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Original Article

Effectiveness and Safety of Tenofovir Amibufenamide in the Treatment of Chronic Hepatitis B: A Real-world, Multicenter Study

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Abstract

Background and Aims: Chronic hepatitis B (CHB) remains a significant global health challenge, and effective antiviral therapies are essential for long-term management. This study aimed to evaluate the real-world effectiveness and safety of tenofovir amibufenamide (TMF) in a cohort of patients with chronic hepatitis B (CHB). ***Methods:*** In this multicenter, prospective, real-world cohort study, 194 CHB patients were recruited from four hospitals between August 2021 and August 2022. Patients were divided into treatment-naïve (TN, n = 123) and treatment-experienced (TE, n = 71) groups. The TN group was further subdivided into TMF (n = 63) and tenofovir disoproxil fumarate (TDF, n = 60) subgroups. In the TE group, patients transitioned from prior antiviral therapies (entecavir or TDF) to TMF after meeting criteria for poor virological response or safety concerns. Treatment response was evaluated in terms of virological effectiveness and alanine transaminase normalization rates. Virological response (VR), ALT normalization rates, renal function markers, and lipid profiles were monitored. ***Results:*** In the TN cohort, VR rates at 24 and 48 weeks were 42.86% and 90.48% for TMF, and 60.00% and 83.33% for TDF. ALT normalization rates at 24 and 48 weeks for TMF were 56.82% and 70.45% (according to AASLD 2018 standards). In the TE group, VR rates at 24 and 48 weeks were 83.1% and 91.55%, respectively. ALT normalization rates were 86.67% and 93.33% (local standards), and 66.67% and 76.67% (AASLD 2018 standards) ($z = -2.822$, $P = 0.005$). Additionally, TMF showed improved renal safety over TDF, with no significant differences in lipid concentrations. ***Conclusions:*** TMF is comparable to TDF in terms of CHB treatment effectiveness, with better renal safety and no impact on lipid levels. In TE patients, transitioning to TMF therapy does not affect antiviral treatment outcomes.

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Introduction

The global prevalence of chronic hepatitis B virus (HBV) infection is decreasing due to the widespread use of the hepatitis B vaccine, especially in children younger than five years.[1,2] However, as of 2019, there were approximately 316 million individuals with chronic HBV infection worldwide, with a prevalence of 4.1%.[1] Patients with chronic HBV infection have an increased risk of developing liver failure, liver cirrhosis, or hepatocellular carcinoma (HCC) in the future.[3] Moreover, 555,000 deaths from hepatitis B-related diseases occurred worldwide in 2019. Therefore, HBV infection remains a major global public health issue.[1]

HBV antiviral treatment can prevent or even reverse disease progression, reduce the incidence of liver cancer, and lower the mortality associated with hepatitis B-related diseases.[3,4] Currently, first-line clinical anti-HBV therapies include interferons and nucleos(t)ide analogs, such as entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF).[2,5–7] The clinical cure of hepatitis B is defined as the loss of hepatitis B surface antigen (HBsAg) and the presence of undetectable HBV DNA. The clinical cure rate of hepatitis B with the use of pegylated interferon is 3–7%. However, interferon treatment is limited by poor tolerability and adverse reactions, such as myelosuppression and exacerbation of existing neuropsychiatric symptoms (e.g., depression).[7,8] Unless a functional cure is achieved using oral nucleotide analogs, antiviral drugs, which have high effectiveness and safety requirements, should be administered. The first-line treatment drugs (entecavir [ETV], TDF, TAF, and tenofovir amibufenamide [TMF]) recommended by the guidelines can reduce the risk of drug resistance compared

Keywords: Antiviral Agents; Chronic Hepatitis B; Hepatitis B virus; Treatment Outcome; Safety; Multicenter Study.

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with lamivudine and adefovir.[2,6] However, ETV has a low drug resistance rate in nucleos(t)ide-naïve patients, with a five-year resistance rate reported to be approximately 1.2%.[1,9] In patients with pre-existing lamivudine resistance, the five-year resistance rate to ETV increases significantly, reaching up to 51%.[9] Additionally, ETV-induced viral suppression is not as robust as TDF-induced viral suppression. Compared with patients receiving ETV, those receiving TDF treatment have a lower risk of developing HCC.[9–11] However, the long-term use of TDF is associated with an increased risk of bone and kidney damage compared with ETV.[10] TAF has better bone and kidney safety, but its ability to inhibit viral replication in newly treated patients with chronic hepatitis B (CHB) is less effective and it also affects lipid metabolism.[12,13] Therefore, there is still a need for safer antiviral drugs with high antiviral effectiveness.

TMF was launched in China in June 2021. Structurally, a methyl group was added to the amidate group of TAF to optimize the structure, improve liposolubility and cell membrane penetration, and enhance the plasma stability of TMF.[14,15] Recent phase III clinical trials with durations of 48 and 96 weeks showed that TMF is a better choice for treating CHB because it is noninferior in effectiveness and safer than TDF.[16,17] Currently, multicenter, real-world clinical studies on TMF are scarce. This study analyzes the antiviral effectiveness of TMF in treating patients with CHB, providing a reference for the subsequent selection of antiviral therapy for these patients.

Methods

Study design and patients

Patients with CHB who visited the Second Affiliated Hospital of Xi'an Jiaotong University, the Fourth People's Hospital of Qinghai Province, 3201 Hospital Affiliated to Xi'an Jiaotong University, or the Infection Department at the Affiliated Hospital of Yan'an University between August 2021 and August 2022 were selected. The inclusion criteria for the patients were as follows: 1) meeting the guidelines for the prevention and treatment of chronic hepatitis B (2021 edition)[6]; 2) age between 18 and 65 years, with no sex limitations; and 3) patients, including those in the treatment-experienced (TE) groupwho had been treated with ETV or TDF for 96 weeks without achieving a complete virological response, those who showed early markers of renal function impairment, and those who were switched to TMF treatment after providing consent. The exclusion criteria were as follows: 1) evidence suggesting HCC or serum alpha-fetoprotein concentrations >100 ng/L; 2) coinfection with hepatitis C or D, AIDS, autoimmune hepatitis, or active hepatitis caused by other conditions; 3) severe cardiopulmonary dysfunction, advanced tumors, central nervous system disease (e.g., a history of epilepsy), or other systemic diseases; 4) a history of allergies to nucleosides or nucleoside analogs; and 5) pregnant or breastfeeding patients.

