OPEN

Liver Transplantation for Hepatitis D Virus in the United States: A UNOS Study on Outcomes in the MELD Era

Tatyana Kushner, MD, MSCE,[1] Ben L. Da, MD,[2] Aryana Chan, AGNP,[1] Douglas Dieterich, MD,[1] Keith Sigel, MD, PhD,[3] and Behnam Saberi, MD[1,4]

Background. Without available curative therapies for delta hepatitis (hepatitis delta virus [HDV]), hepatic decompensation and hepatocellular carcinoma (HCC) among HDV patients often necessitates liver transplantation (LT). The objective of this study was to evaluate outcomes of LT among hepatitis B virus (HBV)/HDV patients in the United States. **Methods.** We performed the first US-based retrospective study of patients who underwent LT for HDV compared with HBV (monoinfection) in the years 2002–2019. We evaluated posttransplant survival and predictors of survival. **Results.** We identified a total of 152 HBV/HDV and 5435 HBV patients who underwent LT. HDV patients were younger at transplant (52 versus 55, $P < 0.001$), less commonly Asian (16% versus 36%, $P < 0.001$), more likely to be HCV Ab positive (42% versus 28%, $P < 0.001$), and less likely to be listed for LT with HCC (38% versus 51%, $P = 0.001$), more likely to have ascites (73% versus 64%, $P = 0.019$), had worse coagulopathy (mean INR 2.0 versus 1.82, $P = 0.04$), and were more likely to receive a HCV-positive donor organ (7% versus 3%, $P = 0.001$). Post-LT overall survival and graft survival were similar between HDV and HBV patients, including among patients with HCC. Older age, HCV coinfection, HCC, and higher model for end-stage liver disease at transplant were associated with higher posttransplant mortality. **Conclusions.** HDV patients were sicker and more likely to be listed for LT for decompensated disease compared with HBV patients. Post-LT survival was similar between HDV and HBV patients, in contrast to prior international studies that suggested worse post-LT survival in HBV patients due to higher rates of HBV reactivation.

(*Transplantation Direct* 2022;8: e1253; doi: 10.1097/TXD.0000000000001253).

Received 17 August 2021. Revision received 21 September 2021.

Accepted 23 September 2021.

[1] *Department of Medicine, Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, NY.*

[2] *Department of Medicine, Division of Hepatology, Sandra Atlas Bass Center for Liver Diseases and Transplantation, Barbara and Zucker School of Medicine for Hofstra/Northwell Health, Manhasset, NY.*

[3] *Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai, New York, NY.*

[4] *Division of Gastroenterology/Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.*

The authors declare no funding or conflicts of interest.

B.S. is a guarantor of article. T.K., B.D., B.S., and D.D. were involved in concept and design. T.K., B.D., and K.S. were involved in acquisition of data. T.K., B.D., K.S., and B.S. were involved in statistical analysis and interpretation of data. T.K., B.D., B.S., D.D., and K.S. were involved in drafting and revision of manuscript. All authors approve the final version of the article.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Correspondence: Tatyana Kushner, MD, MSCE, Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, One Gustave L Levy Pl, Box 1123, New York, NY 10029. (Tatyana.kushner@mssm.edu).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001253

INTRODUCTION

Hepatitis delta virus (HDV) infection is considered the most severe form of human viral hepatitis infection, associated with a rapid progression to cirrhosis and an increased risk of hepatocellular carcinoma (HCC), mortality, and need to undergo liver transplantation (LT).[1-5] Although previous studies estimate that HDV infection affects about 15–20 million people worldwide (approximately 5% of the hepatitis B virus [HBV]-infected population), more recent studies have reported that this figure could be much higher.[6,7] In the United States, HDV prevalence is not well understood partially due to incomplete testing and reporting.[8] However, higher rates of HDV infection in the United States may be attributed to transmission among high-risk groups, such as injection drug users,[9] and an influx of prevalent infections among immigrants from areas where HDV is endemic.[10]

Treatment options for HDV infection are limited. There are currently no FDA-approved therapies, and pegylated-interferon alpha is the only medical therapy recommended by the American Association for the Study of Liver Disease (AASLD).[11] Consequently, many patients with HDV progress to cirrhosis and its complications, for which LT may be the only option.[12] There are limited data on LT outcomes among patients with HDV. Studies from the pre antinucleos(t)ide analogue therapy era suggested higher posttransplant survival rates for HDV patients who underwent LT compared with HBV monoinfected patients.[13-15] The main hypothesized mechanism

for these improved outcomes is HBV viral suppression by the HDV virus resulting in a decreased risk of HBV recurrence after LT.[16,17] With the availability of combination antinucleos(t)ide analogue therapy and hepatitis B immunoglobulin (HBIG) for prophylaxis for HBV post-LT, it is expected that post-LT outcomes for HBV monoinfected patients should improve.[18,19]

In this study, we utilized the United Network for Organ Sharing (UNOS) database to compare baseline patient and clinical characteristics as well as the posttransplant outcomes of patients with HBV monoinfection and HBV/HDV coinfection who underwent deceased donor LT (DDLT) in the United States. Although we assessed trends in rates of LT from the earliest available UNOS data, we focused our analysis on patient characteristics, transplant outcomes, and predictors of survival in the model for end-stage liver disease (MELD) era.

METHODS

Data Source

The data reported here have been supplied by the UNOS as the contractor for the Organ Procurement and Transplantation Network. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the US Government. As UNOS is a publicly available deidentified patient-level database, institutional review board approval was not required according to the policies of UNOS after consultation with the Beth Israel Deaconess Medical Center institutional review board.

Patient Population

We identified all patients with a listing diagnosis of HDV (ie, HBV/HDV coinfection) and HBV (ie, HBV monoinfection without HDV infection) in the UNOS Database. All adult HBV and HDV patients in the "MELD era" (January 2002 to December 2019) who underwent DDLT were included. LT recipients listed as status 1A, living donor transplants, and pediatrics (age < 18)were excluded from the analysis.

