American Journal of Transplantation 25 (2025) 1502–1514

Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: www.amjtransplant.org

Original Article

Liver transplantation for hepatitis D virus/hepatitis B virus coinfection in Italy: An intention-to-treat analysis of long-term outcomes

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Abbreviations: CNT, Italian National Transplant Centre; HBV, hepatitis B virus; HBIg, immunoglobulin against antigen of the hepatitis B virus; HBsAg, antigen of the hepatitis B virus; HDV, hepatitis D virus; HCC, hepatocellular carcinoma; IQR, interquartile range; ITT, intention-to-treat; LT, liver transplantation; MELD, model for end-stage liver disease; NA, nucleos(t)ides analog; WL, waiting list.

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https://doi.org/10.1016/j.ajt.2025.03.003
Received 29 September 2024; Received in revised form 2 March 2025; Accepted 3 March 2025
Available online 7 March 2025

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ARTICLE INFO

Keywords:
hepatitis D infection
hepatitis B infection
liver transplantation
viral prophylaxis
outcomes
chirrosis
hepatocellularcarcinoma

ABSTRACT

Patients with hepatitis D virus (HDV)/hepatitis B virus (HBV)-related end-stage liver disease candidates for liver transplantation (LT) have traditionally been regarded as a special population, although their outcomes are controversial. An intention-to-treat (ITT) analysis of long-term outcomes of HDV/HBV-coinfected patients waitlisted for LT in Italy, between 2011 and 2020, was performed and compared with HBV-monoinfected LT candidates. Of 1731 HBV-infected LT candidates, 1237 (71.5%) had HBV monoinfection and 494 (28.5%) HDV/HBV coinfection. At listing, HDV/HBV-coinfected patients were significantly younger, listed mainly for decompensated cirrhosis, and with fewer hepatocellular carcinoma (HCC) cases; (26% vs 65.8%; $P < .0001$) compared with HBV-monoinfected patients. HDV/HBV-coinfected patients showed better 5-year ITT survival (83.2%; 95% CI: 79.4%-83.4%, vs 71.6%; 95% CI: 68.8%-74.2%; $P < .0001$). ITT-multivariable analysis identified the presence of HCC, advanced recipient age, and high model for end-stage liver disease-Na scores as mortality risk factors. Five years after LT, 99.1% of HDV/HBV-coinfected patients received oral nucleos(t)ide analogs, with immunoglobulins against antigen of the hepatitis B virus in

91.8% of cases. HBV and HDV viral recurrences were 1.1% and 0.2%, respectively, whereas recurrent or de novo HCC were 8.9% and 0.3%, respectively. In Italy, HDV/HBV-coinfected patients waitlisted for LT showed more favorable outcomes compared with HBV-monoinfected patients, both before and after LT. These excellent results, from the largest cohort reported so far, suggest that HDV/HBV-coinfected LT recipients do not represent a risky population and may be considered for simpler long-term antiviral prophylactic strategies.

1. Introduction

Hepatitis D virus (HDV) infection is considered the most severe form of chronic viral hepatitis.[1] HDV is a small defective RNA virus that is strictly dependent on the life cycle of hepatitis B virus (HBV), as it requires the surface antigen of the hepatitis B virus (HBsAg) for its replication, assembly, and transmission.[2] Although the spread of vaccination against HBV has reduced the number of individuals who are susceptible to HDV infection—at least in high-income countries—the burden of HDV infection is currently not as low as envisaged.[3-5] This is mainly due to the continued entry of migrants from HDV-endemic and HBV-endemic areas and the emergence of new HDV genotypes.[6,7]

From a clinical perspective, HDV/HBV coinfection is associated with a rapid disease progression toward cirrhosis and an increased risk of clinical complications, such as liver decompensation and hepatocellular carcinoma (HCC).[1] Despite the remarkable advances of antiviral treatments against HBV infection and the initial promising results of novel drugs against HDV,[8-10] liver transplantation (LT) represents at present—and most likely for years to come—the only therapeutic option available to HDV/HBV-coinfected patients.[11-13] However, several clinically relevant open questions remain, such as the likelihood of long-term posttransplant survival, the risk of viral and HCC recurrences, and the most appropriate antiviral prophylaxis.

The Italian registry study on the evolution of indications for LT showed that HBV-related cirrhosis represented the primary indication for LT in 23.5% of patients, and among these, 25% had HDV coinfection.[14] Therefore, the Italian cohort of HDV/HBV-coinfected LT patients probably represents the largest cohort available to date.

In this study, we aimed to analyze the outcomes of patients waitlisted for LT in Italy due to HDV/HBV-related end-stage liver disease and to investigate the strategies adopted to prevent disease recurrence.

2. Methods

2.1. Study design

This is an observational cohort study comparing LT candidates with HDV/HBV coinfection with those with HBV monoinfection who were waitlisted in Italy from 2011 to 2020, with final outcomes being evaluated as of February 1, 2024. This study complies with the ethical guidelines of the Declaration of Helsinki, and it was approved by the Italian National Transplant Centre (CNT) and the Institutional Review Board of the University Hospital Policlinico Tor Vergata, Rome, Italy (No. 256.20).

The primary aim of this study was to compare the short-term and long-term outcomes of HDV/HBV-coinfected LT candidates compared with those of HBV-monoinfected LT candidates, using an intention-to-treat (ITT) approach. This study's secondary aims focused on the cohort of HDV/HBV-coinfected patients and included the assessment of antiviral therapy/prophylaxis before and after LT, the extent of HBV and HDV viral recurrence, and the risk of HCC recurrence or de novo incidence after LT.

2.2. Study population

All adult patients (N = 1731) listed for LT in Italy between January 1, 2011, and December 31, 2020, who were affected by HBV monoinfection or HDV/HBV coinfection were included in the analysis. Exclusion criteria were recipient age <18 years, LT combined with other organs, patients listed for retransplantation, LT for acute liver failure, and living-donor LT. In addition, 27 patients were excluded as dropped out from the LT waiting list (WL) due to clinical improvement.

