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# Clinical Outcomes and Changes in Renal Function of Chronic Hepatitis B Patients Receiving Oral Antiviral Treatment-a Real-World Study With 6-years Follow-Up

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***Abstract***

***Background:*** *To study the prognosis and renal function changes of patients with chronic hepatitis B who receiving oral antiviral treatment over the past six years .*

***Methods:*** *A retrospective and prospective cohort consisting of 162 patients who regularly took first-line antiviral drugs were diagnosed and treated in the Department of Gastroenterology, Huairou Hospital, Beijing was constructed. From February 2018 to February 2024, Among them, 108 patients were treated with ETV , 54 patients were treated with TDF. Their baseline, 1 year, 2 years, 3 years, 4 years, 5 years, and 6 years' HBV-DNA, kidney function, blood routine, coagulation function, blood calcium, blood phosphorus, β 2-microglobulin, and glomerular filtration rate (eGFR) were collected, and the incidence of cirrhosis and hepatocellular carcinoma in the past 6 years were analyzed.*

***Results:*** *162 patients were enrolled, with an average age of (52±10.6) years. Among them, 36 were HBeAg positive and 126 were HBeAg negative. During the 6-year follow-up period, 2 cases died ,One case of liver cancer and three cases of liver cirrhosis occurred in the TDF group..Four cases of liver cancer and four cases of liver cirrhosis occurred in the ETV group. Clearance of hepatitis B surface antigen: 2 cases of surface antigen became negative after NUCs treatment (12 years of treatment), 4 cases of spontaneous negative (of which One case progressed to hepatocellular carcinoma after surface antigen became negative).HBV-DNA status: During the 6-year follow-up period, 3 patients developed hypoviremia (less than 200IU/ml), while the HBV-DNA of remaining patients remained below the detection limit. There was no significant difference in HGB, PLT, ALB, cholinesterase levels,blood calcium, blood phosphorus, blood creatinine, bloodβ2-microglobulin, INR and glomerular filtration rate (eGFR) at 1, 2, 3, 4, 5, and 6 years in two groups of patients (P>0.05).*

***Conclusion:*** *Long term use of ETV and TDF has no significant effect on renal function in patients with hepatitis B. Even if hepatitis B surface antigen (HBsAg) becomes negative, there remains a risk of progression to hepatocellular carcinoma, close clinical monitoring is still necessary.*

**Keywords:** Chronic Hepatitis B, Tenofovir Disoproxil, Entecavir, Renal Function, β2 Microglobulin Hepatocellular Carcinoma.

**Abbreviations**
**ETV:** Entecavir
**TDF:** enofovir Disoproxil Fumarate
**HBV-DNA:** hepatitis B virus-deoxyribonucleic acid

**HGB:** Hemoglobin
**GFR:** Glomerular Filtration Rate
**CHE:** Cholinesterase
**ALB:** Albumin
**INR :** International Normalized Ratio
**β2-MG:** β2-Microglobulin
**Ca:** Calcium
**P:** Phosphorus
**PLT:** Platelet
**Scr:** Serum Creatinine
**HBsAg:** hepatitis B surface antigen
**HBV:** Hepatitis B virus
**CHB:** chronic hepatitis B
**Nas:** nucleosides
**HIV:** Human Immunodeficiency Virus
**HBeAg:** Hepatitis B e Antigen

## Introduction

According to data from the Chinese Center for Disease Control and Prevention, there are over 20 million patients with chronic hepatitis B among the existing chronic HBV infected individuals nationwide. The annual incidence of CHB patients progressing to cirrhosis without antiviral treatment is 2% -10% [1,2].

In areas with high prevalence of HBV, over 80% of hepatocellular carcinoma patients are associated with HBV infection. Active antiviral treatment can reduce the serum HBV DNA load of infected persons, delay or even reverse liver fibrosis, curb the progression of cirrhosis to decompensation, reduce the incidence rate of HCC, and significantly prolong the survival time of CHB patients. Nucleoside analogues are currently the main drugs for antiviral treatment of CHB, with the characteristics of rapid inhibition of HBV replication, convenient oral administration, and good safety. However, reports of related renal damage are gradually increasing, and if not detected and treated in a timely manner, they may cause serious clinical consequences [3-6] .