HBV infection was defined as either having positive hepatitis B surface antigen or having a diagnosis code for hepatitis B including diagnosis codes for hepatitis B with or without coinfection with hepatitis C.[20,21] HDV infection was defined as having a diagnosis code for delta hepatitis. HIV infection was defined as having a positive HIV antibody result. HCV infection was defined as testing positive for HCV antibody or having diagnostic codes for HCV.

Variable Collection

From the UNOS database, we obtained demographics (age at transplant, sex, and race), clinical history (diabetes, BMI, HIV coinfection, and dialysis), liver disease history (history of portal vein thrombosis, history of TIPS, hepatic encephalopathy, ascites, and hepatitis C antibody positivity), and pre-LT laboratory values, including the pre-LT MELD score and the MELD exception score. We also obtained donor characteristics including donor hepatitis C antibody positive, HBcAb-and HBsAg-positive status, as well as donor risk index (DRI), which was calculated in accordance with Feng et al.[22] We coded etiology of liver diseases as HDV or HBV. We also subcategorized patients with HDV or HBV into those who were transplanted with HCC versus those transplanted without HCC.

Statistical Analysis

Baseline patient characteristics were compared between HBV and HDV patients utilizing chi-square test or t-tests for categorical or continuous variables, respectively. Nonparametric tests of trend were performed to evaluate change in the numbers of transplants/waitlist dropout over time.[23] Kaplan–Meier curves were plotted comparing overall survival and graft survival between the 2 groups. Kaplan–Meier posttransplant graft and patient survival and 95% confidence intervals were estimated and compared between HBV and HDV using the log-rank test. Follow-up time after LT was defined as the number of years from LT to death, retransplant, or the last follow-up. Subjects remaining alive or lost to follow-up were censored at the date of last follow-up. We evaluated predictors of survival first in univariate analysis and then in multivariate analysis. Variables selected for multivariate analysis were selected based on significance at $P < 0.05$ in univariate analysis, or based on their clinical relevance. P values < 0.05 were considered statistically significant. Analyses were performed using Stata version 16.1 (College Station, TX).

RESULTS

Overall, we identified 218 patients who were transplanted with HBV/HDV coinfection; 8324 patients were transplanted for HBV from 1987 to current. During the same time period, an additional 106 HDV patients and 2806 HBV patients were listed for LT. Figures 1 and 2 demonstrate the number of listings for LT and actual LTs over time in HBV and HDV patients with and without HCC. The median follow-up duration of all patients in the cohort was 5.4 y (IQR 1.93, 10.1),

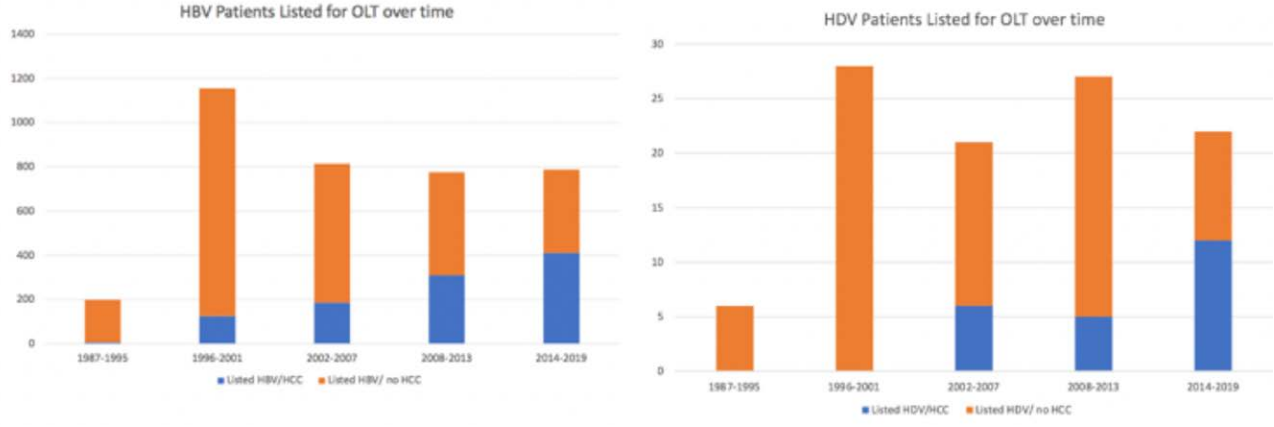

FIGURE 1. Temporal trends in listing for transplant for HDV vs HBV. HBV, hepatitis B virus; HDV, hepatitis D virion.

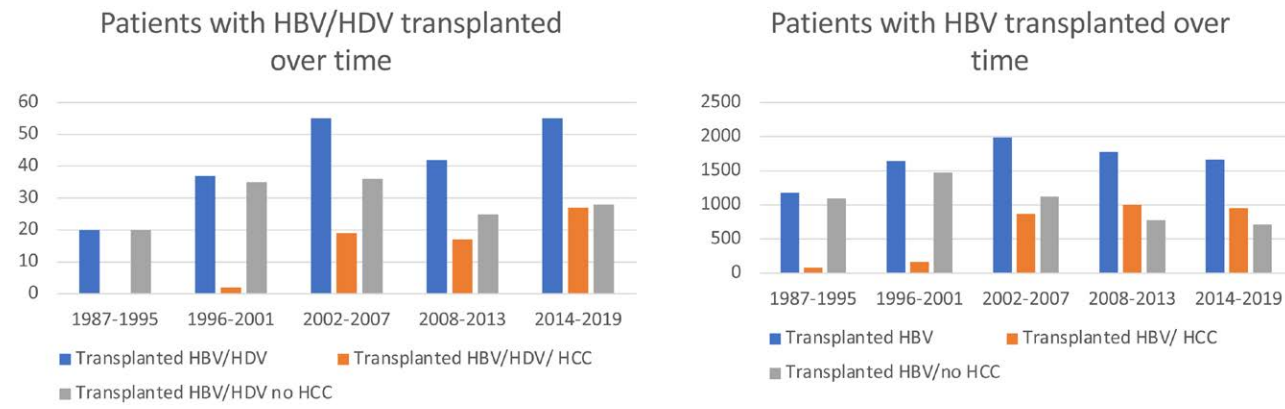

FIGURE 2. Temporal trends for transplant for HDV vs HBV. HBV, hepatitis B virus; HDV, hepatitis D virion.

