LLV group were higher than those in the MVR group at baseline, and 48, 72, and 96 weeks, with statistical differences at baseline (P=0.038) and 48 weeks (P =0.034). Chart B illustrates the trend of LSM values during transient elastography in both LLV and MVR groups over the follow-up period. Both groups showed a downward trend in LSM over time, with a more pronounced decline in the MVR group; however, no significant difference was observed during follow-up. Chart C presents the progression of the APRI score in both the LLV and MVR groups. Throughout the follow-up period, both groups generally showed a decreasing trend in APRI scores. At 72 weeks (LLV:0.799, MVR:0.476, 95% CI 0.002–0.644, P=0.047) and 96 weeks (LLV:0.769, MVR:0.353, 95% CI 0.112–0.721, P=0.003), the APRI scores were higher in the LLV group than those in the MVR

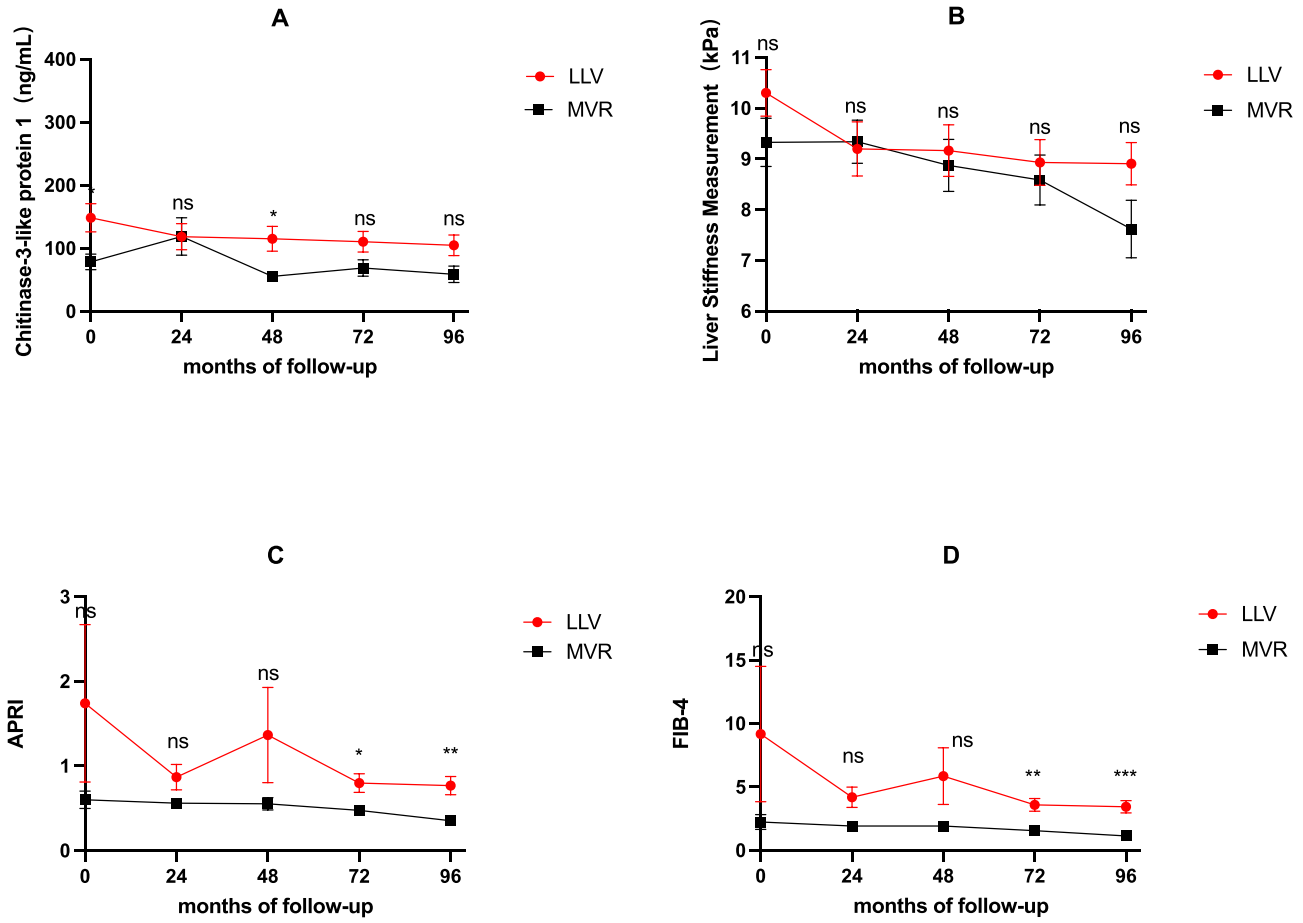

Figure 2 The trend of changes in (**A**) CHI3L1 levels, (**B**) LSM, (**C**) APRI, and (**D**) FIB-4 index in the LLV group and the MVR group, during the 96-week follow-up period. (*Denote p < 0.05, **Denote p < 0.01, ***Denote p < 0.001, "ns" indicates no statistically significant difference).

