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Research Article

Comparing Long-Term Outcomes of Entecavir and Tenofovir Disoproxil Fumarate in Liver Transplant Patients

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Objectives. There are no detailed reports on the long-term outcome of patients treated with tenofovir disoproxil fumarate (TDF) compared with entecavir (ENT) following liver transplantation. We aimed to assess the association between TDF use and long-term outcome compared to recipients using ENT. *Methods*. This retrospective observational study included patients who underwent liver transplantation between January 2015 and May 2019 at the First Affiliated Hospital of Zhejiang University School of Medicine and Hangzhou Shulan Hospital. Cox regression, propensity score matching (PSM), and inverse probability of treatment weighting (IPTW) were performed to assess HBV recurrence, renal dysfunction, and patient survival in liver transplant patients treated with TDF compared with ENT. *Results*. A total of 907 patients met the inclusion criteria and were included in the final analysis, among which, there were 109 (12.0%) patients treated with TDF and 798 (88.0%) patients treated with ENT. During the follow-up period, 166 patients died, 15 (13.8%) in the TDF group, and 151 (18.9%) in the ENT group. No significant association was found between TDF or ENT use and patient survival (HR, 0.72, 95% CI 0.41-1.23; $P = 0.226$) by PSM analysis. Similarly, differences in the antiviral agents were not significantly associated with hepatitis B recurrence (HR, 1.19, 95% CI 0.62-2.28; $P = 0.603$), but TDF use was significantly related to renal dysfunction after liver transplantation (HR 1.70, 95% CI, 1.21-2.37; $P = 0.002$). Similar results were obtained in subsequent sensitivity analyses. *Conclusions*. In this study, the results showed that the use of TDF after liver transplantation is as safe and effective as the use of ENT in preventing hepatitis B recurrence. However, renal function in recipients treated with TDF requires careful monitoring.

1. Introduction

Since Thomas E. Starzl performed the first liver transplantation in March 1963, this has become the definitive treatment option for end-stage liver disease and unresectable hepatocellular carcinoma (HCC) [1, 2]. Until the early 1990s, the results of liver transplantation for hepatitis B virus (HBV)-related transplant indications were remarkably unsatisfactory, due to the high rate of HBV reinfection in allografts in the early posttransplant period and the eventual death of patients due to HBV recurrence [3]. Consequently, liver transplantation for HBV-associated liver disease is considered a contraindication [4]. However, with the advent of combined prophylaxis with antiviral agents consisting of hepatitis B immunoglobulin (HBIG) and nucleos(t)ide analogues (NAs), the recurrence rate is consistently around

10% and the 60-month survival rate of patients is comparable to that of liver transplantation for other indications [5].

From the early use of NAs such as lamivudine or adefovir combined with HBIG to prevent HBV recurrence after liver transplantation, to the recent use of new potent NAs such as entecavir (ENT) and tenofovir disoproxil fumarate (TDF), which have a higher genetic barrier to resistance, these are now the first-line antiviral agents currently recommended by international guidelines for the prevention of HBV recurrence after liver transplantation [6, 7]. There is now evidence of the good safety and efficacy of ENT long-term treatment for the prevention of HBV recurrence after transplantation [8, 9]. Fung et al. reported that treatment with ENT was effective in preventing HBV recurrence after liver transplantation in recipients with chronic hepatitis B, with a probability of serum hepatitis B surface antigen (HBsAg) clearance up to 92%, and a 5-year cumulative survival rate of over 85% [8]. However, an incidence of high resistance to ENT has been reported in patients with genotypic resistance to lamivudine, while only isolated cases of HBV showing clinical resistance to TDF have been reported [10, 11]. Currently, several studies have demonstrated that TDF may induce some nephrotoxicity in liver transplantation patients, which is associated with postoperative renal dysfunction [12–14]. However, there are no detailed reports on the long-term outcome in patients treated with TDF following liver transplantation. Therefore, the purpose of this study was to assess the relationship between TDF use and HBV recurrence, renal dysfunction, and long-term survival compared to recipients using ENT by Cox regression, propensity score matching (PSM), and inverse probability of treatment weighting (IPTW).

2. Methods

2.1. Patients. This retrospective observational study collected data mainly on patient demographic characteristics, indications for transplantation and laboratory findings, and this study mainly included patients who received liver transplantation between January 2015 and May 2019 at the First Affiliated Hospital of Zhejiang University School of Medicine and Hangzhou Shulan Hospital. The exclusion criteria applied mainly as follows: retransplantation, cholangiocarcinoma, intraoperative arrest, the use of other NAs, and combined kidney-liver transplantation, and patients lost to follow-up. No organ donations were obtained from executed prisoners. The present study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine, and in accordance with the ethical guidelines of the Declaration of Helsinki.