with a range of 0–18 y. The median follow-up for HDV/HBV coinfected patients was 4.9 y (IQR 1.8, 9.9); and the median follow-up for HBV patients was 5.4 (1.9, 10.1). Among HBV patients, there was a clear increase over time for listing and transplant for patients with HCC ($P = 0.05$) in the MELD era (and a corresponding decline in LT for non-HCC patients, $P = 0.001$). For HDV patients, there was not as clear a trend ($P = 0.112$), with higher numbers of non-HCC HDV transplants in the most recent years.

Patient and Donor Characteristics

Our MELD era analytic cohort included a total of 152 HDV and 5435 HBV patients who underwent LT 2002–2019. The majority were male in both groups (see Table 1). HDV compared with HBV patients were less frequently Asian (16% versus 36%) and younger (mean age 52 versus 55). HBV patients were more likely to have diabetes 24% versus 16% ($P < 0.05$), although mean BMI was not significantly different between groups. HDV coinfected patients were significantly more likely to have positive HCV antibody (42% versus 28%, $P < 0.001$) but were less likely to have a history of HCC than HBV patients (38% versus 51%, $P = 0.001$). At time of LT listing, HDV patients had higher native MELDs (22 versus 19, $P = 0.01$) and lower albumin (3.0 versus 3.2, $P = 0.008$), as well as higher prevalence of ascites (73% versus 64%, $P = 0.019$) compared with HBV patients. There were no significant differences in need for life support or mechanical ventilation (<5% in both groups). Donor age, race, BMI, and cold ischemia time were similar between groups (Table 1). HCV-positive donors were more common among HDV patients (7% versus 3%, $P = 0.001$), which was expected given higher prevalence of HCV positivity among HDV recipients. Of note, DRI was higher in HBV compared with HDV patients (1.69 versus 1.53, $P < 0.05$). In regards to UNOS regions of LTs, region 5 had the most number of LTs for HDV, followed by regions 3 and 7, with lowest number of HDV LTs performed in region 1. Similar trends were seen in HBV patients (Table 2).

Baseline characteristics of HBV (n = 2821) and HDV patients (n = 63) with HCC were also examined (Table S1, **SDC**, http://links.lww.com/TXD/A385). Similar to overall study cohort, HBV/HCC patients were more likely to be Asian compared with HDV/HCC patients (50% versus 25%, $P = 0.001$). In addition, HDV/HCC patients were more likely to have HCV coinfection (48% versus 25%, $P < 0.001$) and lower albumin (3.2 versus 3.5, $P < 0.001$) and higher native MELD (16 versus 13, $P < 0.001$). HCC tumor characteristics, AFP, largest tumor size, tumor number, and history of locoregional therapy were similar between groups.

Clinical Outcomes

Among those listed for LT, there appeared to be a declining trend over time among HBV patients for waitlist dropout due to death or being too sick for transplant ($P = 0.020$), although for HDV, there was not a significant decline over time ($P = 0.309$) (Figure S1, **SDC**, http://links.lww.com/TXD/A385). Cumulative posttransplant survival and graft survival were similar between HBV and HDV patients (Figure 3, Figure S2, **SDC**, http://links.lww.com/TXD/A385), with 1-, 5-, and 10-y cumulative survival of 92.6%, 78.4%, and 68.6% in HDV patients versus 91.0%, 79.1%, and 68.2% in HBV patients ($P = 0.78$). The recorded causes of death posttransplant are listed in Table 3, which demonstrates malignancy to be the highest risk of death with 328 (23%) and 7 (18%) of transplant recipients having malignancy listed as the cause of death. Overall survival and graft survival were also similar in HBV and HDV patients with HCC (Figure 4, Figure S3, **SDC**, http://links.lww.com/TXD/A385).

Predictors of posttransplant survival in the entire cohort (HBV and HDV patients) are shown in Table 4. Older age, HCV AB-positive status, having HCC, being on dialysis, non-Asian race, and earlier transplant year were associated with higher mortality in the multivariate analysis. Upon stratification of analysis by Asian versus non-Asian race, similar results were obtained, with no significant differences between groups (Figures S5, S6, **SDC**, http://links.lww.com/TXD/A385). HDV was not a significant predictor of post-LT survival.

In univariable analysis evaluating predictors of survival among HDV patients, older age, HCV coinfection, lower albumin, higher DRI, and having an HCV-positive donor were associated with increased mortality. In multivariable analysis among HDV patients, older age and lower albumin were associated were associated with higher mortality (Table 5).

DISCUSSION

In this first nationwide analysis of liver transplant outcomes for HDV patients compared with HBV monoinfected patients in the United States during the MELD era, we found a significant decrease over time in LT for decompensated HBV disease with a concomitant increase in transplant for HCC, despite a stable rate of transplant over time for decompensated HDV disease. In addition, we saw a decline

TABLE 1.

