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# Liver transplantation for HBV-related liver disease: Impact of prophylaxis for HBV on HCC recurrence

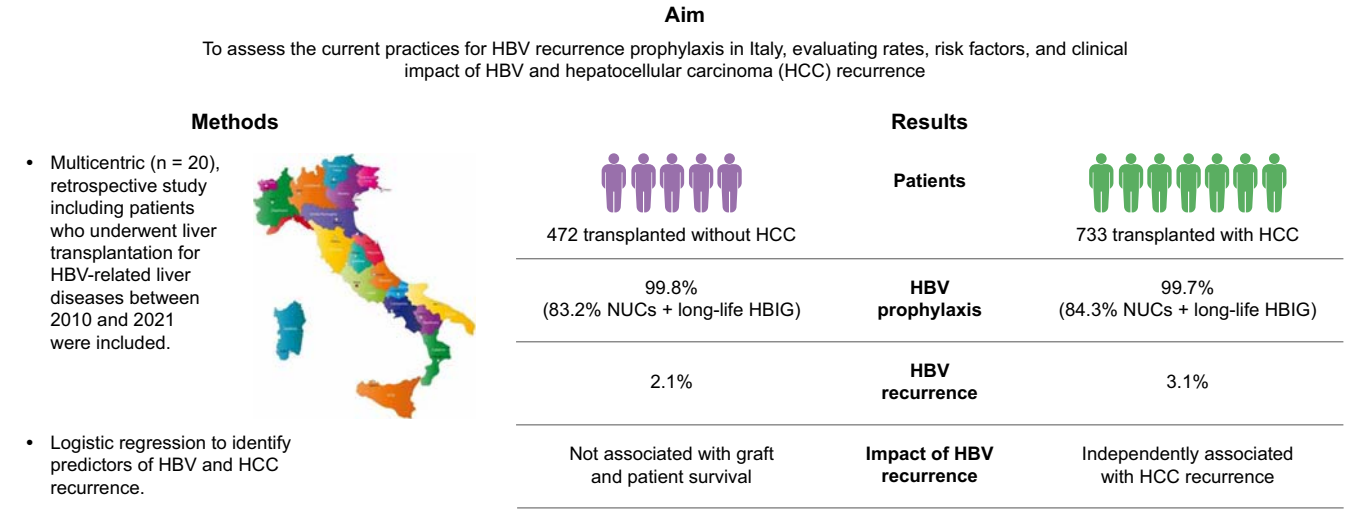
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## Graphical abstract




## Highlights:

- The first nationwide study assessing results of liver transplant for patients with HBV in Italy.
- HBV recurrence was rare and not associated with reduced survival.
- In patients transplanted for HCC, HBV recurrence was associated with HCC recurrence.

## Impact and implications:

In Italy, the combination of high-barrier nucleos(t)ide analogues and hepatitis B immunoglobulins remains the most widely used regimen for antiviral prophylaxis following liver transplantation for HBV-related liver disease. Hepatitis B recurrence after liver transplantation is a rare event and not associated with reduced survival. In transplant recipients with hepatocellular carcinoma, HBV recurrence was independently associated with hepatocellular carcinoma recurrence, though this may simply reflect an epiphenomenon without any causal relationship.

https://doi.org/10.1016/j.jhepr.2024.101278

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JHEP|Reports

# Liver transplantation for HBV-related liver disease: Impact of prophylaxis for HBV on HCC recurrence

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JHEP Reports **2025**. vol. 7 | 1–12

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**Background & Aims:** Conflicting data exist regarding optimal prophylaxis for HBV recurrence (HBV-R) after liver transplantation (LT), particularly in patients with hepatocellular carcinoma (HCC). We assessed current practices for HBV-R prophylaxis in Italy, evaluating rates, risk factors, and the clinical impact of HBV-R and HCC-R.

**Methods:** We performed a multicentric, retrospective study involving 20 Italian LT centers. All patients who underwent LT for HBV-related liver diseases between 2010 and 2021 were included. Logistic regression was used to identify predictors of HBV-R and HCC-R. Survival curves were estimated with the Kaplan-Meier method and compared with the log-rank test.