2.3. Data sources, variables, and definitions

Data were obtained from the CNT Italian Transplant Information System, which is a prospective database reporting patient/graft status and posttransplant complications at last follow-up. Additional data of HDV/HBV-coinfected patients were obtained from the 22 transplant centres belonging to the Italian Transplant Network. According to the CNT rules, LT candidates with HCC had to fulfil one of the following HCC listing criteria: Up-To-Seven criteria,[15] University of California San Francisco criteria,[16] or Barcelona Clinic Liver Cancer algorithm.[17]

Patients with HBV monoinfection were defined as those being seropositive for HBsAg and seronegative for anti–HDV antibody; patients with HDV/HBV coinfection were defined as those being seropositive for anti–HDV antibody. Virologic data related to the HDV/HBV-coinfected cohort were double checked with the transplant centres' records. Serum HBsAg levels were quantified by automated chemiluminescent microparticle immunoassay and HBV-DNA levels by quantitative real-time polymerase chain reaction.

The following variables were collected for the whole patient cohort—(1) at the time of waitlisting: candidate's demographics,

biochemical parameters, model for end-stage liver disease (MELD)-Na score,[18] presence and stage of HCC, and status regarding coinfection with hepatitis C virus (HCV) or HIV; (2) at time of LT: recipient's biochemical parameters, donor demographics and virologic features, type of LT, and cold ischemia time. Additional data were recorded within the cohort of HDV/HBV-coinfected patients, as follows: antiviral therapy (type of nucleos[t]ide analogs [NAs]; way of administration and dosages of immunoglobulins against antigen of the hepatitis B virus (HBIgs) given peritransplant, after LT, and at time of the last follow-up; and anti-HBs titers, whenever available); viral recurrence after LT (defined for HBV by HBsAg and/or HBV-DNA detectability in serum and defined for HDV by HDV-RNA serum detectability); recurrent or de novo HCC; and episodes of acute and chronic rejection.

To analyze the primary outcomes, we considered the following: (1) time from waitlisting to LT and time from waitlisting to dropping out from the WL (dropping out included both patients who died on the WL as those who were delisted due to clinical deterioration); (2) posttransplant graft survival (defined as time from LT to death or retransplantation, which ever occurred first); and (3) ITT patient survival (defined as the length of time between waitlisting and the occurrence of death either before or after LT).

2.4. Statistical analysis

Categorical variables were described using absolute and relative frequencies. For continuous variables, median and interquartile range (IQR) values were reported. In univariate marginal analyses, continuous variables were compared using the Wilcoxon rank-sum test. For qualitative variables, the χ^2 test or Fisher exact test. We analyzed the probability of transplant and dropout from the WL using the cumulative incidence function with competing risks. Graft survival was evaluated using the Kaplan–Meier method and the log-rank test was used to compare strata. Multivariable analysis was performed by Cox model.[19,20] Two-sided P values of $<.05$ were considered statistically significant. Details of statistical analysis are reported in Supplementary Materials. All analyses were performed using SAS, version 9.4, and R, version 4.3.[21,22]

3. Results

3.1. Characteristics of patients waitlisted for LT with HDV/HBV coinfection or HBV monoinfection

Of 1731 HBV-infected patients who were waitlisted for LT, 1237 patients (71.5%) presented with HBV monoinfection and 494 patients (28.5%) presented with HDV/HBV coinfection. The number of patients with HDV/HBV coinfection who were waitlisted per year remained stable during the entire observational period (median number/year: 52; IQR: 49-60), as described in Figure 1.

Baseline data are summarized in Table 1. At waitlisting, HDV/HBV-coinfected patients were significantly younger (median age: 53 years; IQR: 46-58 years) than HBV-monoinfected candidates (median age: 57 years; IQR: 52-62 years; $P < .0001$], with 38.3% of HDV/HBV-coinfected patients being younger than 50 years. HDV/HBV-coinfected patients were more often of female gender (36.6% vs 13.7%; $P < .0001$). Nonnative Italian LT candidates represented 38.5% (n = 190) of the HDV/HBV-coinfected group compared with 19.2% (n = 237) of the HBV-monoinfected group ($P < .0001$).

HDV/HBV-coinfected patients had less frequent HCV coinfection compared with the HBV-monoinfected cohort (11.7% [n = 58] vs 18.4% [n = 228], respectively; $P = .0007$). The presence of HCC at the time of waitlisting was consistently lower among HDV/HBV-coinfected compared with HBV-monoinfected patients (26.7% [n = 132] vs 65.8% [n = 814], respectively; $P < .0001$). HDV/HBV-coinfected patients with HCC had significantly higher MELD-Na scores than HBV-monoinfected patients with HCC (median MELD-Na: 14; IQR: 10-17, vs 11; IQR: 9-15, respectively; $P < .0001$), whereas no significant differences were observed among patients without HCC in the 2 cohorts. HCC