Baseline characteristics before liver transplant

	HBV (n = 5435)	HBV/HDV (n = 152)	*P*
Demographics			
Age, y	52 (46, 60)	56 (49, 62)	<0.001
Gender n (%), female	1157 (22%)	31 (20%)	0.79
Race, n (%)			<0.001
White	2343 (43%)	88 (58%)	
Hispanic	411 (8%)	16 (11%)	
African American/Black	624 (11%)	20 (13%)	
Asian	1966 (36%)	25 (16%)	
Other	91 (2%)	3 (2%)	
Clinical history			
Diabetes	1291 (24%)	24 (16%)	0.02
BMI	26 (24, 30)	27 (24, 31)	0.17
Dialysis	519 (10%)	15 (10%)	0.90
HIV (+)	89 (2%)	2 (1%)	0.27
Liver disease history			
Portal vein thrombosis	549 (10%)	18 (12%)	0.48
TIPS	456 (8%)	12 (8%)	0.83
Hepatic encephalopathy	2783 (51%)	88 (58%)	0.10
Ascites	3466 (64%)	111 (73%)	0.02
HCV (+)	1511 (28%)	63 (42%)	<0.001
HCC	2821 (52%)	63 (42%)	0.01
Laboratories at transplant listing			
Albumin (g/dL)	3.2 (2.6, 3.8))	3.0 (2.5, 3.6))	0.01
Bilirubin (mg/dL)	2.5 (1, 8.2)	3.9 (1.8, 8.7)	0.28
Creatinine (mg/dL)	1.0 (0.8, 1.5)	1 (0.8, 1.5)	0.35
INR	1.5 (1.2, 2.1))	1.7 (1.3, 2.3))	0.04
Sodium (mEq/L)	137 (135, 140), n = 4472	137 (135, 139), n = 119	0.07
MELD score	17 (10, 28)	20 (14, 29)	0.01
MELD exception score	28 (22, 32)	27 (22, 32)	0.71
Clinical characteristics			
Life support	109 (2%)	4 (3%)	0.59
Mechanical ventilation	89 (2%)	1 (1%)	0.34
Median wait time (median, IQR)	104 (19, 335)	114 (30, 292)	0.46
Donor characteristics			
Donor age	44 (27, 55)	40 (27, 54)	0.09
Donor gender (% female)	3196 (59%)	95 (63%)	0.36
Donor race			0.28
White	3361 (62%)	99 (65%)	
Hispanic	744 (14%)	15 (10%)	
African American/Black	974 (18%)	31 (20%)	
Asian	257 (5%)	7 (5%)	
Other	99 (2%)	0 (0%)	
Donor BMI	26 (23, 30)	27 (24, 31)	0.20
Cold ischemia time	6.5 (5, 8))	6.6 (5.0, 8.0))	0.78
Donor hepatitis C positive (%)	146 (3)	11 (7)	0.001
Donor HBcAb positive (%)	567 (10)	9 (6)	0.07
Donor HBsAg positive (%)	17 (0.31)	0 (0)	0.49
DRI	13 (1.2, 2.3)	1.3 (1.1, 1.8)	0.01
Posttransplant initial immunosuppression regimen[a]			
Induction			
Prograf	119 (3%)	3 (3%)	0.87
Steroids	2887 (59%)	122 (91%)	0.82
Cellcept	55 (2%)	77 (100%)	0.71
Thymoglobulin	406 (97%)	0 (0%)	0.84
Maintenance			
Prograf	4009 (100%)	112 (100%)	0.53
Steroids	4193 (86%)	122 (91%)	0.96
Cellcept	1908 (99%)	77 (100%)	0.53

Values expressed as median (IQR) for continuous variables or n (%) for categorical variables unless otherwise stated.
All variables contain less than 1% missing data unless otherwise stated.
[a]Ten percent or more missing data.
BMI, body mass index; DRI, disease risk index; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt.

TABLE 2.

UNOS regions of transplants

	HBV (n = 5435)	HBV/HDV (n = 152)	Total
Region, n (%)			
1	212 (3.9)	3 (2.0)	215 (3.9)
2	642 (11.8)	13 (8.5)	655 (11.7)
3	793 (14.6)	23 (15.1)	816 (14.6)
4	423 (7.8)	10 (6.6)	433 (7.8)
5	1182 (21.8)	40 (26.3)	1222 (21.8)
6	219 (4.0)	6 (4.0)	225 (4.0)
7	443 (8.2)	18 (11.8)	461 (8.3)
8	282 (5.2)	12 (8.0)	294 (5.3)
9	548 (10.1)	6 (4.0)	554 (9.9)
10	340 (6.3)	6 (4.0)	346 (6.2)
11	351 (6.5)	15 (10.0)	366 (6.6)
Total	5435 (100)	152 (100)	5587 (100)

HBV, hepatitis B virus; HDV, hepatitis D virion; UNOS, United Network for Organ Sharing.

in waitlist dropout for HBV patients over time for being too sick for transplant or death, which was not seen in HDV. HDV patients were overall younger and "sicker" at time of transplant as shown by higher native pre-LT MELDs compared to HBV patients supporting the continued importance of transplant as an option for decompensated disease in HDV patients. However, despite HDV patients being "sicker" at time of transplant, in contrast to historic studies with data obtained before effective newer generation antinucleos(t)ide analogue therapy and HBIG protocols, 5-y overall and graft survival were virtually identical between HBV and HDV patients (including among those transplanted for HCC), suggesting that current immunoprophylaxis regimens and posttransplant care have equalized posttransplant outcomes between the 2 groups.

Our finding that HDV patients are younger and "sicker" than their HBV counterparts is not surprising given that the natural history of disease leads to more rapid fibrosis progression in HDV patients. In addition, although we have effective therapies for HBV suppression, which may have contributed to the decline over time in listings and transplants of HBV patients for decompensated disease (as opposed to HCC), therapies for HDV patients are still limited, and therefore LT may be a more crucial option. Although overall there were fewer patients undergoing LT for HDV (compared to HBV patients), we recognize that in addition to HDV being relatively rare, this may also be reflective of under-testing/screening of HBV patients for HDV in the United States.[8,24] Our study demonstrates that the more rapid progression to decompensated disease among HDV patients demonstrates the importance of screening patients for HDV.[11] Although currently there are no approved treatments in the United States for HDV, with the recent approval of bulevirtide in Europe,[25] as well as the investigation of new therapies including the prenylation inhibitor, lonafarnib, and HDV particle export inhibitors nucleic acid polymers, there is hope in new treatment possibilities for HDV,[26] which may decrease the need for LT for in HDV.