Research methods

Treatment-naïve (TN) patients who met the criteria for receiving TMF (25 mg, once daily) or TDF (300 mg, once daily) treatment were included in the study. TE patients who had previously received ETV (0.5 mg, once daily) or TDF (300 mg, once daily) antiviral therapy for a minimum of 96 weeks but experienced poor treatment efficacy or kidney safety issues were eligible to transition to TMF (25 mg, once daily). From treatment weeks 4 to 12, patients were visited once at four weeks and then once every 12 weeks thereafter. Adherence was evaluated every 12 weeks. Baseline data and laboratory evaluations of the patients were collected, including hematology analysis, serum chemistry tests, blood lipids, and renal function measurements (e.g., serum creatinine concentrations, estimated glomerular filtration rate [eGFR], cystatin C, and early renal response). Urinary β2-microglobulin, urinary α1-microglobulin, and urinary N-acetyl-β-D-glucosaminidase (NAG) concentrations were included in the analysis of tubular function impairment.

Endpoints

The main indicators of treatment effectiveness were a complete virological response (HBV DNA concentrations < 20 IU/mL) and a change in the amount of HBV DNA (log IU/mL) at 24 and 48 weeks.

Secondary indicators of effectiveness were based on local laboratory standards (ULN: men, ≤50 IU/L; women, ≤40 IU/L) and AASLD 2018 standards (ULN: men, ≤35 IU/L; women, ≤25 IU/L). Other secondary indicators included changes in the alanine transaminase (ALT) normalization rate, serology (HBsAg and hepatitis B e antigen [HBeAg] negative conversion rates and HBsAg and HBeAg seroconversion rates), renal function, and blood lipid values.

Statistical analysis

All data were analyzed using SPSS 26.0. The values of HBV DNA, HBsAg, and HBeAg were logarithmically transformed for statistical analysis. HBV DNA concentrations below the lower limit of detection were assigned a value of 19 IU/mL (1.28 log10 IU/mL). Continuous variables with a normal distribution are expressed as the mean ± standard deviation and were compared using the t-test. Non-normally distributed continuous variables are expressed as median (Q1, Q3) and were compared using nonparametric tests. Categorical variables are expressed as numbers (percentages), and comparisons were performed using the chi-square test or Fisher's exact test. A *P*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The TMF and TDF groups included 329 patients. To date, 194 subjects have been followed up for 48 weeks. The patients were stratified into the TN (n = 123) and TE (n = 71) groups. The TN group was further divided into the TMF (n = 63) and TDF (n = 60) groups. Among the study subjects, there were 109 (56.19%) male patients and 85 (43.81%) female patients, aged 21–65 years (mean age: 40.46 ± 10.43 years). Patients in the TMF and TDF groups were stratified based on clinical characteristics, ensuring alignment with real-world clinical practices.

Antiviral effectiveness and safety in newly treated patients

Baseline characteristics of newly treated patients: The baseline characteristics of the newly treated patients are shown in Table 1. In the TMF group, 42 (66.67%) patients were male, with a mean age of 39.16 ± 10.64 years. Approximately 59.32% of the patients in this group were HBeAg-positive, and 14.29% had liver cirrhosis. The median ALT concentration was 48.00 IU/L (31.00, 86.00), the median HBV DNA concentration was 5.13 log10 IU/mL (2.85, 7.44), and the mean quantitative HBsAg concentration was 3.74 ± 0.82 log10 IU/mL. In the TDF group, which comprised

Table 1. Baseline characteristics of the newly treated patients

Baseline characteristics	TMF (n = 63)	TDF (n = 60)	*P*-value
Male, n (%)	42 (66.67)	30 (50.00)	0.061
Age, years, $\bar{x} \pm s$	39.16 ± 10.64	39.58 ± 10.43	0.824
Liver cirrhosis, n (%)	9 (14.29)	7 (11.67)	0.666
HBeAg positive, n (%)	35/59 (59.32)	35/60 (57.14)	0.913
ALT,IU/L,*M* (*Q1*,*Q3*)	48.00 (31.00, 86.00)	46.00 (25.00, 62.00)	0.347
HBV DNA level log10 IU/mL, *M* (*Q1*,*Q3*)	5.13 (2.85, 7.44)	4.88 (3.23, 7.56)	0.649
HBsAg levels,log10IU/mL, *M* (*Q1*,*Q3*)	3.95 (3.38, 4.52)	3.51 (3.08,4.04)	0.158
Serum creatinine, umol/L, $\bar{x} \pm s$	57.41 ± 10.61	53.41 ± 17.68	0.336
eGFR, mL/m/1.73 m^2, $\bar{x} \pm s$	123.32 ± 9.23	120.09 ± 13.88	0.340
Cystatin C, mg/L, $\bar{x} \pm s$	0.84 ± 0.20	0.85 ± 0.23	0.908
Blood calcium, mmol/L, $\bar{x} \pm s$	2.31 ± 0.09	2.29 ± 0.09	0.525
Blood phosphorus, mmol/L, $\bar{x} \pm s$	1.00 ± 0.15	1.00 ± 0.17	0.900
Total cholesterol, mmol/L, $\bar{x} \pm s$	4.91 ± 0.91	4.50 ± 1.19	0.174
Triglycerides, mmol/L, $\bar{x} \pm s$	1.31 ± 0.62	1.57 ± 1.22	0.429

TMF, tenofovir amibufenamide; TDF, tenofovir disoproxil fumarate; HBeAg, hepatitis Be antigen; HBV, hepatitis B virus.

30 (50%) male patients, the mean age was 39.58 ± 10.43 years, 57.14% were HBeAg-positive, and 11.67% had cirrhosis. The median ALT concentration was 46.00 IU/L (25.00, 62.00), the median HBV DNA concentration was 4.88 log10 IU/mL (3.23, 7.56), and the mean HBsAg concentration was 3.55 ± 0.64 log10 IU/mL. Both groups showed similar baseline characteristics.