2.2. Management of Patients. During the follow-up period, all patients who received liver transplants were managed according to standard protocols as previously described [15]. Briefly, the immunosuppressive regimen was a combination therapy of mycophenolate mofetil, tacrolimus, and bariximab, with prednisolone used as appropriate [16]. All recipients received antiviral therapy with TDF or ENT in combination with HBIG to prevent recurrence of HBV [5]. TDF is eliminated mainly through renal excretion, so it is recommended to adjust the dosing interval for patients with renal insufficiency during the study period according to the antiviral agent instructions [14]. All recipients were followed up every three months after stabilization from liver transplantation.

2.3. Endpoints and Definitions. The primary endpoint of the study was patient survival, and secondary endpoints were renal dysfunction and HBV recurrence. Patient survival was defined as the time from the day of liver transplantation to death or until the last follow-up in April 2021. Renal dysfunction was defined as a decrease of at least 20% or more from baseline estimated glomerular fltration rate (eGFR) levels that persisted until the last follow-up [14, 17]. Baseline eGFR was defined as the value tested at 30 days postliver transplantation, and the Chronic Kidney Disease Epidemiology Collaborative Equation was used to calculated level of eGFR [18]. HBV recurrence was defined as the reappearance of HBsAg and/or HBV DNA after initial seroclearance.

2.4. Statistical Analysis. The hazard ratio (HR) and 95% confidence interval (CI) was used to show the relationship between NAs use and the three endpoints by Cox proportional risk model analysis. First, the initial multivariate Cox regression model included recipient age, gender, BMI, HCC, hypertension, diabetes mellitus, Model for End-stage Liver Disease (MELD) score at transplantation, baseline eGFR, HBsAg level, and HBV DNA detectable, donor age, gender, and BMI, other clinical factors such as blood loss, cold ischemic time, surgery duration, ABO incompatibility, and severe postoperative complications. In addition, considering the imbalance at baseline characteristics, we performed a PSM model to minimize potential selection bias for the use of NAs among patients which included all the same covariates as the Cox regression model.

We further performed a secondary sensitive analysis that used IPTW control for potential confounders [19], and the final analysis included the same covariance as the propensity score matching analysis. Estimated propensity scores were obtained as predicted probabilities for each subject using of TDF or ENT. Standardized differences were used to assess the balance before and after weighting of the covariates included in the propensity score model, with a statistic of less than 0.10 indicating a clinically significant balance [20]. The statistical analysis was used *R* version 3.4.3 (R Foundation, Vienna, Austria).

3. Results

3.1. Characteristics of the TDF Group and ENT Group. A total of 1261 recipients received liver transplantation during the study period from January 2015 to May 2019. Of these, 1018 patients were treated with antiviral prophylaxis for the prevention of HBV recurrence. Fifty-six recipients who received other drugs and 55 patients who died within 3 months were excluded from the analysis. Finally, 907 patients met the inclusion criteria and were included in the final analysis. Among these patients, there were 109

(12.0%) patients treated with TDF and 798 (88.0%) treated with ENT (Figure 1). The median follow-up period for the entire cohort was 37.50 (IQR 25.82–54.63) months, and was 44.60 (IQR 27.50-58.47) months in the TDF group and 36.63 (IQR 25.58-53.57) months in the ENT group. Of 907 recipients, 124 (13.7%) were female, and their mean age was 48 years. HCC was diagnosed in 484 (41.2%) patients.

Recipient and donor characteristics according to the different antiviral agents used are shown in Table 1. No significant differences were found in age, body mass index (BMI), gender, MELD score at transplantation, presence of HCC-related indications and HBV-related indications, surgery duration, and blood loss between the TDF and ENT groups. Clinical characteristics including donor age, BMI, and gender were also comparable in the two groups. The proportion of recipients with severe complications (Clavien-Dindo ≥3a [21]) after liver transplantation was significantly lower in the TDF group (31; 28.4%) than in the ENT group (304; 38.1%; $P = 0.050$). The baseline eGFR levels were also significantly lower in the TDF group (108, IQR 95-120 mL/min/1.73 m^2) than in the ENT group (103, IQR 86-114 mL/min/1.73 m2, $P = 0.001$).