Our findings of similar overall posttransplant survival between HDV coinfected and HBV monoinfected patients is comparable to more recent studies performed internationally (see Table 6 for summary of prior studies evaluating transplant outcomes in HDV patients). This is in contrast to multiple earlier studies that have reported increased HBV recurrence in HBV patients and worse outcomes,[30,33] with high levels of HBV replication pretransplant being associated with a higher risk of HDV recurrence posttransplant[29] (which is not the case for HDV). With well-defined immunoprophylaxis and nucleoside treatment algorithms,

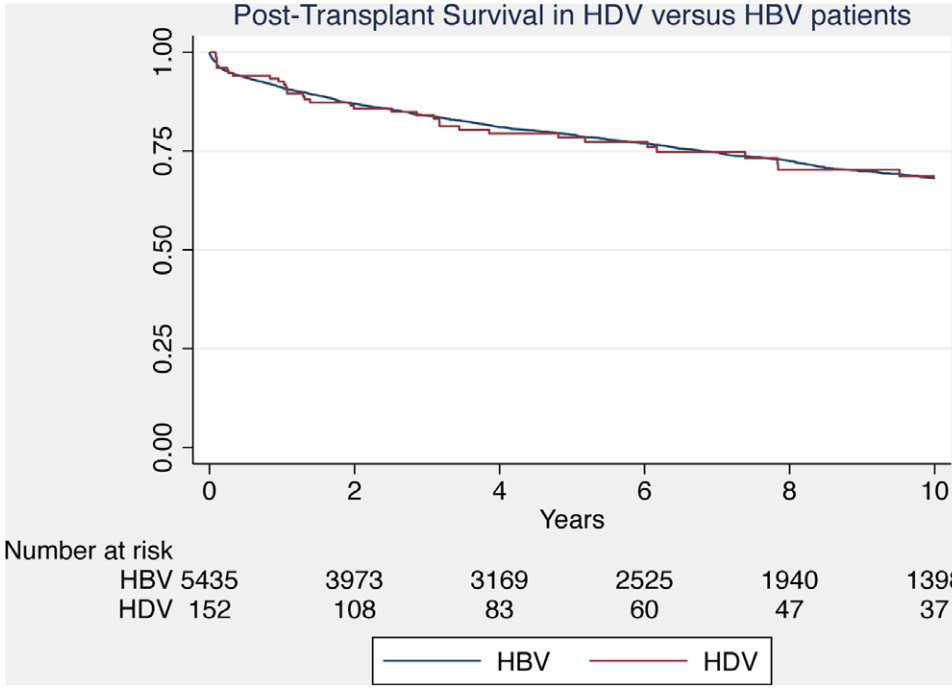

FIGURE 3. Posttransplant survival HBV monoinfected patients compared to HBV/HDV coinfected patients (P = 0.77). HBV, hepatitis B virus; HDV, hepatitis D virion.

TABLE 3.

Cause of death post-LT among HBV vs HDV patients.

	HBV (n = 1398)	HBV/HDV (n = 40)
Cardiovascular	158 (11%)	3 (8%)
Malignancy	328 (23%)	7 (18%)
Infection	159 (11%)	2 (5%)
Multiorgan Failure	97 (7%)	4 (10%)
Graft-related	114 (8%)	4 (10%)
Cerebrovascular	41 (3%)	2 (5%)
Other	230 (16%)	7 (18%)
Unknown	271 (19%)	11 (25%)

HBV, hepatitis B virus; HDV, hepatitis D virion; LT, liver transplantation.

our study demonstrates that in the current era, similar to other recent studies, increased HBV viral recurrence post-LT appears to be no longer contributing, and inferior outcomes are no longer seen. Similarly, European studies have incorporated HBIG protocols into their management of post-transplant HBV/HDV patients for at least 2 decades (Table 6).

Our study identified a very high rate of HCV coinfection among HDV patients, which is consistent with prior studies that have similarly suggested that there is a high prevalence of hepatitis C coinfection in hepatitis delta patients in the United States. A 2015 study conducted within the US Veterans' Affairs medical system found that 59% of hepatitis-delta-positive patients were coinfected with hepatitis C.[8] This finding is not surprising given the fact that both infections are commonly associated with behaviors such as injection drug use and high-risk sexual contact. Worldwide, this correlation is strong as well. A recent systematic review and meta-analysis composed of 376 population samples from 95 countries noted that HDV prevalence is higher in people who inject drugs and who are infected with HCV and HIV.[34] Thus, in Western Europe, as well as in the United States, the relationship between intravenous drug use and hepatitis delta infection remains notable.[3] Given widely available DAA therapies for HCV, however, most HDV patients will likely have had their HCV treated before LT and ideally slow progression of their liver disease. On the other hand, given the high prevalence of HCV coinfection, HDV patients will continue to have the opportunity to receive HCV-positive livers, possibly decreasing their transplant wait time.