Changes in HBV DNA concentrations and the negative conversion rate: In the cohort of 123 newly treated patients, the median HBV DNA concentrations at baseline, 24 weeks, and 48 weeks in the TMF group were 5.26 log10 IU/mL (2.85, 7.69), 1.78 log10 IU/mL (1.28, 3.10), and 1.28 log10 IU/mL (1.28, 1.28), respectively, with a significant reduction over time (χ^2 = 109.449, P < 0.001). Similarly, in the TDF group, these concentrations were 4.88 log10 IU/mL (3.30, 7.56), 1.28 log10 IU/mL (1.28, 2.55), and 1.28 log10 IU/mL (1.28, 1.28), respectively, which also significantly decreased over time (χ^2 = 174.938, P < 0.001). The virological response rates at 24 and 48 weeks were 42.86% and 90.48% in the TMF group, and 60.00% and 83.33% in the TDF group, respectively (Fig. 1A). Notably, while the virological response rates in the TMF group showed a higher increase from 24 to 48 weeks compared to the TDF group, statistical comparisons between the TMF and TDF groups at 24 and 48 weeks revealed no significant differences (24 weeks: χ^2 = 3.615, P = 0.057; 48 weeks: χ^2 = 1.386, P = 0.239). Among HBeAg-positive patients, 25.71% and 85.71% of patients in the TMF group, and 42.86% and 74.29% of the patients in the TDF group achieved a virological response after treatment for 24 and 48 weeks, respectively (Fig. 1B). In HBeAg-negative patients, the virological response rates were 66.67% and 95.83% in the TMF group and 84.00% and 96.00% in the TDF group at 24 and 48 weeks, respectively (Fig. 1C).

ALT normalization rate: According to hospital standards, 33 TMF-treated patients and 27 TDF-treated patients had abnormal baseline ALT concentrations. After 24 and 48 weeks of treatment, ALT normalization was achieved in 84.85% and 90.91% of patients in the TMF group and in 92.59% and 96.30% of patients in the TDF group, respectively, with no significant difference between the groups (χ^2 = 0.276, P = 0.599; χ^2 = 0.097, P = 0.755, respectively) (Fig. 1D). According to the AASLD standards, 44 patients in the TMF group and 42 in the TDF group had abnormal ALT concentrations at baseline. The normalization rates were 56.82% and 70.45% in the TMF group, and 61.90% and 78.57% in the TDF group at 24 and 48 weeks, respectively, with no significant differences between the groups (Fig. 1E).

Changes in HBsAg and HBeAg concentrations: In the newly treated TMF group, one (1.59%) patient achieved negative conversion and seroconversion of HBsAg at 48 weeks of treatment, with a baseline HBsAg concentration of 5.76 IU/mL. The HBeAg negative conversion rate occurred in 14.29% (5/35) of TMF patients and 8.57% (3/35) of TDF patients, with no significant difference (Table 2). In the newly treated TMF group, HBsAg concentrations significantly decreased from a median of 3.95 log10 IU/mL (3.30, 4.41) at baseline to 3.74 log10 IU/mL (3.30, 4.16) at 48 weeks (χ^2 = 10.684, P = 0.005). Similarly, in the TDF group, HBsAg concentrations significantly decreased from 3.51 log10 IU/mL (2.97, 3.98) at baseline to 3.25 log10 IU/mL (2.89, 3.88) at 48 weeks (χ^2 = 23.958, P < 0.001). No significant difference in HBsAg concentrations was found between the TMF and TDF groups at baseline, or after 24 or 48 weeks of treatment (Table 2).

Changes in renal function: During treatment in the TMF group, serum creatinine concentrations remained stable over 48 weeks, ranging from 57.41 to 57.97 μmol/L (F = 0.114, P = 0.889), and eGFR values were consistent (123.32 to 121.22 mL/m/1.73 m^2, F = 1.377, P = 0.264). Serum phosphorus and calcium concentrations remained stable (F = 2.592, P = 0.100; F = 2.280, P = 0.118). In the TDF treatment group, serum creatinine concentrations significantly increased from baseline to 48 weeks (from 53.41 to 58.65 μmol/L) (F = 4.044, P = 0.027; t = −2.582, P = 0.016). The eGFR slightly decreased at 48 weeks compared with baseline, but this was not significant (115.76 vs 120.09 mL/m/1.73 m^2, F = 1.321, P = 0.285). At 48 weeks, no significant differences in serum creatinine concentrations (t = −1.384, P = 0.172), eGFR (t = 1.528, P = 0.132), phosphorus concentrations (t = 0.954, P = 0.345), or calcium concentrations (t = 1.597, P = 0.117) were observed between the TMF and TDF groups (Fig. 2A–D).

Changes in blood lipid concentrations: In the TMF group, the mean total cholesterol (TC) concentrations at