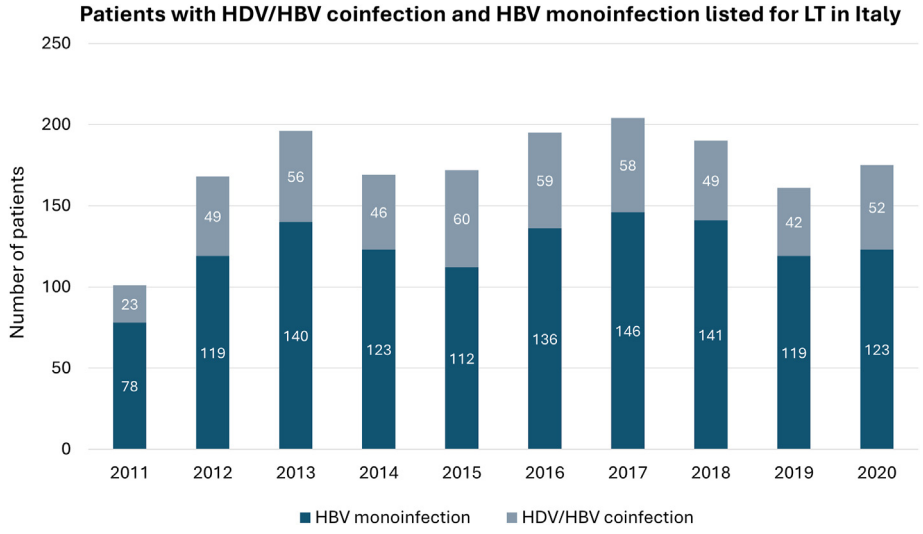

Figure 1. Patients with HDV/HBV coinfection or HBV monoinfection listed for LT in Italy between 2011 and 2020. Overall, HDV coinfection was present in 28.3% of patients infected with HBV during the study period. HBV, hepatitis B virus; HDV, hepatitis D virus; LT, liver transplantation.

Table 1
Characteristics of patients waitlisted for LT with HDV/HBV coinfection or HBV monoinfection in Italy.

Variables at waitlisting	HDV/HBV coinfection (n = 494) n (%) or median (IQR)	HBV monoinfection (n = 1237) n (%) or median (IQR)	*P*
Age (y)	53 (46-58)	57 (52-62)	<.0001
Sex (male)	313 (63.36)	1067 (86.26)	<.0001
BMI	25 (23-27)	26 (23-28)	<.0001
Nonnative Italian	190 (38.46)	237 (19.16)	<.0001
Native area of origin			<.0001
Eastern Europe	172 (87.76)	132 (55.69)	
Africa	10 (5.26)	54 (22.79)	
Asia	3 (1.52)	36 (15.19)	
Americas	2 (1.02)	8 (3.38)	
Northern Europe	3 (1.53)	7 (2.95)	
Presence of HCC	132 (26.72)	814 (65.80)	<.0001
HCV coinfection	58 (11.74)	228 (18.43)	.0007
HIV coinfection	14 (2.98)	47 (4.01)	.3164
Creatinine (mg/dL)	0.76 (0.64-0.93)	0.84 (0.71-1.00)	<.0001
Bilirubin (mg/dL)	2.90 (1.69-5.23)	1.60 (0.87-3.30)	<.0001
INR	1.55 (1.36-1.84)	1.30 (1.13-1.55)	<.0001
Sodium (mmol/L)	138 (135-140)	139 (136-141)	<.0001
MELD-Na score			
Patients without HCC	19 (16-24)	19 (15-25)	.7488
Patients with HCC	14 (10-17)	11 (9-15)	<.0001
Blood group			.5711
0	206 (41.70)	481 (38.88)	
A	186 (37.65)	494 (39.94)	
B	23 (4.66)	71 (5.74)	
AB	79 (15.99)	191 (15.44)	

BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; IQR, interquartile range; LT, liver transplantation; MELD, model for end-stage liver disease.

characteristics (stage, number/size of lesions, and previous treatment) were similar in the 2 groups (Supplementary Table 1).

3.2. Probability of undergoing LT or dropout from the WL in patients with HDV/HBV coinfection or HBV monoinfection

A total of 446 (90.3%) HDV/HBV-coinfected patients and 1057 (85.4%) patients with HBV monoinfection underwent LT with a deceased-donor graft, after median times of 90 and 107 days, respectively. Among HDV/HBV-coinfected patients, 44 (8.9%) dropped out of the WL after a median time of 154 days; these included 32 patients (6.5%) who died and 12 (2.4%) who became too sick to be transplanted. Among HBV-monoinfected patients, 162 patients (13.1%) dropped out of the WL, including 78 patients (6.3%) who died and 84 (6.8%) who dropped out due to clinical deterioration. At the time of data extraction, 4 (0.8%) HDV/HBV-coinfected patients and 18 (1.4%) HBV-monoinfected patients were still awaiting LT.

Univariate analyses showed that HDV/HBV-coinfected patients had a higher probability ($P = .0139$) of being transplanted compared with HBV-monoinfected patients (Figure 2A), a difference that was confirmed by multivariable analysis (Table 2). The 6-month and 1-year after waitlisting, HDV/HBV-coinfected patients had a probability of being transplanted of 67.6% (95% CI: 63.3%-71.6%) and 80.4% (95% CI: 76.6%-83.6%), respectively, while HBV-monoinfected patients had a probability of undergoing LT of 62.1% (95% CI: 59.3%-64.7%) and 74.9% (95% CI: 72.4%-77.3%; $P = .0139$), respectively.

Cox multivariable regression showed that MELD-Na, ABO blood type, and the presence of HDV/HBV coinfection were the only significant predictors of undergoing LT (Table 2). HDV/HBV-coinfected patients with MELD-Na values of ≥25 had a higher likelihood of undergoing LT compared with HBV-monoinfected LT candidates, regardless of the presence of HCC, while the probability was lower for patients with MELD-Na values of ≤15. In both cohorts, the likelihood of being transplanted was reduced by around 25% in patients with blood group O or B compared with that in those with blood group A.

Figure 2A also shows the cumulative probability of dropping out from the WL, which appeared to be significantly lower in HDV/HBV-coinfected patients compared with that in HBV-monoinfected patients ($P = .0262$). The predictors of WL dropout, identified by Cox multivariable regression, included the presence of HCC, MELD-Na, and lack of HDV/HBV coinfection: HDV/HBV-coinfected patients had a similar chance of dropping out from the WL compared with HBV-monoinfected patients with MELD-Na values of 20, but higher probability to drop out at MELD-Na >25 (Supplementary Table 2). Patients with HCC were at the highest risk of WL dropout (hazard ratio [HR]: 1.71), regardless of the presence of HDV/HBV coinfection.