There are several limitations to our study. Because of the nature of the UNOS database, we do not have available laboratory data including HBeAg status, HDV RNA, and HBV DNA levels pretransplant and posttransplant (and no data on which of the HBV patients ever had HDV screening), there are limited explant pathology data available, and incomplete cause of death data available due to loss to follow up. In addition, we determined HDV and HCV coinfection based on diagnosis codes rather than laboratory data (although misclassification is likely low for these diagnosis codes). Unfortunately, we also did not have access to post-transplant HBV prophylaxis regimens in patients included in our study nor rates of disease recurrence, nor do we have data on HCV treatment. The number of patients in the HBV/HDV coinfected cohort was relatively small, which limited the ability to delineate significant covariates impacting survival among HBV/HDV coinfected patients. Nonetheless, this is the most updated analysis of transplant outcomes in HDV patients (pertaining to the current protocols of HBV immunoprophylaxis) and is the only comprehensive study of post-LT outcomes for HDV in the United States.

In summary, although HDV patients are sicker at the time of LT compared to HBV monoinfected patients, they have equal graft survival and overall survival after LT. Although multiple treatments for HDV are currently under investigation,[35-39] there are still limited treatment options available, and LT remains an

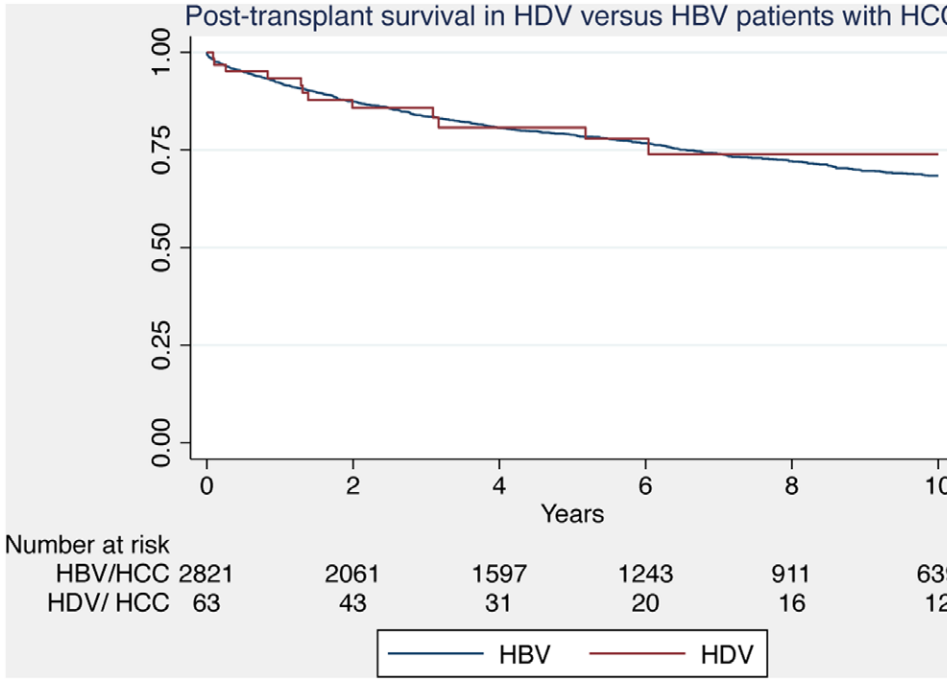

FIGURE 4. Posttransplant survival in HBV compared to HDV patients with HCC (P = 0.69). HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis D virion.

TABLE 4.

Univariate and multivariate predictors of posttransplant survival among entire cohort

	Univariate			Multivariate		
		95% CI for HR			95% CI for HR	
	HR	Lower upper	*P*	HR	Lower upper	*P*
Recipient characteristics						
Age[a]	1.20	1.13–1.26	<0.001	1.25	1.18–1.33	<0.001
Female gender	0.99	0.873–1.112	0.84			
Race						
Asian	0.67	0.60–0.76	<0.001	0.71	0.63–0.82	<0.001
Hispanic	0.83	0.68–1.01	0.07	0.78	0.64–0.95	0.01
AA/Black	0.88	0.75–1.04	0.14			
HDV	1.05	0.77–1.43	0.77			
HCV Ab positive	1.43	1.29–1.58	<0.001	1.31	1.17–1.46	<0.001
HCC	0.95	0.86–1.05	0.29	1.20	1.05–1.38	0.008
Creatinine	1.09	1.06–1.11	<0.001			
Albumin	0.94	0.88–0.99	0.04			
MELD	1.01	1.01–1.02	<0.001	1.01	1.01–1.02	<0.001
Ascites	1.114	1.03–1.27	0.02			
HE	1.12	1.01–1.24	0.03			
Dialysis	1.74	1.50–2.03	<0.001	1.44	1.19–1.76	<0.001
Donor characteristics						
Donor age (10 y)	1.03	1.00–1.06	0.04			
DRI	1.05	0.98–1.12	0.20			
Transplant factors						
Transplant year[b]	0.89	0.84–0.95	<0.001	0.85	0.80–0.90	<0.001
HBcAb-positive donor	0.97	0.83–1.14	0.72			
HBsAg-positive donor	0.96	0.36–2.55	0.93			
HCV donor	1.04	0.74–1.46	0.82			

[a]Every 10-y increase.
[b]Every 5-y increase.
DRI, disease risk index; HBcAb, hepatitis B core antibody; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis delta virus; HE, hepatic encephalopathy; MELD, model for end-stage liver disease.

TABLE 5.

Univariate and multivariate predictors of posttransplant survival in HDV patients

	Univariate			Multivariate		
		95% CI for RR			95% CI for RR	
	HR	Lower upper	*P*	HR	Lower upper	*P*
Recipient characteristics						
Age (10 y)	1.44	1.05–1.10	0.03	1.42	1.00–2.02	0.05
Female gender	1.18	0.53–2.67	0.68			
Race						
Asian	0.40	0.12–1.33	0.14			
Hispanic	1.93	0.83–4.49	0.13			
AA/Black	0.61	0.21–1.76	0.36			
HCV	2.18	1.16–4.09	0.02			
HCC	1.08	0.57–2.04	0.80			
Creatinine	0.99	0.80–1.23	0.94			
Albumin	0.59	0.39–0.93	0.02	0.55	0.34–0.88	0.01
MELD	0.99	0.96–1.02	0.53			
Ascites	1.18	0.58–2.40	0.66			
HE	0.76	0.41–1.40	0.37			
Donor characteristics						
Donor age	1.24	1.01–1.52	0.04			
DRI	1.71	1.08–2.72	0.02			
Transplant factors						
Transplant year	0.73	0.50–1.04	0.08			
HBcAb-positive donor	1.65	0.59–4.63	0.34			

DRI, disease risk index; HBcAb, hepatitis B core antibody; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis delta virus; HE, hepatic encephalopathy; MELD, model for end-stage liver disease.