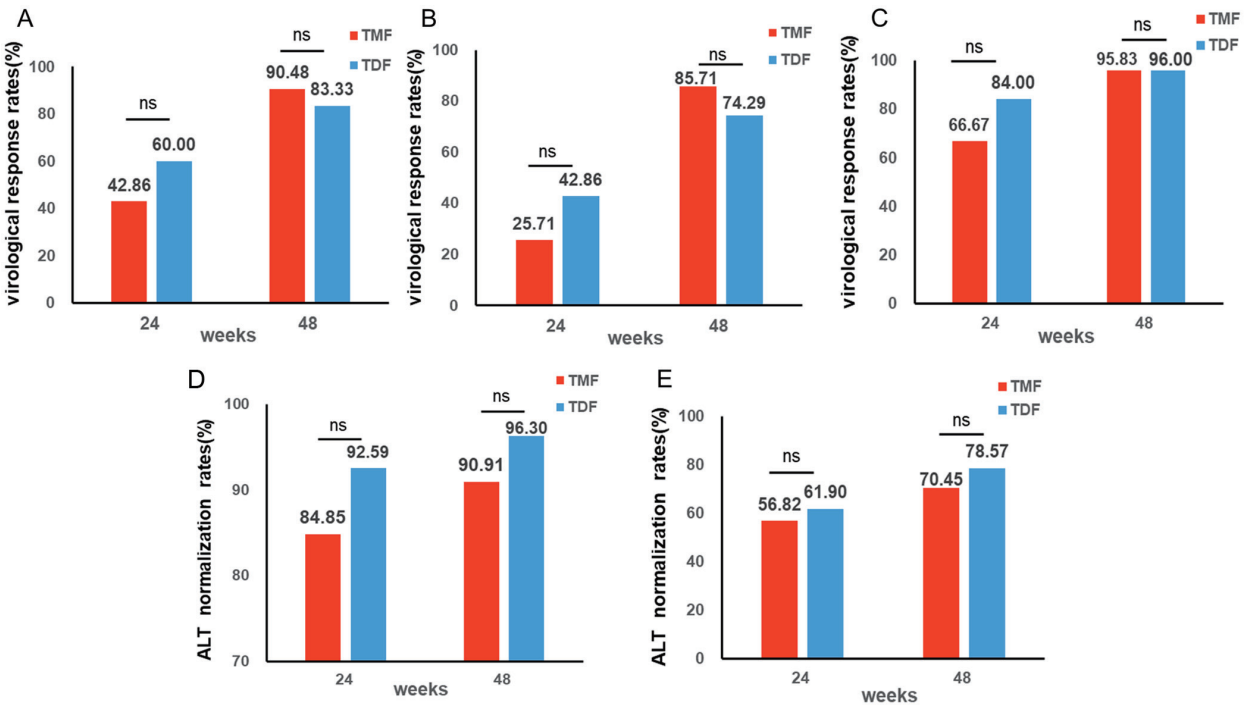

Fig. 1. Antiviral effectiveness and ALT normalization rate in the TN group. (A) VR rates in the entire TN group after 24 and 48 weeks of treatment; (B) VR rates in HBeAg-positive TN patients after 24 and 48 weeks of treatment; (C) VR rates in HBeAg-negative TN patients after 24 and 48 weeks of treatment; (D, E) ALT normalization rate in the TN group after 24 and 48 weeks of treatment based on laboratory standards (D) and AASLD standards (E). ns, $p > 0.05$. ALT, alanine transaminase; TN, treatment-naïve; VR, Virological response; AASLD, American Association for the Study of Liver Diseases; TMF, tenofovir amibufenamide; TDF, tenofovir disoproxil fumarate.

baseline, 24 weeks, and 48 weeks were 4.91 ± 0.91 mmol/L, 5.03 ± 0.82 mmol/L, and 4.96 ± 0.84 mmol/L, respectively, with no significant difference between the three time points (F = 0.913, *P* = 0.423). Triglyceride (TG) concentrations slightly increased from 1.31 ± 0.62 at baseline to 1.50 ± 0.65 mmol/L at 48 weeks, but this was not significant (F = 3.079, *P* = 0.073).

In the TDF group, TC concentrations remained constant throughout the treatment period (4.50 ± 1.19 at baseline and 4.43 ± 0.86 mmol/L at 48 weeks) (F = 0.119, *P* = 0.889). TG concentrations decreased from 1.57 ± 1.22 mmol/L at baseline to 1.19 ± 0.67 mmol/L at 48 weeks, but this was not significant (F = 1.070, *P* = 0.387). TC and TG concentrations were not significantly different between the TMF and TDF groups at 48 weeks (t = 1.585, P = 0.126 for TC; t = 1.179, *P* = 0.249 for TG) (Fig. 2E and F).

Antiviral effectiveness and safety in previously treated patients

Baseline characteristics: The baseline data for the previously treated patients are shown in Table 3. There were 71 previously treated patients, 52.11% of whom were men, with a mean age of 42.44 ± 10.28 years. Among these patients, 46.48% were HBeAg-positive, 16.90% had cirrhosis, and the median ALT concentration was 29.00 IU/L. The median HBV DNA concentration was 1.28 log10 IU/mL, and 50.70% achieved a complete virological response at baseline. The median HBsAg concentration was 3.24 log10 IU/mL. Most prior treatments included TDF (70.42%), with 19.72% using ETV and 9.86% using a combination of ETV and TDF.

Changes in HBV DNA concentrations and the negative conversion rate: Among TE patients, 83.1% and 91.55% achieved undetectable HBV DNA levels after switching to TMF treatment at 24 and 48 weeks, respectively. HBV DNA concentrations remained consistent at 1.28 log10 IU/mL at baseline, 24 weeks, and 48 weeks, with significant consistency in HBV DNA levels over time (χ^2 = 35.748, *P* < 0.001) (Fig. 3A). Among these patients, 25 individuals with low-level viremia (LLV, defined as HBV DNA levels between 20 and 2,000 IU/mL) who switched to TMF achieved HBV DNA negative conversion rates of 64% at 24 weeks and 84%

Table 2. Negative conversion rate and seroconversion rate of HBsAg and HBeAg in newly treated patients

Groups	HBsAg negative conversion rate	HBsAg seroconversion rate	HBeAg negative conversion rate	HBeAg seroconversion rate	48W HBsAg levels, log10IU/mL, *M* (*Q1*, *Q3*)
TMF group	1.59 (1/63)	1.59 (1/63)	14.29 (5/35)	8.57 (3/35)	3.74 (3.30,4.16)
TDF group	0	0	8.57 (3/35)	2.86 (1/35)	3.25 (2.89, 3.88)
Statistical value	/	/	0.141	0.265	−1.154
P-value	1.000	1.000	0.707	0.607	0.294

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis Be antigen; TMF, tenofovir amibufenamide; TDF, tenofovir disoproxil fumarate.