In addition, 103 patients in the TDF group matched at a 1 : 4 ratio with 412 recipients in the ENT group after PSM. The PSM model included variables such as recipient age, gender, BMI, HCC, hypertension, diabetes mellitus, MELD at transplantation, baseline eGFR, HBsAg level, and detectable HBV DNA, donor age, gender, and BMI, other clinical factors including cold ischemic time, blood loss, ABO incompatibility, and severe postoperative complications (Table S1). The baseline demographic and clinical characteristics of the two groups were comparable, except that TDF group (10, 9.7%) had a slightly smaller proportion of female patients than the ENT group (55, 13.4%), and the standardized difference was 0.11 (Table 2). We further performed a secondary sensitivity analysis using IPTW, and the weighted baseline characteristics of recipients and donors after IPTW were comparable (Table 3), with all standardized differences less than 0.10 (Figure S1).

3.2. The Association of TDF and ENT Use with Patient Survival. During the follow-up period, 166 patients died, 15 (13.8%) in the TDF group and 151 (18.9%) in the ENT group. No significant difference was found in patient survival ($P = 0.145$), and cumulative patient survival rates were 96.3% and 85.1% at 1 and 5 years in the TDF group compared with 90.6% and 79.0% in the ENT group, respectively (Figure 2(a)). The death risk was relatively lower in TDF group compared with ENT group, but the difference was not statistically significant (HR, 0.68; 95% CI, 0.40-1.15; $P = 0.148$; Table 4). By using a Cox model with NAs as a time-dependent exposure variable and adjusting for baseline characteristics, the difference was also not significant compared with patients treated with ENT (adjusted HR (aHR), 0.70, 95% CI, 0.41-1.19; $P = 0.188$; Table S2).

In the cohort after PSM analysis, the mortality rate in the TDF group was 14.6%, which was not significantly different from the 19.4% in the ENT group ($P = 0.223$, Figure 2(b)). By using Cox model analysis, no significant association was found between TDF use or ENT use and patient survival (HR, 0.72, 95% CI 0.41-1.23; $P = 0.226$; Table 4). Additional multivariable IPTW analysis yielded similar results (HR, 0.62, 95% CI, 0.35-1.09; $P = 0.099$; Table 4; Figure S2).

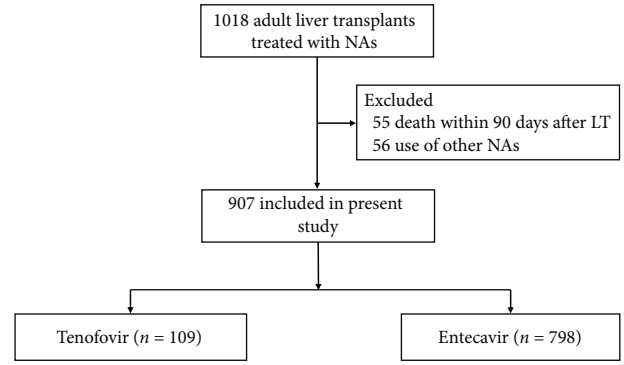

Figure 1: Process of patient-selection. Abbreviations: NA: nucleos(t)ide analogue; LT: liver transplantation.

3.3. The Association of TDF and ENT Use with Renal Dysfunction. After excluding 8 recipients with baseline eGFR levels below 30 mL/min/1.73 m^2, 250 patients had renal dysfunction in the entire cohort with a median follow-up time of 33.83 months. Renal dysfunction was found in 54 of 109 (49.5%) patients in the TDF group, compared with 196 of 788 (24.9%) patients in the ENT group. The rate of renal dysfunction was higher in patients using TDF than in those using ENT ($P < 0.001$), and cumulative renal dysfunction rates were 2.3% and 66.7% at 1 and 5 years in the TDF group compared with 4.2% and 40.1% in the ENT group, respectively (Figure 3(a)). In a crude analysis, Kaplan–Meier curves showed a HR of 1.99 (95% CI, 1.47-2.68, $P < 0.001$), and after adjusting the baseline characteristics of recipients and donors, the HR was 1.80 (95% CI, 1.31-2.45, $P < 0.001$) in the multivariable Cox analysis (Table S3).

In the PSM analysis, among the 515 recipients in the two groups, renal dysfunction was 27.7% in the ENT group compared with 47.6% in the TDF group, and the HR was 1.70 (95% CI, 1.21-2.37; $P = 0.002$, Figure 3(b)). In the IPTW analysis, similar results were obtained, and patients treated with TDF had a significantly increased risk of renal dysfunction compared to those treated with ENT (HR, 1.80; 95% CI, 1.29-2.51, $P < 0.001$, Table 4, Figure S3).