According to the revised guidelines for the prevention and treatment of chronic hepatitis B in China in 2024, nucleoside ide (NAs) antiviral drugs entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) are recommended as first-line drugs due to their high efficacy and low resistance. Long term ADV or TDF treatment can lead to proximal tubular injury, which may cause low blood phosphorus, osteomalacia. Etc[7-10].

There are different opinions on the impact of ETV on renal function in CHB patients. This study compared the long-term effects of ETV and TDF on renal function by monitoring serum creatinine (sCr), estimated glomerular filtration rate (eGFR), serumβ2-microglobulin in CHB patients. The results are reported as follows [11-14].

## Materials and Methods

### Study Population

Inclusion criteria: 162 chronic hepatitis B patients who received TDF or ETV treatment from March 2018 to March 2024 met the diagnostic criteria of the 2022 Guidelines for the Prevention and Treatment of Chronic Hepatitis B , and the included patients had received NAs treatment for at least 24 months.

**Exclusion criteria:** Acute hepatitis B, organ transplantation, hepatitis C virus or HIV co infection, sepsis or gastrointestinal bleeding, known kidney disease or estimated glomerular filtration rate (eGFR)<60mL/(min.1.73m2), and patients who have used any immunomodulators during antiviral therapy.

### Study Design

Comprehensive medical history collection and clinical examination were conducted at baseline, collecting demographic, clinical characteristics, biochemical, virological indicators, and abdominal ultrasound of patients. Afterwards, follow up every 48 weeks to record blood routine, liver and kidney function, electrolytes, β2-microglobulin, estimated glomerular filtration rate, and HBV-DNA, record the incidence of cirrhosis, Hepatocellular Carcinoma, and comorbidities. Follow up for a total of 6 years (288 weeks). Use the MODULP800 fully automated biochemical analyzer (Roche, Germany) to measure blood biochemical indicators and analyze hemoglobin, platelets, albumin,cholinesterase,creatinine, blood calcium, phospho,β2-microglobulin levels, and estimate glomerular filtration rate at 1, 2, 3, 4, 5 and 6 years of treatment; This study has been approved by the Medical Ethics Committee of Beijing Ditan Hospital,and all patients have signed informed consent forms.

### Detection Method

Serum HBV markers were detected using the Roche Cobas E 601 modular fully automatic electroche miluminescence immunoassay system and its matching reagent kits; serum HBV-DNA was detected by fluorescent quantitative PCR (with a lower detection limit of 40 IU/mL) using the SLAN-48P/96S fully automatic quantitative PCR analyzer provided by Shanghai Hongshi Medical Technology Co,Ltd; serum biochemical indicators were detected using the MODULP800 fully automatic biochemical analyzer (Roche Diagnostics, Germany) and its matching reagents [15].

### Statistical Analysis

Statistical analysis was performed using SPSS 25.0 software. Measurement data approximating a normal distribution were expressed as mean±standard deviation, and comparisons between groups were made using the t-test. Non-normally distributed measurement data were expressed as median. comparisons between groups were made using the Mann-Whitney U test . The chi-square test or Fisher's exact test was utilized for categorical variables. For comparisons among three or more groups, one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was used for normally distributed data, and the Kruskal-Wallis H test was employed for non-normally distributed data. All statistical tests were two-tailed, and P-value□0.05 was considered statistically significant [16].

### Observation Indicators

General information mainly includes demographic data such as gender and age of enrolled patients.The incidence of cirrhosis and hepatocellular carcinoma were recorded.