3.3. Outcomes after LT

3.3.1. Donor and transplant characteristics

Donor and transplant characteristics are summarized in Supplementary Table 3. Donor characteristics were similar for HDV/HBV-coinfected patients and HBV-monoinfected patients, except for body mass index (slightly lower in HDV/HBV-coinfected group) and for the HBsAg seropositive status. In fact, 28 (2.7%) LT recipients with HBV monoinfection received a graft from a HBsAg-positive donor, whereas only 1 (0.2%) HDV/HBV-coinfected patient received a graft from a HBsAg-positive donor ($P = .0001$). Recipients' characteristics at time of LT are detailed in Supplementary Table 4.

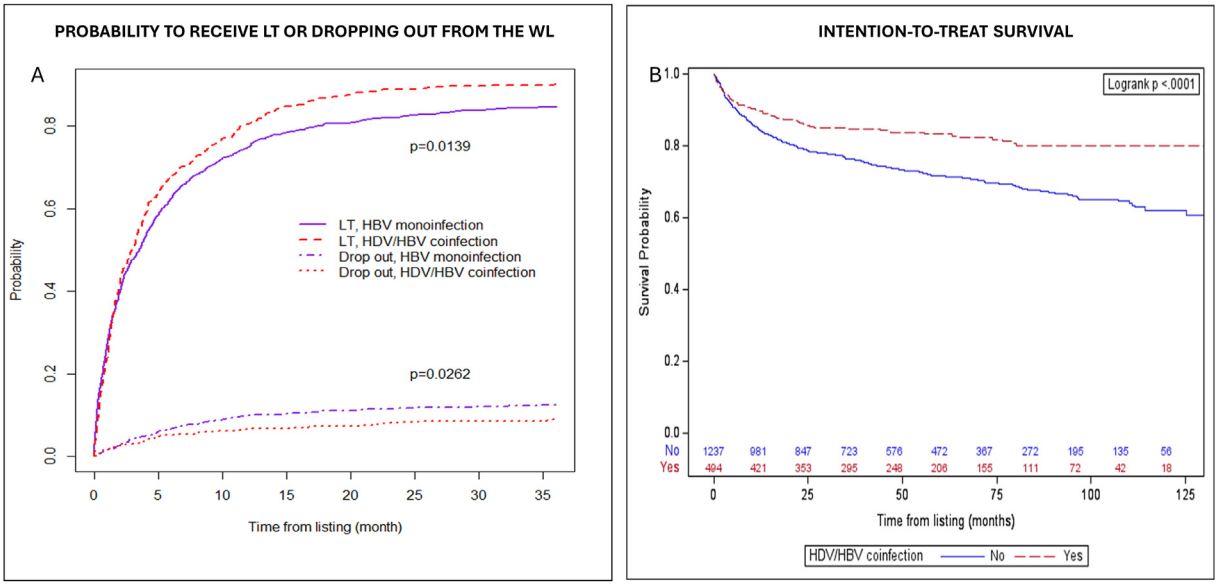

Figure 2. Outcomes of patients with HDV/HBV coinfection or HBV monoinfection listed for LT in Italy. (A) probabilities of receiving LT or dropping out from the LT waiting list; (B) ITT survival of patients waitlisted for LT with or without HDV/HBV coinfection. The red line refers to patients affected by HDV/HBV coinfection and the blue line to patients affected by HBV monoinfection. HBV, hepatitis B virus; HDV, hepatitis D virus; LT, liver transplantation.

Table 2
Multivariable analysis showing predictive factors for receiving LT.

Variable	Contrast		Hazard ratio	95% CI	*P*
ABO blood type					<0.0001
	0 vs A		0.75	0.66-0.84	
	AB vs A		1.29	1.02-1.63	
	B vs A		0.76	0.65-0.90	
HDV/HBV coinfection					.0004
MELD-Na					<.0001
HDV/HBV coinfection[a] MELD-Na					.0003
	HDV/HBV coinfection vs	At MELD-Na 10	0.74	0.61-0.90	
	no HDV/HBV coinfection	At MELD-Na 15	0.89	0.78-1.02	
		At MELD-Na 20	1.08	0.95-1.23	
		At MELD-Na 25	1.31	1.08-1.59	
		At MELD-Na 30	1.59	1.19-2.11	
	MELD-Na × 5 points	At HDV/HBV coinfection	1.41	1.29, 1.54	
	MELD-Na × 5 points	At HBV monoinfection	1.16	1.11, 1.22	

HCC, hepatocellular carcinoma; HDV, hepatitis D virus; LT, liver transplantation; MELD, model for end-stage liver disease.

[a] A significant interaction was observed between the variables HDV/HBV coinfection and MELD-Na. This implies that the effect of HDV/HBV coinfection was different at different score of MELD-Na; therefore, the hazard ratios were estimated combining the 2 variables. The multivariable model was stratified according to the centers' volume of LT activity and the following covariates were included: presence of HDV/HBV coinfection, MELD-Na score, presence of HCC, age, gender, nationality, body mass index (BMI), height, ABO blood type, HCV coinfection, and the year of waitlisting.

3.3.2. Posttransplant graft survival

In the HDV/HBV-coinfected cohort, 38 (8.5%) patients died after LT, and 19 (3.8%) were retransplanted within a median follow-up of 58 months (IQR: 27-84 months). In the HBV-monoinfected group, 184 (14.9%) patients died after LT, and 45 (3.6%) were retransplanted within a median follow-up period of 61 months (IQR: 36-92 months). Hepatic-related causes of death were 21.1% in the HDV/HBV-coinfected group (including 1.61% of HCC recurrence), compared with 39.9% in the HBV-monoinfected group (including 21.5% of HCC recurrence; $P = .0480$). Within the entire cohort, 28 patients were lost to follow-up after LT.