3.4. The Association of TDF and ENT Use with HBV Recurrence. In patients with HBV-related transplantation indications, after a median follow-up time of 37.40 months, 81 (10.5%) patients were found to have hepatitis B markers in peripheral blood. The HBV recurrence rate in the TDF group (12 cases, 12.6%) was slightly higher than that in the ENT group (69 cases, 10.6%), but the difference between the two groups was not statistically significant ($P = 0.566$). The 1- and 5-year cumulative HBV recurrence probability was 8.7%, 13.7% in the TDF group, and 4.4% and 13.0% in the ENT group, respectively (Figure 4(a)). The log-rank test

Table 1: Baseline characteristics of recipients and donors.

Variable	EVT ($n = 791$)	TDF ($n = 108$)	P value
Recipient age (years)	48 ± 10	48 ± 10	0.878
Recipient gender (n, % female)	113 (14.2%)	11 (10.1%)	0.246
Recipient BMI (kg/m^2)	22.24 ± 3.21	22.30 ± 3.57	0.841
Recipient HCC (n, %)	368 (46.1%)	48 (44.0%)	0.683
Hypertension (n, %)	107 (13.4%)	21 (19.3%)	0.099
Diabetes mellitus (n, %)	124 (15.5%)	23 (21.1%)	0.139
MELD at transplantation	15 (10-26)	14 (9-26)	0.955
International normalized ratio	1.42 (1.17-2.05)	1.48 (1.20-2.23)	0.446
Bilirubin (μmoI/L)	51 (20-290)	48 (21-302)	0.967
Creatinine (μmoI/L)	65 (54-79)	64 (52-75)	0.071
Baseline creatinine (μmoI/L)	72 (59-87)	64 (53-81)	0.001
Baseline eGFR (mL/min/1.73 m^2)	103 (86-114)	108 (95-120)	0.001
HBV-related indication (n, %)	778 (97.5%)	104 (95.4%)	0.213
HBsAg ($\log^{10}$ U/mL)	2.58 (1.76-3.15)	2.46 (1.89-3.33)	0.721
HBV DNA detectable	335 (42.0%)	53 (48.6%)	0.188
HBV DNA ($\log^{10}$ IU/mL)	5.30 ± 1.77	5.27 ± 1.56	0.934
Donor age (years)	39 ± 13	39 ± 13	0.875
Donor gender (n, % female)	126 (15.8%)	17 (15.6%)	0.959
Donor BMI (kg/m^2)	22.90 ± 3.08	22.56 ± 2.64	0.267
Cold ischemic time (hours)	9.85 ± 3.32	9.25 ± 3.33	0.079
Duration of surgery (hours)	5.55 ± 1.19	5.42 ± 1.47	0.284
Blood loss (100 mL)	10 (8-16)	10 (6-15)	0.149
ABO incompatibility (n, %)	113 (14.2%)	17 (15.6%)	0.688
Recipient severe postoperative complications (n, %)	304 (38.1%)	31 (28.4%)	0.050
Follow-up (months)	36.63 (25.58-53.57)	44.60 (27.50-58.47)	0.086

Abbreviations: ENT: entecavir; TDF: tenofovir; HBsAg: hepatitis B surface antigen; MELD: Model for End-stage Liver Disease; BMI: body mass index; HBV: hepatitis B; HCC: hepatocellular carcinoma; eGFR: estimated glomerular filtration rate.

showed that the risk of HBV recurrence was comparable between the TDF and ENT groups (HR 1.20; 95% CI 0.65–2.21; $P = 0.566$; Table 4). Multivariate Cox regression analysis confirmed this finding in the two groups (HR 1.10; 95% CI 0.58–2.09; $P = 0.766$; Table S4). In the PSM cohort, the HBV recurrence rate in patients treated with TDF was 12.6%, which was not significantly different from the ENT group of 10.5% ($P = 0.603$), and there was no significant association between TDF or ENT use and HBV recurrence (HR, 1.19, 95% CI 0.62-2.28; $P = 0.603$; Table 4; Figure 4(b)). Additional multivariable IPTW analysis yielded similar results (HR, 1.10, 95% CI, 0.58-2.09; $P = 0.705$; Table 4, Figure S4).