### Virology and Liver and Kidney Function Indicators

Collect patients' baseline liver and kidney function, blood routine, blood calcium, blood phosphorus, serumβ2-microglobulin and estimate glomerular filtration rate (eGFR) at 1, 2, 3, 4, 5, and 6 years. According to the simplified MDRD fomular, eGFR

is calculated as eGFR[(ml/(min.1.73 m2)]= 175× (creatinine) -1.154×(age) -0.203× (0.742 female)]

## Results

### General Information

162 patients, with an average age of (52±10.6) years, 104 males and 58 females; 108 cases were treated with ETV, 54 cases were treated with TDF, 36 cases were positive for HBeAg, and 126 cases were negative for HBeAg.

The flowchart of case collection is shown in Figure 1.

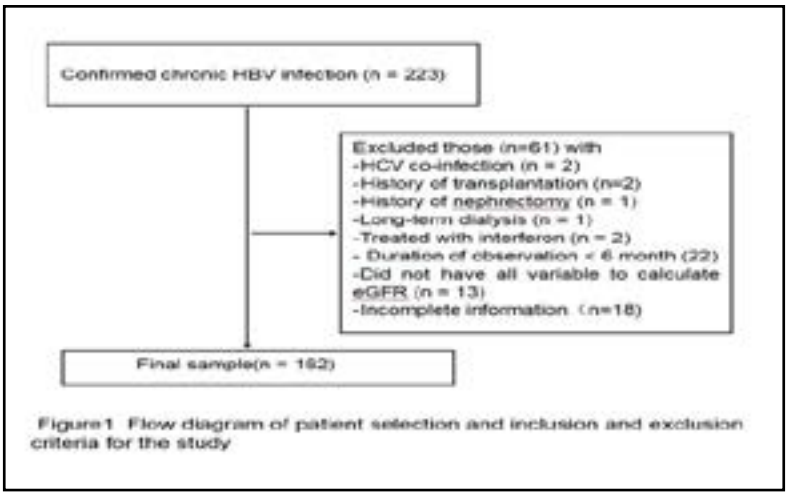


Figure1 Flow diagram of patient selection and inclusion and exclusion criteria for the study

### Clinical Outcomes

During the 6-year follow-up observation, 2 cases died (case 1: 31 year old male, with concurrent diabetes mellitus□pulmonary infection induce fulminant liver failure complicated with multiple organ failure; case 2: 66 year old male, HBV-related cirrhosis complicated with diabetes, combined with acute drug-induced liver injury leading to liver failure and subsequent multiple organ failure), 5 cases of newly developed hepatocellular carcinoma, 17 cases of newly developed liver cirrhosis (A total of 35 cases with decompensated cirrhosis in this study,of which 18 cases achieved recompensation) [16].

### Clearance of Hepatitis B Surface Antigen

2 cases of surface antigen became negative after NAs treatment (continuous treatment for 12 years), 14 cases achieved spontaneous seroconversion.

### Complications

22 cases with diabetes, 2 cases with lung cancer, 1 case with cervical cancer, 1 case with gastric cancer, 1 case with cerebral infarction, 4 cases with coronary heart disease.

Liver and Kidney Function Related Indicators in CHB Patients Treated with Nucleoside Drugs

Characteristics of the HBV patients at baseline is shown in Table 1.

Table1 .Characteristics of the HBV patents at baseline (n=162)

| baseline | Entecavir (n=108) | Tenofovir(n=54) | P value |
|---|---|---|---|
| Age (y) | 53.6±10.2 | 51.2±12.0 | 0.42 |
| Male(%) | 63.1% | 69.0% | 0.51 |
| Diabetes(%) | 15 (13.8%) | 7 (12.9%) | 0.45 |
| Hypertension(%) | 11 (10.1%) | 6 (11.1%) | 0.30 |
| creatinine(umol/l) | 65.5±13 | 67±12 | 0.84 |
| eGFR(MDRD mL/min/1.73 m | 100.7±18 | 106.2±16.9 | 0.283 |
| Duration of observation(y) | 6 | 6 | 1 |
| Decompensated cirrhosis(%) | 12 (11.1%) | 6 (11.1%) | 0.26 |
| Hepatocellular carcinoma(%) | 3 (2.7%) | 0 | 0.24 |
| Calcium(mmol/L) | 2.23±0.2 | 2.31±0.2 | 0.58 |
| Phosphate(mmol/L) | 1.05±0.4 | 1.07±0.4 | 0.64 |

Baseline data of the two groups were collected and analyzed

Data about HGB, PLT, ALB, cholinesterase,INR,Blood creatinine, blood Ca, blood phosphorus,serum bloodβ2-microglobulin, and glomerular filtration rate at 1, 2, 3, 4, 5, and 6 years for two groups of patients were shown in Table 2 and Figure2.