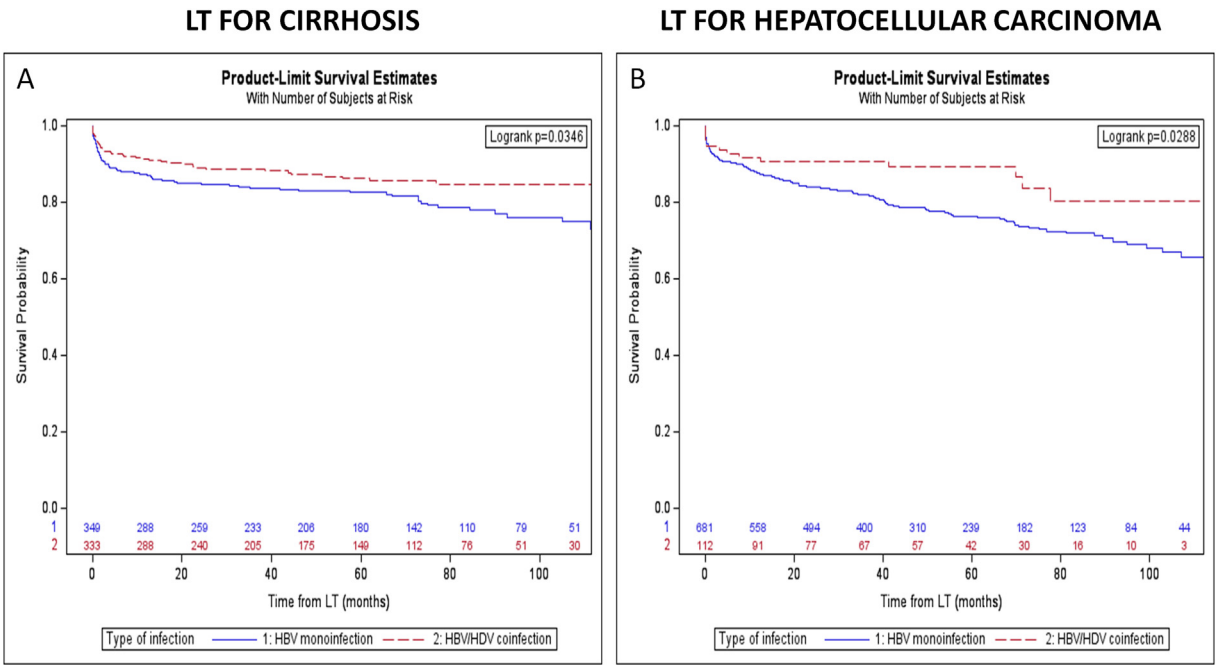

Figure 3. Graft survival after LT in HDV/HBV-coinfected and HBV-monoinfected patients waitlisted for LT due to cirrhosis (A) or hepatocellular carcinoma (B). The red line refers to graft survival of patients with HDV/HBV coinfection and the blue line to graft survival of patients with HBV monoinfection. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LT, liver transplantation.

In univariate analyses, HDV/HBV-coinfected LT recipients showed significantly better outcomes compared with HBV-monoinfected patients ($P < .0001$), with 5-year graft survival rates of 86.9% (95% CI: 83.1%-89.9%) and 78.6% (95% CI: 75.8%-81.2%) respectively. HDV/HBV-coinfected recipients showed superior posttransplant outcomes compared with HBV-monoinfected patients if they were transplanted for either cirrhosis ($P = .0346$) or HCC ($P = .0288$), as shown in Figure 3.

Multivariable regression analysis (Supplementary Table 5) confirmed that LT recipients with HDV/HBV coinfection had a lower risk of graft failure compared with HBV-monoinfected patients (HR: 0.61). Although the MELD-Na score did not show a significant association with graft survival, when its single components of the MELD-Na were analyzed, high creatinine levels (>1.5 mg/dL) at LT appeared to be associated with lower short-term graft survival (Supplementary Figure S1). The presence of HCC at waitlisting had a time-dependent effect on graft survival: patients with and without HCC showed a similar risk of graft failure until 1 year after LT, whereas those with HCC had distinctly poorer outcomes thereafter (Supplementary Figure S2). The presence of HCV coinfection had no effect on graft survival (Supplementary Figure S3), nor influenced the multivariable Cox model (Supplementary Table 6). Moreover, being nonnative Italian did not affect graft outcomes (Supplementary Table 7).

3.3.3. ITT patient survival

ITT analysis was performed to investigate rates of patient survival from the time of waitlisting until the date of the final post-LT follow-up. Overall, during the study period 428 (24.7%) patients died after a median follow-up time of 62 months (IQR: 36-929 months), including 82 HDV/HBV-coinfected patients and 346 HBV-monoinfected patients. Univariate analyses showed that the ITT 5-year survival rate was significantly greater in HDV/HBV-coinfected patients (83.2%; 95% CI: 79.4%-83.4%) than in the HBV-monoinfected patients (71.6%; 95% CI: 68.8%-74.2%; $P < .0001$), as shown in Figure 2B. In the ITT-multivariable analysis, waitlisted patients with HDV/HBV coinfection had almost 50% lower chance of death than did waitlisted patients with HBV monoinfection if transplanted (Table 3). The risk of death increased also for advancing recipient age and for every 5 points of MELD-Na score. In addition, waitlisted patients with HCC had a higher risk of death compared with those waitlisted without HCC, regardless the HDV coinfection (HR: 1.56).