4. Discussion

In the present study, we analyzed the long-term outcomes of 907 liver transplant recipients treated with TDF and ENT, with a median follow-up of 39.58 (range, 3.00–77.03) months. Fifteen (13.8%) patients treated with TDF died, compared with 151 (18.9%) patients treated with ENT, and there was no significant association between TDF use and patient survival compared with ENT use by PSM analysis (HR, 0.72, 95% CI 0.41-1.23; $P = 0.226$). Similarly, differences in the antiviral agents were not significantly associated with hepatitis B recurrence (HR, 1.19, 95% CI 0.62-2.28; $P = 0.603$), but TDF use was significantly related to renal dysfunction after liver transplantation. Renal dysfunction was 27.7% in the ENT group compared with 47.6% in the TDF group, and the risk of renal dysfunction was increased by at least 70% in different models.

TDF and ENT are the first-line antiviral agents currently recommended by international guidelines for the prevention of HBV recurrence, although TDF may have a relatively higher resistance barrier [10, 11], the potential negative impact of TDF on kidney function remains a concern [22, 23]. The mechanisms of TDF-related nephrotoxicity mainly include inhibition of renal tubular cell transport and accumulation of endogenous compounds leading to short-term toxicity and long-term mitochondrial damage [23, 24]. Several current studies have shown a significantly increased rate of postoperative renal dysfunction in patients treated with TDF compared to those treated with ENT [25–27]. A Korean cohort study found significantly lower serum uric

Table 2: Baseline characteristics of recipients and donors after matching.

Variable	EVT ($n = 412$)	TDF ($n = 103$)	SD	P value
Recipient age (years)	48 ± 10	48 ± 10.0	0.02	0.822
Recipient gender (n, % female)	55 (13.4%)	10 (9.7%)	0.11	0.320
Recipient BMI (kg/m^2)	22.39 ± 3.19	22.31 ± 3.45	0.02	0.837
Recipient HCC (n, %)	197 (47.8%)	46 (44.7%)	0.06	0.566
Hypertension (n, %)	65 (15.8%)	19 (18.5%)	0.07	0.512
Diabetes mellitus (n, %)	66 (16.0%)	20 (19.4%)	0.09	0.408
MELD at transplantation	15 (10-25)	14 (9-26)	0.01	0.932
Baseline eGFR (mL/min/1.73 m^2)	107 (94-116)	108 (94-119)	0.08	0.539
HBsAg ($\log^{10}$ U/mL)	2.53 (1.62-3.20)	2.41 (1.43-3.32)	0.02	0.942
HBV DNA detectable	189 (45.9%)	49 (47.6%)	0.03	0.757
Donor age (years)	40 ± 13	40 ± 13	0.02	0.888
Donor gender (n, % female)	65 (15.8%)	17 (16.5%)	0.02	0.857
Donor BMI (kg/m^2)	22.66 ± 3.04	22.69 ± 2.50	0.01	0.923
Cold ischemic time (hours)	9.53 ± 3.32	9.48 ± 3.24	0.02	0.890
Duration of surgery (hours)	5.45 ± 1.20	5.44 ± 1.50	0.01	0.896
Blood loss (100 mL)	10 (6-15)	10 (6-15)	0.04	0.695
ABO incompatibility (n, %)	58 (14.1%)	16 (15.5%)	0.04	0.706
Recipient severe postoperative complications (n, %)	136 (33.0%)	31 (30.1%)	0.06	0.572

Abbreviations: ENT: entecavir; TDF: tenofovir; HBsAg: hepatitis B surface antigen; MELD: Model for End-stage Liver Disease; BMI: body mass index; HBV: hepatitis B; HCC: hepatocellular carcinoma; SD: Standardized difference; eGFR: estimated glomerular filtration rate.

Table 3: Baseline characteristics of recipients and donors after inverse probability of treatment weighting.