group. Chart D reveals the trend of the FIB-4 score during the follow-up period, where the FIB-4 score in the LLV group significantly decreased at 24 weeks and then stabilized. At 72 weeks (LLV:3.589, MVR:1.563, 95% CI 0.609–3.442, P=0.002) and 96 weeks (LLV:3.445, MVR:1.146, 95% CI 0.952–3.647, P<0.001), the FIB-4 scores were significantly lower in the MVR group compared to the LLV group.

Discussion

The relationship between LLV and LF progression is critical in treating and managing CHB. Prior research has indicated that after five years of first-line NA treatment in CHB patients, 26.8% exhibit persistent or intermittent low-level HBV DNA (12–2000 IU/mL) in their serum.[8] Studies in China have shown that approximately 30% of entecavir-treated patients for 78 weeks still had detectable low-level HBV DNA (LLOD of 20 IU/mL). Although HBV DNA levels in LLV cases are relatively low, their persistent presence may induce continual liver inflammation. Research by Sun et al suggested that LLV can contribute to liver inflammation and the progression of fibrosis.[9] Additionally, advancements in detection technologies imply that some patients previously categorized as HBV DNA negative might have low-level viral replication.[10] Therefore, comprehensive research on LLV holds significant clinical value.

In this study, all patients underwent at least one year of monotherapy antiviral treatment with NAs, and serum HBV DNA quantification was performed. Of the 92 included patients, 42 were in an LLV state, with an average baseline HBV DNA level of 67.8 IU/mL (range: 30.1 to 260.5 IU/mL). LLV patients displayed either persistent or intermittent LLV during follow-up. Liver function was assessed using the AST/ALT ratio, and the results indicated that the baseline AST/ALT ratios were 1.1 ± 0.5 for the LLV group and 1.36 ± 0.4 for the MVR group (P=0.011), both exceeding 1, suggesting the release of enzymes from the cytoplasm and mitochondria into the blood, associated with chronic active hepatitis.[11]

Although current research suggests that treatment with NAs can improve LF in most CHB patients and continuously improve hepatic histology, a small proportion still experiences progression of LF.[12–14] Studies have indicated that patients with positive HBV DNA (20–200 IU/mL) at 78 weeks of ETV treatment are more likely to experience LF progression compared to those with negative HBV DNA.[9] This study employed various non-invasive methods to compare and analyze LF, including measurement of serum CHI3L1, calculation of FIB-4 score and APRI score, and transient elastography. Although hepatic histology is a more accurate indicator of LF progression and assessment, non-invasive methods offer ample benefits for long-term follow-up and clinical evaluation of CHB patients, improving patient compliance. CHI3L1, a glycoprotein secreted by various liver cells, including hepatic stellate cells, is involved in various inflammatory and fibrotic processes.[15] The hepatic stellate cell activation during LF results in increased production of extracellular matrix proteins such as collagen, and the elevated expression of CHI3L1 is closely associated with this process.[16] Therefore, CHI3L1 is considered a biomarker for LF progression. Measuring serum CHI3L1 levels may thus aid in assessing the degree of LF in chronic liver disease (CLD) patients.[17,18]

The APRI score, calculated based on the ratio of AST to PLT, is used to assess the risk of cirrhosis in adults.[19,20] An APRI score > 2 is indicative of a potential risk of cirrhosis.[21,22] The FIB-4 index, a straightforward and non-invasive method, assesses the degree of LF in patients with CLD by integrating factors such as ALT, AST, PLT, and patient age.[23] For CHB or C patients, a FIB-4 index < 1.45 usually indicates either no significant fibrosis or only mild fibrosis (< grade 2), correlating with a 94.7% concordance rate with liver biopsy pathological results,[24]; whereas a FIB-4 index > 3.25 is suggestive of moderate to severe fibrosis (grade ≥ 3), with an 82.1% concordance rate.[25] Consistent with the 2015 World Health Organization guidelines, the FIB-4 and APRI are recommended for evaluating LF in patients with CHB.[26] Alongside biochemical and virological markers, transient elastography, an important non-invasive assessment method, contributes significantly to LF evaluation.[27,28] TE assesses LF by LSM values. In this study, at baseline, CHI3L1, LSM, APRI, and FIB-4 scores were higher in the LLV group compared to the MVR group. However, only the serum CHI3L1 level showed a statistically significant difference (P=0.016). After 96 weeks of antiviral therapy, both groups demonstrated a decrease in CHI3L1, LSM, APRI, and FIB-4 scores. At 96 weeks, both APRI (LLV: 0.769 vs MVR: 0.353, 95% CI 0.112–0.721, P=0.003) and FIB-4 scores (LLV: 3.445 vs MVR: 1.146, 95% CI 0.952–3.647, P<0.001) were significantly higher in the LLV group. The baseline average age was significantly different between the LLV (43.8 ± 10.5 years) and MVR (58.8 ± 14.2 years) groups (P<0.001). While simple serological markers and transient elastography are useful, they may not fully account for the impact of age on experimental results. Scoring models like FIB-4, which incorporate multiple serological markers and patient age, offer an advantage in providing a comprehensive assessment of LF in patients.