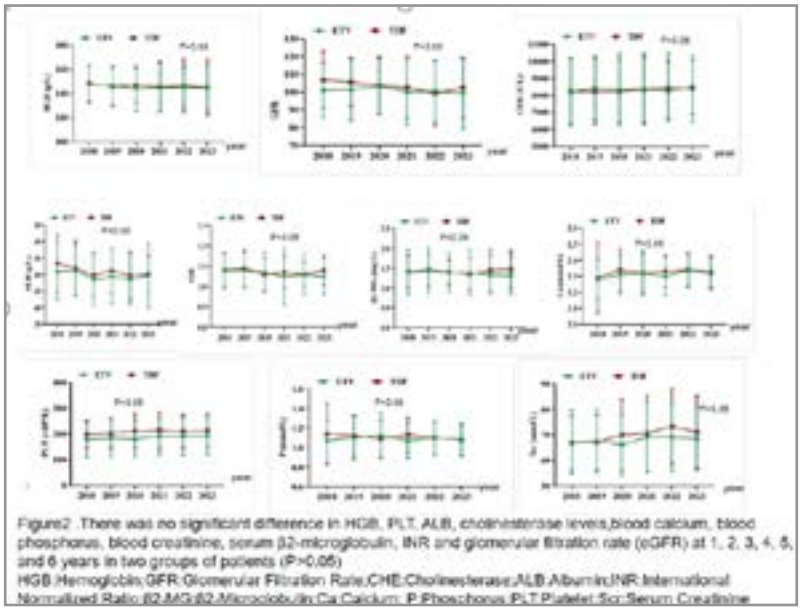

Figure2 .There was no significant difference in HGB, PLT, ALB, cholinesterase levels,blood calcium, blood phosphorus, blood creatinine, serum β2-microglobulin, INR and glomerular filtration rate (eGFR) at 1, 2, 3, 4, 5, and 6 years in two groups of patients (P>0.05)
HGB:Hemoglobin;GFR:Glomerular Filtration Rate;CHE:Cholinesterase;ALB:Albumin;INR:International Normalized Ratio;β2-MG:β2-Microglobulin;Ca:Calcium; P:Phosphorus;PLT:Platelet Scr:Serum Creatinine

## Discussion

Chronic HBV infection has long been a disease that threatens the health of people worldwide. Most patients with chronic hepatitis B in China develop from a state of chronic viral carriage. Due to the enhanced but inadequate immune clearance of HBV by the body, HBV persists, leading to long-term inflammatory activity in liver cells, which can result in adverse outcomes such as liver cirrhosis and its complications, as well as hepatocellular carcinoma. Therefore, antiviral therapy has become the primary treatment for patients with chronic HBV infection [4]. At present, a large amount of data has confirmed that both HBV infection and long-term antiviral treatment can increase the risk of renal injury in patients . The results of the HARPE study showed that 43.5% of patients with chronic hepatitis B had renal dysfunction[eGFR<90mL/(min.1.73m2) [17,18].

Serum creatinine and eGFR are classic indicators for evaluating renal function, and their stability directly reflects the integrity of glomerular filtration function. In this study, we calculated and estimated the level of glomerular filtration rate (eGFR) using MDRD formula [22].We found that the creatinine levels and eGFR of patients remained stable at baseline and during follow-up ,which consistent with the results of previous studies [19-21].