Variable	EVT ($n = 791$)	TDF ($n = 108$)	SD	P value
Recipient age (years)	48.37 ± 9.97	47.96 ± 10.35	0.04	0.701
Recipient gender (n, % female)	13.6%	13.8%	0.01	0.961
Recipient BMI (kg/m^2)	22.25 ± 3.20	22.50 ± 3.96	0.07	0.521
Recipient HCC (n, %)	4.59%	46.8%	0.02	0.853
Hypertension (n, %)	14.1%	14.7%	0.02	0.878
Diabetes mellitus (n, %)	16.2%	17.9%	0.04	0.668
MELD at transplantation	17.81 ± 9.51	17.80 ± 9.38	0.00	0.992
Baseline eGFR (mL/min/1.73 m^2)	99.33 ± 23.96	101.30 ± 21.71	0.09	0.381
HBsAg ($\log^{10}$ U/mL)	2.32 ± 1.25	2.21 ± 1.35	0.08	0.443
HBV DNA detectable	42.8%	44.2%	0.03	0.780
Donor age (years)	39.25 ± 13.00	39.89 ± 12.62	0.05	0.621
Donor gender (n, % female)	15.8%	17.8%	0.05	0.604
Donor BMI (kg/m^2)	22.86 ± 3.08	22.87 ± 2.54	0.00	0.981
Cold ischemic time (hours)	9.78 ± 3.32	9.52 ± 3.40	0.08	0.454
Duration of surgery (hours)	5.54 ± 1.19	5.61 ± 1.73	0.05	0.685
Blood loss (100 mL)	14.50 ± 13.94	13.78 ± 13.18	0.05	0.596
ABO incompatibility (n, %)	14.3%	13.9%	0.01	0.904
Recipient severe postoperative complications (n, %)	37.0%	35.3%	0.04	0.730

Abbreviations: ENT: entecavir; TDF: tenofovir; HBsAg: hepatitis B surface antigen; MELD: Model for End-stage Liver Disease; BMI: body mass index; HBV, hepatitis B; HCC: hepatocellular carcinoma; SD: Standardized difference; eGFR: estimated glomerular filtration rate.

acid and phosphate levels in patients treated with TDF after liver transplantation, and TDF use was an independent risk factor for proximal tubular dysfunction, and significantly increased the risk of proximal tubular dysfunction (OR, 2.34; 95% CI, 1.16-4.69; $P = 0.017$) [13]. Another Korean study similarly indicated that TDF use was independently

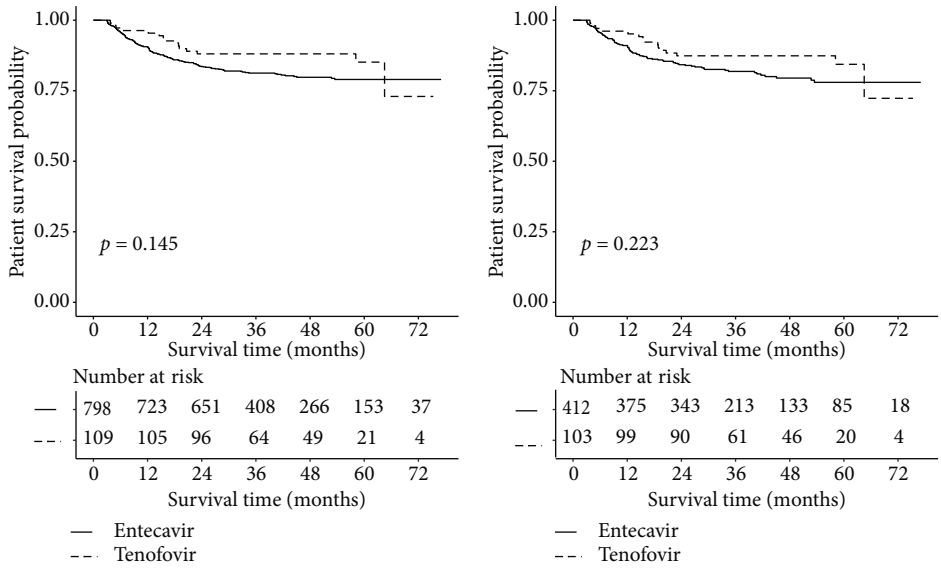

Figure 2: Cumulative incidence of patient survival. (a) Patient survival compared between different antiviral agents before propensity score matching. (b) Patient survival compared different antiviral agents after propensity score matching.

Table 4: Hazard ratios for outcomes with ENT and TNF.

Variable	Crude		PSM		IPTW	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
HBV recurrence	1.20 (0.65 to 2.21)	0.566	1.18 (0.62 to 2.28)	0.603	1.14 (0.57 to 2.28)	0.705
Renal dysfunction	1.99 (1.47 to 2.68)	<0.001	1.70 (1.21 to 2.37)	0.002	1.80 (1.29 to 2.51)	<0.001
Patient survival	0.68 (0.40 to 1.15)	0.148	0.72 (0.41 to 1.23)	0.226	0.62 (0.35 to 1.09)	0.099

Abbreviations: ENT: entecavir; TDF: tenofovir; CI: Confidence interval; HR: hazard ratio; PSM: propensity score matching; IPTW: inverse probability of treatment weighting.