**Results:** We included 1,205 LT recipients (60.8% with HCC). HBV prophylaxis was prescribed in 99.7% of recipients, mostly with lifelong hepatitis B immunoglobulin+nucleos(t)ide analogues (HBIG+NUCs) (83.9%). Rates of HBV-R were 2.1% and 3.1% in patients transplanted without and with HCC, respectively. Median times from LT were 60 [9.5–77.5] and 5.5 [1–13] months, respectively. Recipients on lifelong HBIG+NUCs experienced lower rates of HBV-R than those in whom HBIG was withdrawn, used only during LT, or in those who received NUCs alone (2.3% *vs.* 6.2% *vs.* 1.9% *vs.* 8%, respectively; $p = 0.042$). In recipients with HCC, HCC-R rate was 10.8% (median time from LT: 18 months). At multivariate analysis, HBV-R (odds ratio [OR] 10.329; 95% CI 3.665-29.110), Child-Pugh C (OR 3.519; 95% CI 1.305-9.484), and microvascular invasion (OR 3.088; 95% CI 1.692-5.634) were independently associated with HCC-R. Five-year survival was lower in recipients who experienced HCC-R (32.5% *vs.* 92.4% in those who did not; $p$ <0.001).

**Conclusion:** In Italy, HBV prophylaxis is mostly based on lifelong HBIG+NUCs. HBV-R was rare and not associated with survival in patients transplanted for decompensated cirrhosis. In patients transplanted for HCC, HBV-R was independently associated with HCC-R. The clinical implications of these findings deserve further investigation.

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## Introduction

HBV is a major global health concern.[1] HDV infects approximately 12 to 72 million hepatitis B surface antigen (HBsAg)-positive patients.[2–4] In HBsAg-positive patients, those with HDV coinfection or superinfection have a 2 to 3-fold higher risk of developing advanced liver disease, hepatocellular carcinoma (HCC), and hepatic decompensation compared to patients with HBV infection alone.[5]

Liver transplantation (LT) is the only curative treatment in HBsAg-positive patients with decompensated cirrhosis or hepatocellular carcinoma (HCC) within certain criteria.[6,7] Despite effective strategies to prevent HBV transmission and control HBV chronic infection,[6] in the last decades the numbers of LT for HBV-related liver disease in Europe has remained stable.[8]

Historically, LT was contraindicated in patients with HBV due to the almost universal graft reinfection, leading to recurrent cirrhosis and rapid graft loss.[9] The introduction of hepatitis B immunoglobulins (HBIG) has changed the natural history of HBV recurrent infection after LT.[10,11] In fact, graft and patient survival are now comparable to those of patients transplanted for non-HBV etiologies.[12]

Recent studies suggest that monotherapy with high-barrier nucleos(t)ide analogues (NUCs) such as tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), or

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https://doi.org/10.1016/j.jhepr.2024.101278

entecavir (ETV) might be a safe and effective option for patients transplanted for HBV, with and without HCC.[13,14] However, these studies included mostly patients from Asia in whom HBV and host-related factors for HBV recurrence (HBV-R) may be different than in Europe.[15] Moreover, there has been a significant shift in LT indications with a relative increase in HCC and a simultaneous decrease in decompensated cirrhosis as a primary reason for LT,[8] which may be associated with a higher risk of HBV-R.

A better understanding of rates and risk factors for HBV and HCC recurrence (HCC-R) after transplantation would improve patient management and allocation of healthcare resources.[16]

In this nationwide study, we aimed to i) investigate the current practice for HBV-R prophylaxis after LT in Italy; ii) evaluate rates, risk factors, and clinical impact of HBV and HCC-R after LT; iii) assess long-term graft and patient survival in a contemporary cohort of patients transplanted for HBV-related liver disease.

## Patients and methods

### Patient selection and study design

This is a multicentric, retrospective study initiated by the "Permanent Transplant Commission" of the Italian Association for the Study of the Liver. All LT Italian centers were invited to participate (See supporting information, page 3).