3.3.4. Posttransplant viral recurrence in the cohort of HDV/HBV-coinfected patients

Table 4 illustrates the pre-LT and post-LT antiviral treatments used in HDV/HBV-coinfected patients. Serum HBV-DNA at the time of LT was available for almost all patients (n = 439/446, 98.4%), and it was undetectable in 69.5% (n = 305) of patients. Serum HDV-RNA was tested in about one-third of the patients (n = 177/446, 39.7%) and was detectable in 79.1% (n = 140) of those tested. Among LT recipients who had serum HDV-RNA tested, patients with undetectable HDV-RNA at the time of LT had better long-term survival compared with those with detectable HDV-RNA, near statistical significance ($P = 0.0578$), as depicted in Supplementary Figure S4.

Details on antiviral prophylaxis was available in 440 of the 446 (98.7%) patients. At time of LT, 358 of the 440 (81.4%) HDV/HBV-coinfected patients were receiving antiviral therapy with oral NA, including entecavir (n = 206/440, 46.8%), tenofovir-dipivoxyl (n = 115/440, 26.1%), and lamivudine (n = 37/440, 8.4%). A total of

Table 3
Multivariable analysis showing predictive factors for intention-to-treat patient mortality.

Variable	Contrast		Hazard ratio	95% CI	*P*
Presence of HCC	HCC vs No HCC		1.55	1.20, 1.99	.0007
Age (y) at listing	× 5 y		1.09	1.03, 1.16	.0060
LT					.5667
HDV/HBV coinfection					.4609
MELD-Na					<.0001
LT[a] HDV/HBV coinfection					.0419
LT[a] MELD-Na					<.0001
	LT vs No LT	In HDV/HBV coinfected at MELD-Na 10	0.24	0.14, 0.41	
		In HBV monoinfected at MELD-Na 10	0.41	0.29, 0.56	
		In HDV/HBV coinfected at MELD-Na 25	0.08	0.05, 0.13	
		In HBV monoinfected at MELD-Na 25	0.13	0.09, 0.19	
	HDV/HBV coinfection vs	LT	0.51	0.34, 0.77	
	no HDV coinfection	No LT	0.88	0.62, 1.25	
	MELD-Na × 5-point increment	LT	1.12	1.01, 1.25	
		No LT	1.63	1.48, 1.840	

The multivarible model was stratified according to the centers' volume of LT activity and the following covariates were included: presence of HDV/HBV coinfection, MELD-Na score, presence of HCC, age(y), sex, nationality, BMI, height, ABO blood type, HCV coinfection, year of waitlisting, LT, cold ischemia time, donor age and donor HBcAb. In modeled intention-to-treat patient survival, LT was considered an explanatory variable, and it was included in the Cox model as a time-dependent covariate.
HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; LT, liver transplantation; MELD, model for end-stage liver disease.

[a] Two significant interactions were observed between LT and HDV/HBV coinfection and between LT and MELD-Na. This implies that the efficacy of LT was different in HDV/HBV coinfected and HBV-monoinfected patients depending also on MELD-Na levels and that the effects of HDV/HBV coinfection and MELD-Na were different in transplanted and nontransplanted patients. Hazard ratios were estimated accordingly.

82 of the 440 (18.6%) patients were not receiving NA at the time of LT; among the latter group, HBV-DNA testing was negative in 56 cases, positive in 26 cases, and unknown in 3 cases.

All patients received HBIg intraoperatively, mainly by intravenous infusion (96.2%). After LT, physicians planned to maintain HBsAb titers at 100 IU/ml in 281 (67.87%) patients, at 100-300 IU/ml in 111 (26.82%) patients and >300 IU/ml in 22 (5.31%) patients.

At time of the last follow-up, after a median time of 4.9 years (IQR: 2.3-7.2 years) from LT, ongoing antiviral prophylaxis mainly consisted of entecavir (n = 250, 60.4%), followed by tenofovir-dipivoxyl (n = 108, 26.1%) and lamivudine (n = 52, 12.6%). In addition, 371 (91.8%) patients were still receiving HBIg, mainly given subcutaneously, whereas 33 (8.2%) patients had suspended HBIg treatment after a median time of 15.4 months (IQR: 1.6-24.3 months) from LT. Four (0.96%) HDV/HBV-coinfected LT recipients were no longer receiving any prophylaxis at the last follow-up.

In the whole HDV/HBV cohort, 5 patients (1.1%) developed a recurrent HBV infection after a median of 2 months (range: 2-116 months) from LT: 2 of these, received a liver graft from an anti-HBc antibody positive donor and 1 from an HBsAg-positive/HBV-DNA positive donor (Table 5). Recipient's HBV-DNA was detectable at time of LT in 3 patients only. After LT, all patients showing HBV recurrence were treated with the combination of NA and HBIg. After a median follow-up of 5.7 years (range: 0.5-9.7 years) all LT recipients with HBV recurrence were alive, except 1 patient who died after 2 years.

Among the 5 LT recipients with HBV recurrence, only 1 (0.2%) developed recurrent HDV infection, already detected 3 months after LT, while receiving entecavir and HBIg. Notably, this patient received an HBsAg and HBV-DNA positive graft. Two years after LT, he is currently alive, with good liver function, and still receiving entecavir and HBIg.

Of the 5 patients with HBV recurrence, 4 (80%) had a target HBsAb titer set at 100 IU/mL, yet required maintenance HBIg

Table 4
Antiviral therapy in LT recipients with HDV/HBV coinfection.