TABLE 6.

Prior studies evaluating transplant outcomes in HDV patients

Author	Year	Country	No. of patients	Design	Outcomes	Posttransplant prophylaxis
Ferrarese et al[27]	2006–2016	Italy	106	Single center	LT occurred with a similar prevalence among cohorts Survival: Not evaluated	No information about posttransplant immunoprophylaxis available
Brancaccio et al[28]	2007–2014	Italy	11	Single center	LT occurred in 11 patients 3.44 HDV cases/1000 mo vs 0.78 HBV cases/1000 mo Survival: Not evaluated	Oral nucleos(t)ide analog
Serin and Tokat[29]	2004–2018	Turkey	104	Single center	4 of 104 died during the follow-up period similar mortality between patients with and without HDV recurrence (2.2% vs 7.1%; $P = 0.35$). Survival: Equivalent	HBIG received intraoperatively oral nucleos(t)ide analogue
Lima et al[30]	2002–2011	Brazil	69	Single center	Mortality: HBV monoinfected n = 10; HDV n = 1 Survival[a]: Worse in HBV	No information about posttransplant immunoprophylaxis available
Beckebaum et al[31]	2000–2016	Italy, Germany, Switzerland, The Netherlands, UK	114 HDV 257 HBV	Multicenter	HBV recurrence in 4 (3.5%) HDV patients versus 16 (4.3%) HBV patients HCC recurrence in 15.5% HBV vs 8.1% HDV Survival: Not evaluated	HBIG for ≥1 y in all patients 94% of all patients received nucleos(t)ide analog
Adil et al[32]	2003–2013	Turkey	255	Single center	No HDV recurrence posttransplant Survival: Not evaluated	All patients received HBIG: >103 HBV DNA copies: 5000 IU HBIG in anhepatic phase of the operation; 2000 IU/d HBIG for 7 d after surgery. <1000 HBV DNA copies: 2000 IU HBIG in anhepatic phase of the operation; 500 IU/d HBIG for 7 d after surgery. All received tenofovir 245 mg/d 7 d after liver transplant
Burra et al[15]	1988–2010	European Liver Transplant Database	5912 HBV 1511 HDV 136 HBDCV	Transplant database	HBV without HCC had lower patient and graft survival compared to HDV patients (83%, 78%, 75%, and 68% and 80%, 74%, 71%, and 64%, respectively, compared to 92%, 90%, 89%,86%, and 89%, 86%, 85%, 80%; each $P < 0.001$); No difference in survival in HBV/HDV patients with HCC Survival[a]: Worse in HBV non-HCC patients	No information about posttransplant immunoprophylaxis available
Samuel et al[33]	1984–1990	France	76	Single center	Overall survival rate was 88% at 5 y Survival: Equivalent	First 4 patients 1985–1986: 1 dose 10 000 iu HBIG anhepatic, short-term HBIG 1986–1987: 3000 IU HBIG anhepatic, subsequent HBIG until HBsAg disappearance (10 000 iu HBIG when anti-HBs < 100 IU/L) 1988–1990: 10 000 IU HBIG anhepatic; daily HBIG day 1–6 posttransplant; 1000 IU HBIG when anti-HBs <100 IU/l

Gray indicates HBIG administered intraoperatively or postoperatively.

[a]Survival worse in HBV.

HBDCV, hepatitis B and D coinfected; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis D virion; IU, international units; LT, liver transplant.

important consideration among these patients. Our findings support an aggressive approach to the use of LT in HDV-infected patients especially given the limited medical therapies currently available. With the development of new therapies for HDV, it will be important to continue to evaluate rates and outcomes of LT for decompensated HDV patients with and without HCC.