All adult (≥18-years-old) patients who underwent LT for HBV-related liver disease (±HDV) between January 1, 2010, and December 31, 2021, were considered for inclusion. Exclusion criteria were: HBsAg-positive donor, multiorgan transplantation, HIV coinfection. HBV-R was defined by the positivity of HBsAg and/or detectable HBV DNA in patients who previously achieved HBsAg negativization after LT.[17]

The study was approved by the institutional Ethics Committee of the Padua University Hospital (CESC 5306/AO/22, study ID 19951, data 31/03/2022, Prot. N 0032696 - 11/05/2022). Ethics approval has been obtained from all participating centers. The study complied with the Declaration of Helsinki and good clinical practice guidelines.

### Data collection

Transplant hepatologists of each participating center were responsible for data collection. Given the retrospective nature of this retrospective study, a standardized protocol for the collection of variables could not be defined *a priori*. The case report form was agreed among the participating centers, so that the collection of study variables was homogenous within the participating centers. Data collected from the medical records included pre-transplant, transplant, and post-transplant variables. Pre-transplant-related variables comprised demographics, presence of co-etiology of liver disease (such as autoimmune diseases, metabolic dysfunction-associated steatotic liver disease, alcohol-related liver disease, and HDV and/or HCV coinfection), and type of HBV antiviral therapy. In patients transplanted for HCC, data on downstaging and bridging treatments were included.

Transplant-related variables included liver function according to Child-Pugh and MELD/MELD-Na scores, and virological variables (including HBeAg, anti-HBe, and qualitative and quantitative HBV DNA). In patients transplanted for HCC, explant pathology features including number and maximum diameter of the viable nodules, microvascular invasion, grading, and TNM staging were collected.

Post-transplant variables included use and characteristics of HBV prophylaxis and immunosuppressive therapy, graft and patient survival, and the following clinical outcomes: development of HBV-R and HCC-R (in patients transplanted for HCC). For each of these clinical outcomes, the time from LT (months) was collected.

Patients with and without HCC are two distinct groups for whom transplant indications and management are different,[8,18] and in whom disease recurrence may have a differing impact on prognosis.[19] Hence, transplant recipients were divided into two groups and analyzed separately: patients without HCC, including patients transplanted for decompensated cirrhosis, acute liver failure (ALF),[20] and acute-on-chronic liver failure (ACLF),[21] and patients with cirrhosis and HCC, that is patients who underwent LT in the presence of HCC and who were therefore at risk of recurrence (regardless of the specific indication for LT).

### Statistical analysis

Qualitative data are described using frequency and percentage. Quantitative data are described using median and IQR. Comparison between independent groups were performed using the Mann Whitney *U* test and *t* test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables. Patient and graft survival curves were estimated with Kaplan-Meier method and compared with log-rank test. Univariate and multivariate linear regression analysis were used to identify predictors of HBV and/or HCC-R development among clinical and laboratory variables. Among the variables significantly associated with the outcome at the univariate analysis ($p$ <0.1), only those that were considered clinically significant, non-collinear, and of interest for this study were included in the multivariate model. Statistical significance was set at $p$ ≤0.05. Statistical analyses were performed using SPSS version 28.

## Results

### Patients transplanted without HCC

*Pre-transplant characteristics*

Four-hundred and seventy-two patients (63.1% were male; median age 53 years [45–59]) were included (Table 1). Most patients (52.8%) had HDV coinfection. Primary indication for LT was decompensated cirrhosis (80.1%), followed by ACLF (6.4%), and ALF (12.7%). The median MELD and MELD-Na scores at the time of LT were 20[16–29] and 22,[18–30] respectively. Most patients had Child-Pugh class C cirrhosis (50.8%), followed by class B (41.3%), and class A (4.4%) cirrhosis. Approximately 32.4% of patients had detectable HBV DNA at the time of LT, with 35.9% of these cases having an HBV DNA ≥2,000 IU/ml. Almost all patients were receiving antiviral therapy prior to LT; ETV and TDF were the most used antiviral agents (52.3% and 22.5%), respectively, followed by lamivudine (LAM) and TAF (Table 1).