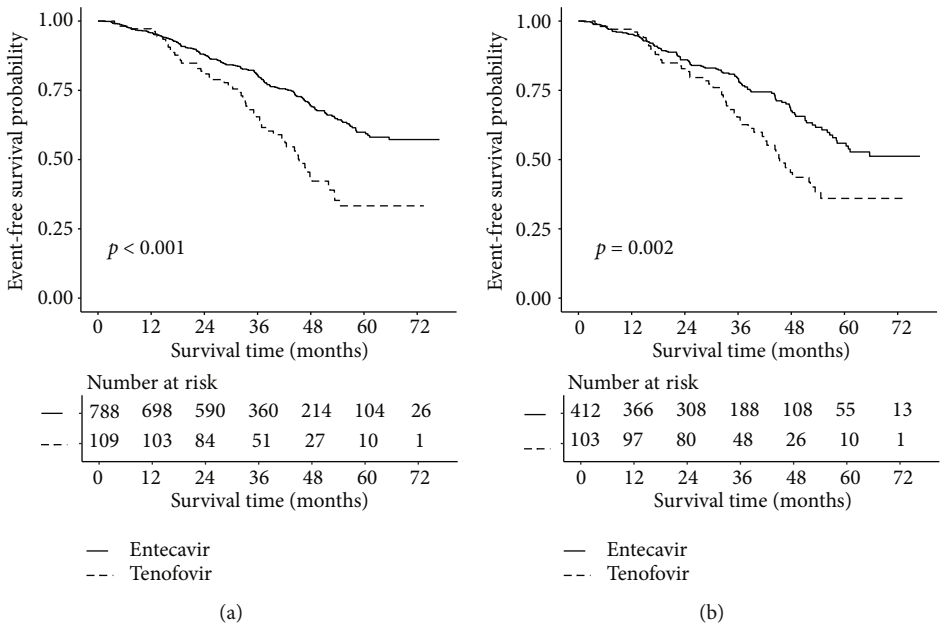

Figure 3: Cumulative incidence of renal dysfunction. (a) Cumulative incidence of renal dysfunction stratified by different antiviral agents before propensity score matching. (b) Cumulative incidence of renal dysfunction stratified by different antiviral agents after propensity score matching.

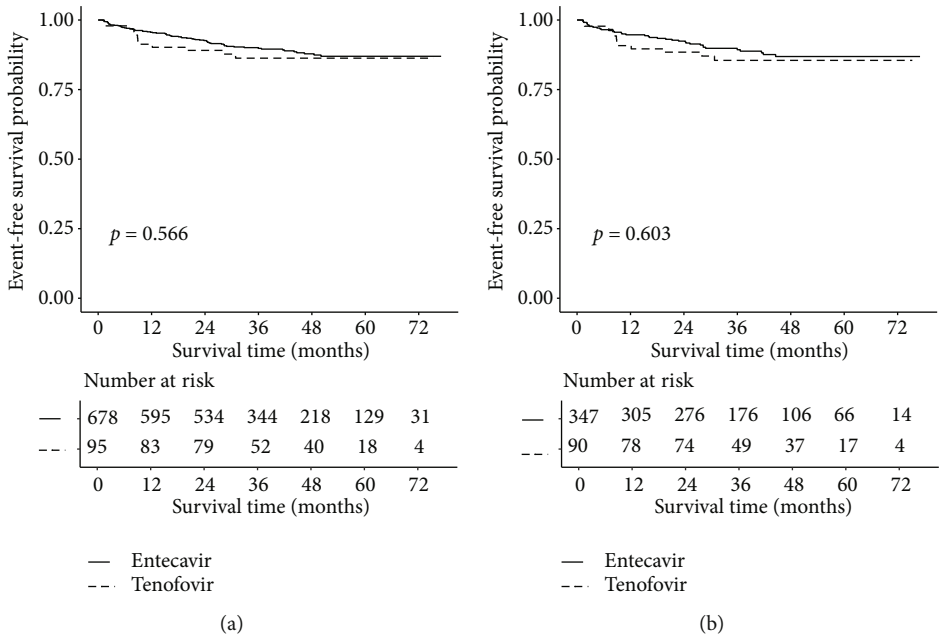

Figure 4: Cumulative incidence of HBV recurrence. (a) Cumulative incidence of HBV recurrence stratified by different antiviral agents before propensity score matching. (b) Cumulative incidence of HBV recurrence stratified by different antiviral agents after propensity score matching.

associated with renal dysfunction after adjusting for diabetes, baseline kidney function, BMI, age, and immunosuppression after a median follow-up of 29 months, in which 235 (29.2%) patients had a significant decrease in eGFR of at least 20% from baseline [14]. Similar to the results in these studies, our study also found that the use of TDF significantly increased the risk of renal dysfunction after liver transplantation compared to the use of ENT.