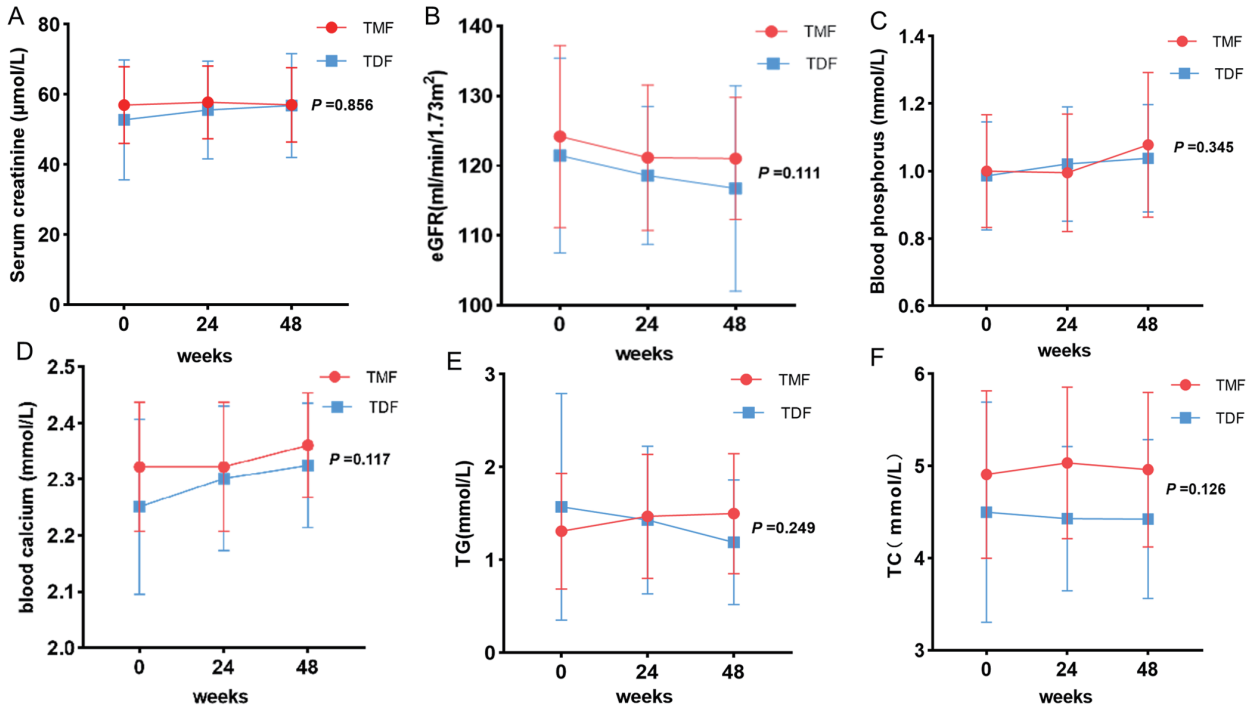

Fig. 2. Renal function and blood lipid changes during antiviral treatment. Changes in serum creatinine levels (A), eGFR (B), serum phosphorus levels (C), serum calcium levels (D), TG levels (E), and TC levels (F) in the TN group. ns, $p > 0.05$. TG, Triglyceride; TC, total cholesterol; TMF, tenofovir amibufenamide; TDF, tenofovir disoproxil fumarate.

Table 3. Baseline characteristics of treated patients

Baseline characteristics	Experienced treatment patients (n = 71)
Male, n (%)	37 (52.11)
Age, years, $\bar{x} \pm s$	42.44 ± 10.28
Liver cirrhosis, n (%)	12 (16.90)
Prior antiviral drugs, n (%)	
ETV	14 (19.72)
TDF	50 (70.42)
ETV + TDF	7 (9.86)
HBeAg positive, n (%)	33 (46.48)
ALT, IU/L, *M* (*Q1*,*Q3*)	29.00 (20.00, 40.00)
HBV DNA levels, log10 IU/mL, *M* (*Q1*,*Q3*)	1.28 (1.28, 2.13)
Number of HBV DNA <20 IU/mL, n (%)	36 (50.70)
20–2,000 IU/mL, n (%)	25 (35.21)
>2,000 IU/mL, n (%)	10 (14.08)
HBsAg levels,log10IU/mL, *M* (*Q1*,*Q3*)	3.24 (2.54, 3.62)
Serum creatinine, umol/L, $\bar{x} \pm s$	52.60 ± 13.44
eGFR, mL/m/1.73 m^2, $\bar{x} \pm s$	124.53 ± 26.14
Cystatin C, mg/L, $\bar{x} \pm s$	0.83 ± 0.22
Blood calcium, mmol/L, $\bar{x} \pm s$	2.33 ± 0.09
Blood phosphorus, mmol/L, $\bar{x} \pm s$	1.06 ± 0.17
Total cholesterol, mmol/L, $\bar{x} \pm s$	3.81 ± 0.68
Triglycerides, mmol/L, $\bar{x} \pm s$	1.17 ± 0.73

ETV, entecavir; TDF, tenofovir disoproxil fumarate; HBeAg, hepatitis Be antigen; ALT, alanine transaminase; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen.

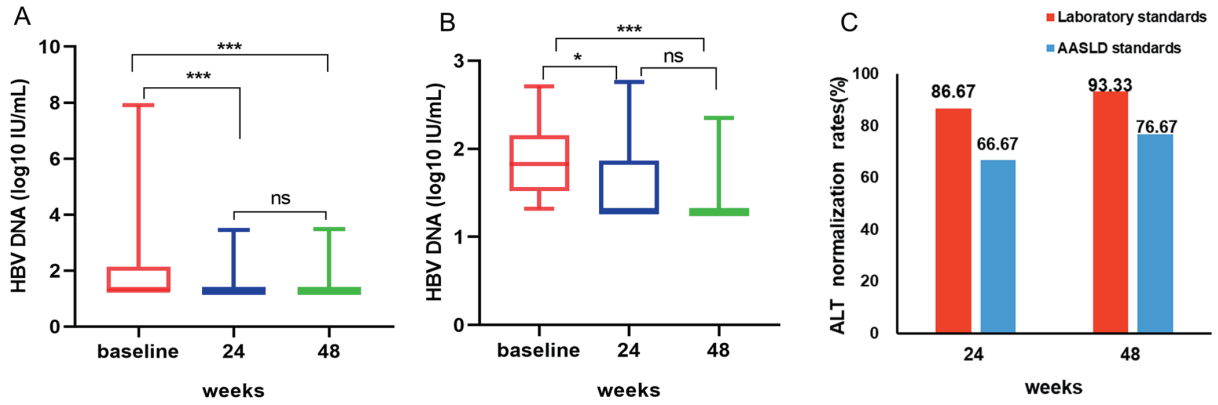

Fig. 3. Antiviral effectiveness and ALT normalization rate in the TE group. (A) Changes in HBV DNA levels in the TE group; (B) Changes in HBV DNA levels in low-level viremia (LLV, defined as HBV DNA levels between 20 and 2,000 IU/mL) in the TE group; (C) ALT normalization rate in the TE group after 24 and 48 weeks of treatment based on laboratory standards and AASLD standards. ns, $p > 0.05$; *$p < 0.05$; ***$p < 0.001$. TE, treatment-experienced; ALT, alanine transaminase; AASLD, American Association for the Study of Liver Diseases; HBV, hepatitis B virus.

at 48 weeks post-treatment.