*HBV prophylaxis and immunosuppressive therapy after LT*

Almost all patients received prophylaxis after LT (465 of 466 with available data, 99.8%). Data regarding the specific type of antiviral prophylaxis were available in 97.2%. The most common strategy was lifelong administration of HBIG in combination with NUCs (83.2%), though we found a significant difference between Northern (87.9%) and Southern (71.3%) Italy ($p$ <0.001). In a small fraction of patients (7.6%) initially treated with HBIG + NUCs, HBIG was withdrawn while continuing lifelong NUCs; the median time between LT and HBIG withdrawal was 12 [1–45] months. Some patients received HBIG only at transplant (4.8%), some received NUCs alone (3.7%), and a few were managed with HBIG alone (0.7%). ETV was the most frequently used NUC (57.8%), followed by TDF (25.8%), LAM (9.3%), and TAF (3.2%). A smaller group of patients (0.8%) received adefovir or a combination of NUCs. Patients receiving HBIG mostly received intramuscular or subcutaneous injections (51.2% and 39.9%, respectively).

Regarding immunosuppressive therapy, calcineurin inhibitors alone were used in 50.8% of patients, with a combination including both a calcineurin inhibitor and a second or third agent (*e.g.*, mTOR inhibitors, mycophenolate mofetil, azathioprine, steroids) being used in 43.7% (Table 1).

*Post-transplant survival and HBV recurrence*

Overall patient and graft survival after LT were 94% and 93.9% at 1 year, and 88.9% and 88.4% at 5 years, respectively (Figs S1 and S2). No differences in terms of overall survival were observed between patients transplanted for decompensated cirrhosis, ACLF, and ALF ($p$ = 0.442) (Fig. S3). The median follow-up was 66 [32–101.73] months.

The overall rate of HBV-R was 2.1% (10/472), occurring at a median time of 60 [9.5–77.5] months from LT (Fig. S4). HBV-R was defined by HBsAg alone in 50% of patients, HBsAg and HBV DNA in 33.3% of patients, and HBV DNA alone in 16.7% of patients. In detail, four patients experienced recurrence of both HBsAg and HBV DNA (two were treated with a combination of lifelong HBIG and NUCs, one with a finite course of HBIG and lifelong NUCs and one with HBIG only at transplant followed by NUCs alone). Among those with available data (three out of four), all participants tested negative for both HBsAg and HBV DNA after the initial HBV-R, after a median time of 6 months [3–6.75] for HBsAg and 6 months (3.75–6) for HBV DNA. Five patients experienced HBsAg recurrence only. Of these, three received lifelong HBIG in combination with NUCs, one was initially treated with HBIG but later switched to NUCs alone, and one received NUCs alone from transplantation. Among the five, three cleared HBsAg after HBV-R, after a median time of 6 months [3–9.5]. One patient, who received HBIG for a limited time followed by NUCs alone, showed only HBV DNA recurrence but became aviremic just 1 month after the recurrence.

Patients who experienced HBV-R had less frequently received HBV-R prophylaxis with lifelong HBIG than those who did not (Table 2). Notably, patients who received lifelong HBIG in combination with NUCs exhibited significantly lower rates of HBV-R compared to those in whom HBIG was withdrawn, those in whom HBIG was given only at transplantation, and those who received NUCs alone (1.3% *vs.* 8.6% *vs.* 4.5% *vs.* 5.9%, respectively; $p$ = 0.047) (Fig. 1). Patients receiving different prophylactic regimens had similar characteristics in terms of age, HBV DNA detectability or levels exceeding 2,000 IU/ml at transplantation, indications for LT (decompensated cirrhosis, ACLF, or ALF), and donor anti-HBc status. We did not observe any difference in HBV-R between patients with and without HDV coinfection. However, it is important to note that HDV-coinfected patients were more likely to receive lifelong HBIG and NUCs as post-transplant prophylaxis compared to HBV-monoinfected patients (89.8% *vs.* 76.8%, $p$ <0.001).