REFERENCES

1. Gish RG, Yi DH, Kane S, et al. Coinfection with hepatitis B and D: epidemiology, prevalence and disease in patients in Northern California. *J Gastroenterol Hepatol.* 2013;28:1521–1525.
2. Béguelin C, Moradpour D, Sahli R, et al; Swiss HIV Cohort Study. Hepatitis delta-associated mortality in HIV/HBV-coinfected patients. *J Hepatol.* 2017;66:297–303.
3. Romeo R, Del Ninno E, Rumi M, et al. A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. *Gastroenterology*. 2009;136:1629–1638.
4. Coghill S, McNamara J, Woods M, et al. Epidemiology and clinical outcomes of hepatitis delta (D) virus infection in Queensland, Australia. *Int J Infect Dis*. 2018;74:123–127.
5. Elsaid MI, Li Y, John T, et al. Economic and health care burdens of hepatitis delta: a study of commercially insured adults in the United States. *Hepatology*. 2020;72:399–411.
6. Chen HY, Shen DT, Ji DZ, et al. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. *Gut*. 2020;73:523–532.
7. Wedemeyer H, Manns MP. Epidemiology, pathogenesis and management of hepatitis D: update and challenges ahead. *Nat Rev Gastroenterol Hepatol*. 2010;7:31–40.
8. Kushner T, Serper M, Kaplan DE. Delta hepatitis within the veterans affairs medical system in the United States: prevalence, risk factors, and outcomes. *J Hepatol*. 2015;63:586–592.
9. Kucirka LM, Farzadegan H, Feld JJ, et al. Prevalence, correlates, and viral dynamics of hepatitis delta among injection drug users. *J Infect Dis*. 2010;202:845–852.
10. Rizzetto M, Alavian SM. Hepatitis delta: the rediscovery. *Clin Liver Dis.* 2013;17:475–487.
11. Terrault NA, Bzowej NH, Chang KM, et al; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016;63:261–283.
12. Koh C, Heller T, Glenn JS. Pathogenesis of and new therapies for hepatitis D. *Gastroenterology*. 2019;156:461.e1–476.e1.
13. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. *N Engl J Med.* 1993;329:1842–1847.
14. Lerut JP, Donataccio M, Ciccarelli O, et al. Liver transplantation and HBsAg-positive postnecrotic cirrhosis: adequate immunoprophylaxis and delta virus co-infection as the significant determinants of long-term prognosis. *J Hepatol*. 1999;30:706–714.
15. Burra P, Germani G, Adam R, et al. Liver transplantation for HBV-related cirrhosis in Europe: an ELTR study on evolution and outcomes. *J Hepatol*. 2013;58:287–296.
16. Wu JC, Chen PJ, Kuo MY, et al. Production of hepatitis delta virus and suppression of helper hepatitis B virus in a human hepatoma cell line. *J Virol*. 1991;65:1099–1104.
17. Sagnelli E, Coppola N, Scolastico C, et al. Virologic and clinical expressions of reciprocal inhibitory effect of hepatitis B, C, and delta viruses in patients with chronic hepatitis. *Hepatology*. 2000;32:1106–1110.
18. Fung J, Chan SC, Cheung C, et al. Oral nucleoside/nucleotide analogs without hepatitis B immune globulin after liver transplantation for hepatitis B. *Am J Gastroenterol*. 2013;108:942–948.
19. Maiwall R, Kumar M. Prevention and treatment of recurrent hepatitis b after liver transplantation. *J Clin Transl Hepatol*. 2016;4:54–65.
20. Rifai G, Anani A, Hanouneh IA, et al. Liver transplantation for hepatitis B in early adulthood: analysis of the United Network for Organ Sharing database. *Transplant Proc.* 2016;48:3362–3367.
21. Waki K, Sugawara Y, Tamura S, et al. Outcome of liver transplantation for recipients with hepatitis B and hepatitis C virus coinfection: analysis of the UNOS data. *Transplantation*. 2011;92:809–814.
22. Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant*. 2006;6:783–790.
23. Conover WJ. *Practical Nonparametric Statistics*. 3rd ed. Wiley; 1999.
24. Da BL, Rahman F, Lai WC, et al. Risk factors for delta hepatitis in a North American cohort: who should be screened? *Am J Gastroenterol*. 2021;116:206–209.
25. Kang C, Syed YY. Bulevirtide: first approval. *Drugs*. 2020;80:1601–1605.
26. Rizzetto M, Hamid S, Negro F. The changing context of hepatitis D. *J Hepatol*. 2021;74:1200–1211.
27. Ferrarese A, Sciarrone S, Gambato M, et al. Letter: clinical outcomes of patients with hepatitis D infection in the liver transplant setting. *Aliment Pharmacol Ther*. 2020;51:482–483.
28. Brancaccio G, Fasano M, Grossi A, et al. Clinical outcomes in patients with hepatitis D, cirrhosis and persistent hepatitis B virus replication, and receiving long-term tenofovir or entecavir. *Aliment Pharmacol Therap*. 2019;49:1071–1076.
29. Serin A, Tokat Y. Recurrence of hepatitis D virus in liver transplant recipients with hepatitis B and D virus-related chronic liver disease. *Transplant Proc*. 2019;51:2457–2460.
30. Lima DS, Murad Júnior AJ, Barreira MA, et al. Liver transplantation in hepatitis delta: south america experience. *Arq Gastroenterol*. 2018;55:14–17.
31. Beckebaum S, Herzer K, Bauhofer A, et al. Transplant patients receiving long-term hepatitis B immunoglobulin prophylaxis. *Ann Transplant*. 2018;23:789–801.
32. Adil B, Fatih O, Volkan I, et al. Hepatiti B virus and hepatitis D virus recurrence in patients undergoing liver transplantation for hepatitis B virus and hepatitis B virus plus hepatitis D virus. *Transplant Proc*. 2016;48:2119–2123.
33. Samuel D, Zignego AL, Reynes M, et al. Long-term clinical and virological outcome after liver transplantation for cirrhosis caused by chronic delta hepatitis. *Hepatology*. 1995;21:333–339.
34. Stockdale AJ, Kreuels B, Henrion MYR, et al. The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. *J Hepatol*. 2020;73:523–532.
35. Hamid SS, Etzion O, Lurie Y, et al. A phase 2 randomized clinical trial to evaluate the safety and efficacy of pegylated intereron lambda monotherapy in patients with chronic hepatitis delta virus infection. Interim results from the LIMT HDV study. *Hepatology*. 2017;66:496A.
36. Bogomolov P, Alexandrov A, Voronkova N, et al. Treatment of chronic hepatitis D with the entry inhibitor myrcludex B: first results of a phase Ib/IIa study. *J Hepatol*. 2016;65:490–498.
37. Wedemeyer H, Bogomolov P, Blank A, et al. Final results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of Myrcludex B in combination with Tenofovir in patients with chronic HBV/HDV co-infection. *J Hepatol*. 2018;68:S3
38. Bazinet M, Pantea V, Cebotarescu V, et al. Initial follow-up results from the REP 301 trial: safety and efficacy of REP2139-Ca and pegylated interferon alpha-2a in caucasian patients with chronic HBV/HDV co-infection. *Hepatology*. 2016;64:912A.
39. Koh C, Canini L, Dahari H, et al. Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial. *Lancet Infect Dis*. 2015;15:1167–1174.