The baseline HBV DNA concentration (1.83 log10 IU/mL) significantly decreased to 1.28 log10 IU/mL at 24 and 48 weeks, as shown by repeated measures analysis (χ^2 = 21.238, $P < 0.001$). However, pairwise comparisons between 24 weeks and 48 weeks did not show significant differences, indicating stabilization of HBV DNA levels post-treatment (Fig. 3B).

ALT normalization rate: In 15 TMF-treated patients with baseline ALT concentration abnormalities, ALT normalization rates were observed to be 86.67% and 93.33% at 24 and 48 weeks, respectively, based on the hospital standard. According to the AASLD guidelines, which apply stricter criteria for ALT normalization, 30 TMF-treated patients achieved normalization rates of 66.67% and 76.67% at 24 and 48 weeks, respectively (Fig. 3C).

Changes in HBsAg and HBeAg concentrations: In TE patients, no patients achieved HBsAg seroconversion at 24 or 48 weeks (Table 4). However, HBeAg negativity reached 6.06% (2/33) at 24 weeks and increased to 15.15% (5/33) at 48 weeks. Median HBsAg concentrations of TMF-treated patients at baseline and at 24 and 48 weeks were 3.24 log10 IU/mL (2.54, 3.62), 3.23 log10 IU/mL (2.38, 3.57), and 3.20 log10 IU/mL (2.47, 3.61), respectively (χ^2 = 37.260, $P <$ 0.001).

Renal function changes: In TE patients, 36 patients were switched to TMF treatment due to abnormal renal tubular monitoring indicators (urine α1-microglobulin, urine β2-microglobulin, and urine NAG). Urine α1-microglobulin concentrations significantly decreased from 22.40 mg/L (15.40, 32.53) at baseline to 14.85 mg/L (7.85, 26.03) at 24 weeks and further decreased to 12.25 mg/L (7.21, 20.43) at 48 weeks (χ^2 = 24.871, $P < 0.001$). Urine β2-microglobulin concentrations significantly decreased from 0.31 mg/L (0.18, 0.63) at baseline to 0.18 mg/L (0.18, 0.31) at 24 weeks and remained stable at 0.19 mg/L (0.18, 0.31) at 48 weeks (χ^2 = 11.762, P = 0.003). There was no significant change in urine β2-microglobulin concentrations between 24 and 48 weeks. Urine NAG activity also significantly decreased from 19.60 U/L (13.63, 22.30) at baseline to 12.60 U/L (8.75, 19.13) at 48 weeks (χ^2 = 11.427, P = 0.003), with no significant differences between 24 and 48 weeks (Fig. 4).

Changes in blood lipid concentrations: In previously treated patients, TC concentrations showed a slight increase from 3.81 ± 0.68 to 3.96 ± 0.60 mmol/L over 48 weeks, but this was not significant (F = 1.821, P = 0.185). TG concentrations ranged from 1.17 ± 0.73 to 1.25 ± 0.63 mmol/L, but this was also not significant (F = 0.734, P = 0.442) (Fig. 4).

Discussion

TMF, which was approved by the China National Medical Products Administration in 2021 for treating HBV infection, was developed by modifying TAF through the addition of a single methyl group.[14] Clinical trials have shown that when TMF is administered at 1/30 of the TDF dose, it exhibits superior plasma stability and shows similar effectiveness in inhibiting HBV.[14] Another study demonstrated that TMF had slightly better anti-HBV performance than TAF.[15] TMF was introduced to the Chinese market relatively late. Currently, some retrospective real-world studies have shown the safety and effectiveness of TMF in treating patients with CHB.[18,19] However, there have been no multicenter, prospective, real-world studies on this topic.

The virological response is an important endpoint in antiviral treatment for patients with CHB. It not only improves

Table 4. Negative conversion rate and seroconversion rate of HBsAg and HBeAg in previously treated patients

	24 Weeks	48 Weeks	*P*-value
HBeAg negative conversion	6.06 (2/33)	15.15 (5/33)	
HBeAg seroconversion	3.03 (1/33)	6.06 (2/33)	
HBsAg negative turning	0 (0/71)	0 (0/71)	
HBsAg seroconversion	0 (0/71)	0 (0/71)	
HBsAg levels,log10IU/mL, *M* (*Q1*, *Q3*)	3.23 (2.38, 3.57)	3.20 (2.47, 3.61)	$P < 0.001$

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen.