At the univariate analysis, the only parameter associated with HBV-R was the use of lifelong HBIG as antiviral prophylaxis after LT (Table 3). Conversely, no significant associations were found between HBV-R and other factors such as age, MELD, MELD-Na, or Child-Pugh scores, HBV DNA positivity or HBV DNA levels ≥2,000 IU/ml at the time of LT, use of anti-HBc-positive donors, or HDV coinfection (Table 3).

All patients with HBV-R showed only mild-to-moderate alanine aminotransferase (ALT) elevation (<3x the upper limit of normal [ULN]), with no impact on hepatic synthesis or survival. Only two patients required hospital admission, primarily for diagnostic purposes. Five patients with HBV-R were also HDV coinfected, but none experienced HDV recurrence after LT.

No differences in overall patient and graft survival were found between patients with HBV-R and those without, $p$ = 0.783 and $p$ = 0.771, respectively (Fig. 2A,B).

## Patients transplanted with HCC

*Pre-transplant characteristics*

Patients who underwent LT with HCC, who accounted for 733/1,205 cases (60.8%), were predominantly male (85.5%), with a median age of 58.61 [54–63] years. HDV coinfection was observed in 37.5% cases. At the time of LT, the median MELD and MELD-Na scores were 12[8–18] and 13,[9–20] respectively. Most patients were classified with Child-Pugh class A (49.5%) cirrhosis. Among this cohort, HBV DNA was detectable in 20.6% of patients, but only 7.3% had HBV DNA ≥2,000 IU/ml. Most patients (93.5%) received antiviral therapy before LT, primarily with ETV (59%) and TDF (29.2%). Median alpha-fetoprotein (AFP) level at the time of LT was 19.3 [4.55–59] ng/ml. Median number of viable nodules in the explanted livers was 2.[1–3] Grade 3 (G3) nodules were found in 23.6% of patients; microvascular invasion was present in 19.8% of cases (Table 1).

*HBV prophylaxis and immunosuppressive therapy after LT*

Almost all patients with HCC (99.7%) received antiviral prophylaxis after LT. Data regarding the specific type of antiviral prophylaxis were available for 719/733 patients (98.1%). Management of HBV prophylaxis was comparable to that used in patients without HCC. The most common approach involved lifelong administration of HBIG in combination with NUCs, which was employed in 84.3% of cases. Some patients received HBIG only at transplant (4.3%) and some underwent the withdrawal of HBIG after an initial period with the continuation of lifelong NUCs (6.4%). The median time between LT and HBIG withdrawal was 4 (1–34.5) months. A smaller percentage of patients (4.7%) received NUCs alone, and a few were managed with HBIG alone (0.3%). ETV was the most frequently