Infection prophylaxis	At LT, n (%)	At last follow-up, n (%)
Antiviral therapy		
Nucleos(t)ides analogs (dosage)		
Entecavir (0.5-1 mg/die)	206 (46.82)	250 (60.39)
Tenofovir dipivoxyl (600 mg/die)	115 (26.14)	108 (26.09)
Lamivudine (100 mg/die)	37 (8.40)	52 (12.56)
None	82 (18.64)	4 (0.96)
Missing data	5 (1.4)	31 (7.0)
HBIg		
HBIg administration		
Yes	446 (100.0)	371 (91.83)
No	—	33 (8.17)[a]
Time of HBIg withdrawal after LT (mo)	—	15.4 (1.6-24.3)
Routes of administration		
Intravenous	429 (96.19)	4 (1.11)
Intramuscular	5 (1.12)	176 (49.03)
Subcutaneous	—	179 (49.86)
Missing data	12 (2.7)	45 (11.1)

Ag, antigen; HB, hepatitis B; HBIg, immunoglobulins against HBsAg; HBV, hepatitis B virus; HDV, hepatitis D virus Ig, immunoglobulins; LT, liver transplantation; NA, nucleos(t)ide analog.

[a] HBIg suspension was considered only for patients with a follow-up of >30 days from LT.

administration likely because titers were below the target threshold.

Of the 33 HDV/HBV-coinfected patients who ceased HBIg prophylaxis after LT, 21 (66.7%) had an HBsAb target title above 100 IU/mL, and none experienced recurrent infection of either HBV or HDV, including 1 patient who had suspended also NA.

3.3.5. Posttransplant recurrent or de novo HCC in the cohort of HDV/HBV-coinfected patients

Among all HDV/HBV-coinfected patients, posttransplant recurrence of HCC was observed in 10 (8.9%) of 112 patients who had HCC at time of LT, and de novo HCC only in 1 case (0.3%). Of these, only 1 patient developed HBV recurrence (1 year after tumor recurrence), and none had HDV recurrence. Two cases of HCC recurrences occurred in patients who were taking NA but had withdrawn HBIg prophylaxis, without evidence of HBV recurrence.

4. Discussion

Patients with HDV-related end-stage liver disease who are candidates for LT have traditionally been regarded as a special population. This is mainly due to the fact that HDV infection is known as the most severe form of viral hepatitis, which is associated with enhanced risks of fibrosis progression, disease decompensation, and the development of HCC.[1,11] To our knowledge, this study analyzed the long-term outcomes of the largest series of HDV/HBV-coinfected patients waitlisted for LT that has been reported to date. The key findings of this study are as follows: (1) HDV/HBV-coinfected LT candidates are rather different from HBV-monoinfected candidates in that they are often less than 50 years, are less often of male gender and are much less likely to have HCC; (2) once they are waitlisted for LT, HDV/HBV-coinfected patients tend to undergo LT earlier compared with HBV-monoinfected patients at high disease severity scores; (3) after LT, HDV/HBV-coinfected patients show better outcomes compared with their HBV-monoinfected counterparts, in both graft survival and ITT patient survival; and (4) HDV/HBV-coinfected patients rarely experience a viral recurrence, and only few experience recurrent or de novo HCC.

Our results deserve several comments. First, there were remarkable demographic and clinical differences between HDV/HBV patients and HBV-monoinfected patients; in particular, the majority of patients with HCC who were waitlisted for LT were HBV monoinfected. In agreement with United Network for Organ Sharing report,[12] we found that, compared with HBV-monoinfected patients, the predominant indication for LT among HDV/HBV-coinfected patients was decompensated liver cirrhosis, whereas HCC was a less frequent indication within this group. This disparity possibly results from the fact that potent HBV antivirals, which have now been in use for 2 decades, have markedly reduced the progression of HBV infection to cirrhosis and then to decompensation, although they are unable to diminish the risk of HCC. In contrast, the first drug for the treatment of chronic HDV infection in adults with compensated liver disease has been approved only recently.[23]

On the contrary, it remains unknown whether the reduced risk of HCC observed among HDV/HBV-coinfected LT candidates reflects a true lower propensity to develop cancer because of the low level of HBV-DNA replication that is typical of these patients.[24] Alternatively, the difference in the prevalence of HCC observed at the time of LT between HDV/HBV-coinfected and HBV-monoinfected patients could be a spurious effect due to the younger age and overrepresentation of females among HDV/HBV-coinfected patients. Further studies are needed to elucidate these issues.

Second, we found that waitlisted HDV/HBV-infected patients have greater chance to receive LT—and lower dropout rate from the WL—compared with patients with HBV monoinfection; this occurred despite the latter group included many more patients with HCC deserving prioritization.[25]

Third, and most importantly, we must ask why both graft and ITT patient survivals were better in HDV/HBV-coinfected patients than those in HBV-monoinfected patients. Notably, our study is the first reporting ITT survivals of HDV/HBV-coinfected LT candidates. Indeed, the better ITT patient survival observed in the HDV/HBV cohort compared with that in the HBV-monoinfected cohort (5-year survival: 83.2% vs 71.6%, respectively; $P <$

Table 5
Details of HDV/HBV-coinfected patients who developed viral recurrence after LT.