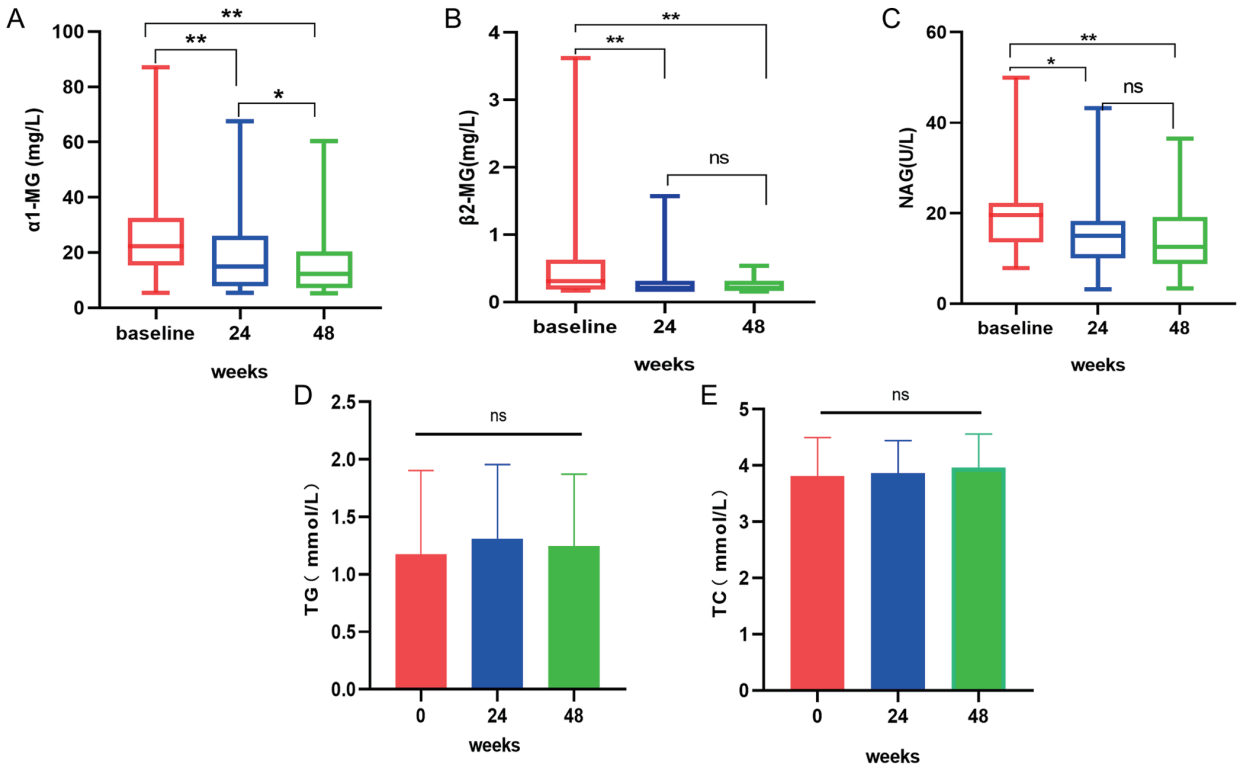

Fig. 4. Urine renal tubule detection indicators and blood lipid changes during antiviral treatment. Changes in urine α1-microglobulin (A), urine β2-microglobulin (B), and urine NAG (C) in patients with abnormal urine renal indicators; Changes in TG levels (D) and TC levels (E) in the TE group. ns, $p > 0.05$; *$p < 0.05$; **$p < 0.01$. TG, Triglyceride; TC, total cholesterol; NAG, N-acetyl-beta-D-glucosaminidase.

liver inflammation and histological fibrosis but also addresses the fact that persistently detectable HBV DNA increases the incidence of HCC.[19,20] In our study, 90.48% of TN patients achieved a virological response (HBV DNA concentrations < 20 IU/mL) after 48 weeks of treatment. Additionally, TMF was effective in inhibiting HBV replication, with its effectiveness not inferior to that of TDF. We found that the amount of HBV DNA in patients in the TMF group decreased from baseline to 48 weeks, and 91.55% of the TE patients achieved a virological response. TMF showed similar antiviral effectiveness to that of TDF in both HBeAg-positive and HBeAg-negative patients. In a recent phase III clinical trial, the VR rate (HBV DNA concentrations < 100 IU/mL) at week 48 was 82%, with the VR rate in HBeAg-positive patients being 55.3%.[16] These rates are lower than those observed in the present study (90.48% and 85.71%). In a retrospective study by Li *et al*.,[18] nearly 93% of TN patients achieved a VR after 24 weeks of treatment, with the VR rate in TE patients being 95% (61/64) and in HBeAg-positive patients being 88.9%. In our study, the antiviral effectiveness at 24 weeks was 42.86% for TN patients and 83.10% for TE patients. This difference is likely related to the definition of VR, which was defined as HBV DNA concentrations < 100 IU/mL in the previous study. Peng *et al*.[19] reported that 78.57% of TN patients achieved a VR at 48 weeks, and the VR rate in HBeAg-positive patients was 74.36%. In their study, VR was defined as HBV DNA concentrations < 10 IU/mL, which is more difficult to achieve. Overall, antiviral effectiveness was positive in the real world, and antiviral effectiveness was not affected in TE patients who switched from other antiviral drugs to TMF.

In this study, after 48 weeks of TMF treatment, the virological response rate in TE patients increased from 50.70% at baseline to 91.55%. Multiple studies[21,22] have indicated that LLV can lead to drug resistance and virological breakthrough, promote the progression of liver fibrosis, and even increase the incidence of HCC. This study further analyzed the antiviral effectiveness of TMF in patients with LLV. After 48 weeks of treatment, 84% of patients with LLV achieved negative HBV DNA conversion. Peng *et al*.[19] showed that 56.06% of patients with LLV achieved negative HBV DNA after 48 weeks of TMF treatment. A possible reason for the greater virological response rate of patients with LLV in this study compared to that in the study by Peng *et al*.[19] is that, in our study, the lower limit of quantitative detection was 20 IU/mL, while the lower detection limit in Peng *et al*.'s study was 10 IU/mL. In summary, this finding is consistent with the differences in the VR rates between TMF and TDF treatment in ordinary patients, patients with LLV, and HBeAg-positive and HBeAg-negative patients at 48 weeks.[16,19]

Early HBeAg and HBsAg blood clearance can greatly reduce the incidence of primary liver cancer.[23] In our study, the rates of HBeAg loss and seroconversion in patients treated with TMF were not inferior to those in patients treated with TDF. A total of 134 patients received TMF treatment, of whom only 10 patients achieved HBeAg clearance (five patients in the TN group and five patients in the TE group). HBeAg loss occurred in 14.29% of the TN HBeAg-positive patients, and approximately 8.57% achieved HBeAg seroconversion. In the TDF group, 8.57% of the HBeAg-positive patients experienced HBeAg loss, and approximately 2.86% achieved HBeAg seroconversion. In a phase III clinical study, 17.2% of patients in the TMF group experienced HBeAg loss, and 9.4% of patients in the TMF group achieved HBeAg seroconversion.[16] A functional cure remains the goal of antivi-

ral therapy for CHB. However, HBsAg seroclearance is a rare event. Long-term treatment with ETV or TDF showed that the eight-year cumulative HBsAg seroclearance rates were 1.69% and 1.34%, respectively.[24] The negative conversion rate of HBsAg after 96 weeks of TAF treatment is not greater than 1%.[12] In our study, one patient in the TN group achieved both HBsAg clearance and seroconversion, with a baseline HBsAg concentration of only 5.76 IU/mL. Consistent with other studies, TMF demonstrates limited effectiveness in achieving HBsAg clearance or seroconversion within a short treatment duration. However, the rate of HBsAg seroclearance tends to increase with prolonged treatment.