To our knowledge, only two studies have compared the use of TDF and ENT on the long-term survival of patients. One showed comparable overall patient survival at 60 months of follow-up for the TDF and ENT groups, with 92.3% and 80.6%, respectively ($P = 0.069$), but the study had a small sample size and did not account for baseline imbalances [13]. Another study reported that patients treated with TDF were associated with an increased risk of renal dysfunction, which was associated with significantly lower overall patient survival, with overall rates of 88.9% and 96.8% for recipients with and without renal dysfunction at 36 months after liver transplantation, respectively ($P < 0.001$). However, the overall survival of patients in the TDF and ENT groups was comparable, and the 3-year survival rates were 95.3% in TDF users and 93.4% in ENT users ($P = 0.349$) [14]. These findings are consistent with the results in our study, where negative results were obtained by statistical analysis using several statistical models, and the use of TDF did not increase the risk of mortality in recipients. Thus, despite the increased risk of renal dysfunction with TDF, similar excellent long-term survival to that with ENT was achieved after a reasonable adjustment of TDF dosage. This may be related to our definition of renal dysfunction, as in the present study this was defined as a decrease in eGFR levels of at least 20% or more from baseline that persisted until the last follow-up. By the end of the follow-up period, only 37 patients in our entire cohort had an eGFR less than 50 mL/min/1.73 m^2, 32 of these patients were in the ENT group compared to only 5 in the TDF group. Thus, similar long-term survival outcomes were obtained in the TDF group and ENT group.

HBV recurrence is another important complication after liver transplantation in patients with HBV-related indications [28]. Among the NAs recommended by the guidelines, HBIG is mainly used in combination with ENT or TDF, and has been proved by many studies to be safe and effective for preventing HBV recurrence after liver transplantation [29, 30]. In a large meta-analysis of 7274 patients from 17 studies, the rate of hepatitis B recurrence was similar in patients treated with TDF and in those treated with ENT (OR 1.11, 95% CI 0.22-5.80) [31]. Similarly, there was no statistically significant difference in the risk of HBV recurrence at a median follow-up time of 37.40 months in the present study.

The main strength of our study is that the relationship between long-term treatment with TDF and ENT and long-term outcomes in liver transplant recipients in a large cohort was determined. We also comprehensively examined the association between the use of these two NAs and HBV recurrence, renal dysfunction, and patient survival using detailed sensitivity analyses and obtained consistent results.

However, there were several limitations in our study. First, the inherent limitations of retrospective studies make it impossible to infer a causal relationship between the use of NAs and long-term outcomes in liver transplant recipients. Second, as the patients were not randomly assigned to TDF treatment or ENT treatment, the results may have been affected by selection bias. Even though a variety of statistical models including PSM and IPTW were used to adjust

for potential bias, some unforeseen confounders (e.g., prehospital and irregular medication use) may still affect long-term outcomes in recipients. Third, no further sensitivity stratification analysis was performed as the majority of cases were treated with ENT and relatively few patients were treated with TDF, due to TDF health insurance policies in China. Further validation of our results by large-scale randomized controlled studies is required for applicability in other global populations.

In conclusion, our study shows that the use of TDF after liver transplantation is equally safe and effective in preventing hepatitis B recurrence as the use of ENT. However, renal function in recipients treated with TDF needs to be carefully monitored.

Data Availability

Data available on reasonable request.

Conflicts of Interest

Authors declare no conflict of interests for this article.

Authors' Contributions

Tingxiao Zhao, Zhe Yang, and Jiong Yu contributed equally to this work.

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Supplementary Materials

Figure S1: standardized differences of variables included in the propensity score model ($n = 907$). Figure S2: the Kaplan-Meier curve for the patient survival after inverse probability of treatment weighting. Figure S3: the Kaplan-Meier curve for the renal dysfunction after inverse probability of treatment weighting. Figure S4: the Kaplan-Meier curve for the HBV recurrence after inverse probability of treatment weighting. Table S1: variables included in the propensity score model. Table S2: univariate and multivariate analyses of patient survival. Table S3: univariate and multivariate analyses of renal dysfunction. Table S4: univariate and multivariate analyses of HBV recurrence. *(Supplementary Materials)*

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