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
At LT					
Recipient data					
Age (y)	55	47	60	50	64
Indication to LT	HDV/HBV	HDV/HBV	HDV/HBV	HDV/HBV	HDV/HBV
HCC	No	No	Yes (multifocal)	Yes	Yes
MELD-Na	13	30	23	11	15
HBsAg	Positive	Positive	Positive	Positive	Positive
HBV-DNA	Positive	Positive	Negative	Negative	Positive
HBV-DNA title (UI/mL)	NA	30	0	0	21
HDV_Ab	Positive	Positive	Positive	Positive	Positive
HDV-RNA	NA	Positive	NA	Positive	NA
HDV-RNA title (UI/mL)	NA	NA	NA	2154	NA
Antiviral therapy pre-LT	None	Entecavir (0.5 mg/d)	Entecavir (0.5 mg/d)	Tenofovir (300 mg/d)	Entecavir (0.5 mg/d)
HBIg at LT	Yes	Yes	Yes	Yes	Yes
Donor					
Age (y)	80	57	72	63	84
HBsAg	Negative	Negative	Negative	Negative	Positive
HBcAb	Negative	Positive	Negative	Positive	Positive
HBV-DNA	Negative	Negative	Negative	Negative	Positive
HDV Ab	Negative	Negative	Negative	Negative	Negative
After LT					
Antiviral therapy post-LT	Entecavir (0.5 mg/d)	Entecavir (0.5 mg/d)	Entecavir (0.5 mg/d)	Tenofovir (300 mg/d)	Entecavir (0.5 mg/d)
HBV recurrence	Yes, after 9 mo	Yes, after 115 mo	Yes, after 11 mo	Yes, after 26 mo	Yes, after 2 mo
HBsAg	Positive	Positive	Positive	Positive	Positive
HBV-DNA	Positive	Negative	Negative	Negative	Positive
HBV-DNA Title (UI/mL)	10	0	0	0	18
HDV recurrence	No	No	No	No	Yes, after 3 mo
HDV-RNA	—	—	—	—	Positive
HCC recurrence	No	No	No	Yes, after 12 mo	No
De novo HCC	No	No	No	No	No
Last follow-up					
Antiviral therapy	Entecavir (0.5 mg/d)	Entecavir (0.5 mg/d)	Entecavir (0.5 mg/d)	Tenofovir (300 mg/d)	Entecavir (0.5 mg/d)
Time from LT (y)	1.9	9.6	8.2	2.2	3
Status at last follow-up	Dead	Alive	Alive	Alive	Alive

AB, antibody; Ag, antigen; HB, hepatitis B; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; Ig, immunoglobulins; LT, liver transplantation; MELD, model for end-stage liver disease.

.0001) is the result of a probability of undergoing LT more quickly, together with a lower chance of failure while waitlisted and a greater likelihood of graft survival after LT; this last finding was also confirmed by multivariable Cox regression. The presence of HCC at the time of waitlisting had a time-dependent effect on graft survival, with a similar risk of graft failure in patients with and without HCC until 1 year after LT, but it became distinctly worse thereafter among patients with HCC.

In our experience, patients with HDV/HBV coinfection only rarely experienced viral recurrences. It is unknown whether this was a consequence of the stringent long-term dual prophylaxis—based on antiviral therapy with NA and HBIg—that was

adopted by most transplant centres (91.3% of patients were receiving HBIg at the last follow-up), or whether it was due to an intrinsic incapacity of HDV to recur unless HBV reactivates.[8] Indeed, in the whole HDV/HBV cohort, HDV and HBV recurrence occurred in only 1 patient (0.2%) and in 5 (1.1%) patients, respectively. Notably, the only case of HDV recurrence was observed in a patient who received the graft from an HBsAg-positive and HBV-DNA–positive donor (because of the very high risk of WL dropout for multifocal HCC), underlining that HBsAg-positive donors should be avoided in HDV-positive recipients.[26]

International recommendations suggest the use of combined NA and HBIg to prevent HDV recurrence, to be given indefinitely after LT.[23,27-29] In our HDV/HBV-coinfected population, 33 patients (8.2%) suspended HBIg (8 of whom already at year 1 post-LT), and 4 (0.96%) were not receiving any antiviral prophylaxis at the last follow-up. Interestingly, none of these patients experienced HDV or HBV recurrence. This suggests that attempts to simplify the expensive currently recommended dual prophylaxis by early HBIg withdrawal, switching to NA monoprophylaxis, might be considered, as proposed by several centers, using both old/newer NA[30-33] or only newer NA (entecavir/tenofovir-dipivoxyl/tenofovir-alafenamide).[34,35] In agreement, a recent multicentre Spanish study showed that of 174 HDV-related LT patients, more than 40% discontinued HBIg 1-2 years after LT with a very low incidence of HDV recurrence (1.7%).[36]

Interestingly, in our cohort, of 5 patients with HBV recurrence, 4 patients had a titer of HBsAb $<$100 IU/mL, requiring HBIg administration. Despite we cannot draw conclusions on the outcomes of patients with HBsAb titers $<$100 UI/mL, we believe that if HBsAb levels remain above this level, suspension of HBIg administration may be safely undertaken, thus providing relevant cost-effectiveness advantages; in contrast, below 100 IU/mL HBIg discontinuation should be considered more cautiously.

This study has some limitations. First, it is based on a retrospective analysis. However, the strength of this nationwide database is that all HDV/HBV patients who were waitlisted for LT in Italy were included, having only 28 patients missed the last follow-up and, whenever necessary, data were integrated with those obtained by individual transplant centers. Other insufficiently represented data were those regarding the presence and quantification of HDV-RNA, specific HBsAb levels, and HCC histologic features for assessing the risk of tumor recurrence. Another limitation is that we were unable to compare the antiviral prophylaxis and virological outcomes in the 2 cohorts, as these data were collected from individual centres only for the HDV/HBV-coinfected population. Yet, to our knowledge, this study provides long-term results from the largest population of HDV/HBV-coinfected LT candidates reported to date.

In conclusion, over the last decade in Italy, HDV/HBV-coinfected patients with end-stage liver disease who were waitlisted for LT had more favorable outcomes than did HBV-monoinfected patients, either before or after LT, thus challenging the prevailing view that they should be regarded as a special population. This concept is further emphasized knowing that HBV-infected LT recipients, ie, our comparator group, are those showing the best posttransplant survival rates compared with all other LT indications in Italy[37] as in other European countries.[38] Furthermore, given the extremely few cases of viral recurrence that were observed, our results fuel the current debate on whether LT recipients with HDV/HBV coinfection might be safely switched, by using the currently available potent NA, at least at some point, to a simpler and more cost-effective antiviral prophylaxis strategy.

Acknowledgments

We thank the Department of Mathematics (MIUR Excellence) of the University of Rome Tor Vergata, Rome, Italy, for their assistance with this study.

Funding

The authors received no funding for this study.

Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose as described by *American Journal of Transplantation*.

Data availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2025.03.003.

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