Normalizing ALT concentrations as soon as possible when treating patients with CHB is important. A large-scale observational study showed that patients whose ALT concentrations were normalized within the first 48 weeks of antiviral treatment had a reduced risk of liver events such as liver malignancies.[23,25] In a previous phase III clinical study of TMF, TMF-treated patients had a greater rate of ALT normalization at 48 weeks (72.1%), and TMF-treated patients had a greater rate of ALT normalization among HBeAg-positive patients than those who received TDF. In our study, in TN patients with CHB, regardless of whether the laboratory standards of our hospital or the 2018 AASLD standards were used, the ALT normalization rate was not significantly different between the TMF and TDF groups. The ALT normalization rate based on the 2018 AASLD standard was 70.45% in our study, which is similar to that in the TMF phase III clinical trial. However, in the TMF phase III clinical study, the ALT normalization rate based on the 2018 AASLD standard was significantly greater than that in the TDF group. Additionally, the difference in the effects of these two drugs on ALT may have been due to the use of real-world hepatoprotective drugs.[16] Moreover, it was slightly inferior to the ALT normalization rate of 78.30% at 48 weeks reported by Peng *et al*.[19] Peng *et al*.'s study showed that the ALT normalization rate, virological inhibition rate, and biochemical reactions in the TMF group were similar to those in the TAF group. It was also considered to be related to a high viral load and persistent liver injury. This possibility was confirmed in the TE group, which had a relatively low viral load. According to the AASLD standard ALT normalization rate, 76.67% of the TE patients in our study achieved normal ALT concentrations at 48 weeks. Li *et al*.[18] reported that, in TE patients at 24 weeks, the percentage of patients whose ALT concentration had normalized was 71% (10/14).

Tenofovir (TFV) is known to be nephrotoxic. In a 10-year clinical study, 5.1% of patients with CHB developed renal dysfunction during TDF treatment.[10] Therefore, nephrotoxicity must be considered when developing TFV prodrugs (e.g., TAF, which has greater kidney safety than TDF).[12] In the phase III clinical trial of TMF, during antiviral treatment at 48 weeks, the TMF group had lower decreases in eGFR and smaller increases in blood creatinine concentrations than the TDF group.[16] Additionally, the number of patients with renal failure in the TDF group was 8.67% greater than that in the TMF group. Li[18] and Peng[19] reported that the risk of kidney injury with TMF was similar to that with TAF. The improved renal safety of TMF may be attributed to its lower dosage (typically 25 mg daily) compared to TDF (300 mg daily). The lower dose results in reduced plasma drug exposure and decreased renal accumulation, thereby minimizing mitochondrial damage in proximal renal tubules—a primary mechanism of TDF-induced nephrotoxicity.[26] This is consistent with previous studies suggesting that reduced renal tubular drug concentrations correlate with a lower risk of nephrotoxicity.[27] In our study, there were no significant differences in changes in blood creatinine concentrations, eGFR, or cystatin C concentrations after 48 weeks of TMF treatment compared with baseline. Therefore, TMF had no adverse effects on renal function. TDF-associated renal damage is mainly caused by mitochondrial damage in the proximal renal tubules, and subsequent renal tubular dysfunction manifests as increased serum creatinine concentrations.[28] Liu[29] found that urine renal tubule detection indicators (especially urine α1-microglobulin and urine NAG) could reflect kidney injury earlier than blood creatinine concentrations, eGFR, and cystatin C concentrations in patients with CHB. In this study, 33 TE patients were switched to TMF for continued treatment because of antiviral drug-associated kidney injury. Concentrations of α1-microglobulin, urine NAG, and urine α2-microglobulin significantly decreased after 24 weeks, suggesting that TMF has good kidney safety in general. Therefore, TMF is a better choice for long-term antiviral treatment for patients with CHB, especially those at risk of kidney damage.

Blood lipids are a risk factor for atherosclerotic cardiovascular disease. The potential mechanism by which TFV affects serum lipids remains to be determined. However, recent studies have shown that patients receiving TAF treatment are more likely to develop hyperlipidemia than those receiving TDF.[12] Moreover, the results of a phase III clinical trial of TMF showed an increase in the TC/high-density lipoprotein-C ratio in the TMF group.[16,17] However, in our study, TMF was associated with fewer lipid disorders. TC concentrations only significantly increased in TE patients after 48 weeks of TMF treatment. This relationship is similar to that found by Peng[19] and Li.[18] The effect of TMF on serum lipids in the present study appeared to be negligible, which is consistent with and less than the effect of TAF on blood lipids.

Strengths and limitations

To the best of our knowledge, this is the first multicenter, prospective, real-world study on TMF with HBV DNA detection reagents sensitive to <20 IU/mL, accurately identifying CHB and LLV patients. However, while serum creatinine concentrations and eGFR are used as markers of renal function, laboratory test data that are not commonly used in clinical practice to reflect early renal proximal tubular injury—such as urine α1-microglobulin, urine NAG, and urine α2-microglobulin—are not without limitations. This study also had the following limitations: First, the follow-up period of 48 weeks may not have been sufficient to completely evaluate the antiviral effect, and a longer follow-up is required to assess antiviral effectiveness. Second, this study lacked information on bone metabolism biomarkers, such as bone turnover markers and dual-energy X-ray absorptiometry, due to their high cost and scope limitations.

Conclusions

TMF is similar to TDF regarding the effectiveness of CHB treatment, with no adverse effects on renal function or lipid concentrations. In TE patients, transitioning to TMF therapy does not affect antiviral treatment and is expected to reverse initial kidney injury.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceptual design of the study (SD), guarantee of the article and manuscript drafting (YL), case collection, data acquisition, statistical analysis (GG, DC), and case collection (XG, GX, HZ). All authors have read and approved the final version and publication of the manuscript.

Ethical statement

This study strictly adhered to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (No. 2022016). All patients provided written informed consent before enrollment.

Data sharing statement

The EXCEL data used to support the findings of this study are available from the first author at liyaping8605@xjtu.edu.cn upon request.

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