There were several studies indicating that LLV promotes progression of liver fibrosis in CHB patients. A study conducted by Sun et al identified that among 163 patients (Ishak≥stage3) with significant fibrosis at baseline, 22 patients (13%) exhibited progression of hepatic fibrosis following liver biopsy both before and after 78 weeks of ETV treatment in a cohort of 239 patients with CHB. Furthermore, the proportion of HBV DNA-positive patients who experienced liver fibrosis progression after 78 weeks of ETV treatment was significantly higher compared to HBV DNA-negative patients (27% vs 6%, p=0.004).[9] Our study found that at baseline and at weeks 48, 72, and 96, the CHI3L1 levels in LLV patients were higher than those in MVR patients. Additionally, LSM showed a decrease in liver stiffness over time in both groups, indicating that the rate of cirrhosis improvement in LLV patients is lower compared to that in MVR patients. Another retrospective study also revealed that LLV and cirrhosis are independent risk factors for end-stage liver disease.[10]

There is currently no consensus or uniform international guideline on the management of LLV in CHB patients who are undergoing treatment with NAs. The 2016 Korean guidelines suggest either switching to another high-barrier antiviral drug or continuing the current treatment for patients already on high-barrier antivirals, though the evidence supporting this recommendation is limited.[29] The 2016 Asia-Pacific Association for the Study of the Liver (APASL) guidelines[30] and the 2017 European Association for the Study of the Liver (EASL) guidelines[5] do not provide specific subsequent treatment plans for such cases. The 2018 American Association for the Study of Liver Diseases (AASLD) guidelines[7] recommend continuing monotherapy with entecavir or tenofovir in LLV cases (< 2000 IU/mL) without considering ALT levels, but the evidence level for this recommendation is low. According to the 2022 version of the Chinese guidelines for the prevention and treatment of CHB,[6] for patients on monotherapy, if HBV DNA is over 20 IU/mL after 48 weeks of treatment and issues of compliance and testing errors are excluded, an adjustment in the NAs treatment plan or the addition of polyethylene glycol interferon-alpha (Peg-IFN-α) treatment may be considered.

In this study, all patients underwent more than 48 weeks of NAs monotherapy, demonstrating good compliance and regular follow-up visits. Throughout the 96-week follow-up period, non-invasive tests – including serological markers, liver elasticity measurements, and serum parameter model scores – showed a decline in both groups. This trend suggests the efficacy of antiviral treatment in reducing LF. However, at the 96-week follow-up, all non-invasive test results in the LLV group were higher compared to those in the MVR group. The average HBV DNA level in the LLV group was recorded at 0.000 IU/mL (range: 0.000 to 35.468 IU/mL). This finding indicates that the presence of LLV may contribute to the progression of LF in patients with CHB, potentially increasing the risk of adverse outcomes.

Our study assesses the impact of long-term hypoviremia on liver fibrosis in treated patients with CHB in a non-invasive methods, which is instructive for clinical work. Non-invasive monitoring tools are useful in clinical work to enhance patient compliance and facilitate long-term management of patients. However, because this study is a single-center retrospective study, it may reduce the reliability of the results, thus large-sample, multicenter, prospective studies are needed to further validate the validity of CHI3L1, LSM, APRI and FIB-4 scores in clinical practice.

Conclusion

Monitoring CHB patients using non-invasive methods has shown that LLV contributes to the progression of LF. This observation underscores the need for proactive adjustments in antiviral treatment strategies to better manage this condition.

Abbreviations

CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; LLV, low-level viremia; NAs, nucleos(t)ide analogs; LF, liver fibrosis; MVR, maintained virological response; LLV, low-level viremia; HBV, hepatitis B virus; CHI3L1, chitinase 3-like 1 protein; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet count; LSMs, liver stiffness measurements; PCR, polymerase chain reaction; LLOD, lower limit of detection; CVR, complete virologic response.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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