As related renal injury is mainly characterized by tubular injury, and monitoring tubular injury indicators is more sensitive than eGFR. The commonly used indicators for evaluating early renal tubular injury are low molecular weight proteins, which are mostly absorbed by the renal tubules after glomerular filtration. When the renal tubules are damaged, this protein increases in the urine. Therefore, in this study,we detected blood calcium, blood phosphorus, and serumβ2-microglobulin . and we observed that blood calcium, blood phosphorus, and serumβ2-microglobulin have no significant changes at baseline and during follow-up ,which consistent with the results of previous studies.We also found that there was no significant difference in HGB, PLT, ALB, INR, cholinesterase levels.

In addition, all patients selected in this study had HBV-DNA levels below the detection limit, ruling out the influence of virological response on renal function. In this study, there were only 54 patients in the TDF group, which because previous some studies have found that TDF carries a risk of causing renal tubular injury, and most hepatitis B patients in our department receive ETV for antiviral treatment [22-24].

During the follow-up period, there were 5 new cases of hepatocellular carcinoma, all of which were HBV-DNA negative, some of which were patients with low surface antigen values, and even one case progressed to hepatocellular carcinoma after he achieved spontaneous seroconversion of HBsAg, indicating that even if the HBV-DNA turns negative and the hepatitis B surface antigen is at a low level, there is still the possibility of progression to hepatocellular carcinoma, which needs close monitoring. which consistent with the results of previous studies [25].

Our study found that there were 17 new cases of cirrhosis, of which 12 cases with a family history of cirrhosis and hepatocellular carcinoma, of which 3 cases without quitting drinking. This fully demonstrates that family history and alcohol consumption are risk factors for cirrhosis, which is consistent with the conclusions of previous studies. In this study, 2 cases was achieved hepatitis B surface antigen (HBsAg) seroconversion after 12 years of continuous NAs treatment. 4 cases spontaneously turned negative (including 3 female patients), indicating that NAs treatment can only control HBV DNA in the long term and has a low surface antigen clearance rate, which is consistent with previous studies[26-28].

In conclusion,This study systematically evaluated the dynamic changes in liver and renal function related indicators (including serum creatinine, blood calcium, blood phosphorus, blood β2-microglobulin, HGB, PLT, ALB, INR cholinesterase levels and estimate glomerular filtration rate [eGFR]) through a 6-year follow-up of 162 patients with chronic hepatitis B (CHB) who were receiving antiviral treatment with entecavir or tenofovir. The results showed that the above indicators did not show significant fluctuations during the treatment period, indicating that long-term antiviral treatment with nucleoside (acid) analogues (NAs) may have a small impact on patients' renal function. This finding provides important reference for the safety of long-term

clinical medication. The limitation of our study is that it is an observational study and cannot exclude the impact of mixed factors, such as the combination of basic diseases ,for instance,-diabetes and hypertension. In addition,there are some inherent limitations of retrospective studies ,such as insufficient data integrity, high risk of bias. At the same time, the lack of urine biomarkers (such as urine microprotein, urine NAG, cystatin) and bone density detection data limits the in-depth discussion of renal tubular injury and bone metabolism.

This study supports the safety of renal function in the long-term treatment of low nephrotoxic NAs, but it still needs to be evaluated individually in clinical practice, especially for the baseline abnormal renal function or high-risk groups (such as the elderly, diabetes patients). Future research can integrate more sensitive early renal injury markers to optimize long-term management strategies for patients of chronic hepatitis B .

## Declarations

### Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki.

This study has been approved by the Medical Ethics Committee of Beijing Huairou Hospital.(Jing Huailun Ke Zi (2025) No. 030-01)and all patients have signed informed consent forms.

### Clinical Trial Number

Not applicable

### Consent for Publication

Not applicable

### Availability of Data and Material

All data generated or analyzed during this study are included in this published article and its supplementary information files

### Competing Interests

None


### Funding

None


### Author's Contribution

YB was major contributor in writing the manuscript. WL, JL and XL collected the data and performed statistical analysis. HW collected and checked the data. JH designed the present study.


### Acknowledgements

YB was major contributor in writing the manuscript. WL, JL and XL collected the data and performed statistical analysis. HW collected and checked the data. JH designed the present study.


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