**Table 1. Baseline characteristics of patients.**

| | Non-HCC patients (n = 472) n (%), median (IQR) | HCC patients (n = 733) n (%), median (IQR) |
|---|---|---|
| Gender, male | 298 (63.1) | 627 (85.5) |
| Age | 53 (45–59.17) | 58.61 (54–63) |
| Detectable HBV DNA | 153 (32.4) | 151 (20.6) |
| HBV DNA ≥2,000 IU/ml | 55 (35.9) | 11 (7.3) |
| HDV coinfection | 249 (52.8) | 275 (37.5) |
| Additional aetiologies | | |
| Alcohol | 45 (9.5) | 60 (8.2) |
| MASLD | 10 (2.1) | 20 (2.7) |
| HCV | 47 (9.9) | 78 (10.6) |
| Child-Pugh stage | | |
| A | 21 (4.4) | 363 (49.5) |
| B | 195 (41.3) | 234 (31.9) |
| C | 240 (50.8) | 128 (17.5) |
| MELD score | 20 (16–29) | 12 (8–18) |
| MELD-Na score | 22 (18–30) | 13 (9–20) |
| Indications for LT | | |
| Decompensated cirrhosis | 378 (80.1) | |
| ACLF | 30 (6.4) | |
| ALF | 60 (12.7) | |
| AFP (ng/ml) | | 19.3 (4.55–59) |
| Use of antivirals before LT, yes | 409 (86.7) | 685 (93.5) |
| LAM | 39 (8.3) | 55 (8) |
| TDF | 106 (22.5) | 201 (29.2) |
| ETV | 247 (52.3) | 404 (59) |
| TAF | 6 (1.3) | 9 (1.3) |
| Others | 9 (1.9) | 12 (1.7) |
| Use of anti-HBc positive donors | 62 (13.1) | 125 (17.1) |
| Downstaging treatments, yes | | 423 (57.7) |
| Liver resection | | 33 (7.8) |
| RFA | | 73 (17.3) |
| TACE | | 122 (28.8) |
| MW | | 10 (2.4) |
| Combination | | 131 (31) |
| Bridging treatments, yes | | 276 (37.7) |
| Liver resection | | 9 (3.3) |
| RFA | | 56 (20.3) |
| TACE | | 131 (47.5) |
| Sorafenib | | 3 (1.1) |
| MW | | 5 (1.8) |
| Combination | | 45 (16.3) |
| Explant pathology | | |
| Number of viable nodules | | 2 (1–3) |
| Diameter of the largest viable nodule, mm | | 25 (16–35) |
| Microvascular Invasion, yes | | 145 (19.8) |
| Grading, G3 | | 173 (23.6) |
| HBV prophylaxis after LT, yes | 465 (99.8)* | 728 (99.7)** |
| NUCs + HBIG lifelong | 382 (83.2) | 606 (84.3) |
| NUCs + HBIG withdrawal | 35 (7.6) | 46 (6.4) |
| NUCs + HBIG at transplant | 22 (4.8) | 31 (4.3) |
| NUCs alone | 17 (3.7) | 34 (4.7) |
| HBIG alone | 3 (0.7) | 2 (0.3) |
| Type of NUCs for HBV prophylaxis after LT | | |
| LAM | 44 (9.3) | 59 (8) |
| TDF | 122 (25.8) | 191 (26.1) |
| ETV | 273 (57.8) | 432 (58.9) |
| TAF | 15 (3.2) | 25 (3.4) |
| Other | 4 (0.8) | 2 (0.3) |
| Type of prophylaxis after LT | | |
| LAM alone | 2 (0.4) | 0 |
| LAM + HBIG | 41 (8.7) | 58 (7.9) |
| hbNUCs alone | 13 (2.8) | 34 (4.7) |
| hbNUCs + HBIG | 396 (83.9) | 611 (83.4) |
| Type of HBIG for HBV prophylaxis after LT | | |
| Intravenous | 34 (8.9) | 43 (5.9) |
| Intramuscular | 195 (51.2) | 285 (38.9) |
| Subcutaneous | 152 (39.9) | 270 (36.8) |

(*continued on next page*)

**Table 1.** (*continued*)

| | Non-HCC patients (n = 472) n (%), median (IQR) | HCC patients (n = 733) n (%), median (IQR) |
|---|---|---|
| Type of immunosuppressive therapy | | |
| CNIs | 231 (50.8) | 351 (47.9) |
| mTORi | 25 (5.5) | 47 (6.4) |
| combination therapy | 199 (43.7) | 317 (43.2) |
| Episodes of rejection | | |
| Acute | 55 (11.7) | 49 (6.7) |
| Chronic | 15 (3.2) | 10 (1.4) |

Qualitative variables are shown as number and percentages and quantitative variables as median values and IQR reported with 25$^{th}$ and 75$^{th}$ percentile values in parenthesis.
ACLF, acute-on-chronic liver failure; AFP, alpha-fetoprotein; ALF, acute liver failure; CNIs, calcineurin inhibitors; ETV, entecavir; HBIG, hepatitis B immunoglobulins; LAM, lamivudine; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; mTORi, mammalian target of rapamycin inhibitors; MW, microwave ablation; NUCs, nucleos(t)ide analogues; RFA, radiofrequency ablation; TACE, trans-arterial catheter embolization; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil.
*Data available in 466 patients, type of antiviral prophylaxis available in 459 patients.
**Data available in 727 patients, type of NUCs for prophylaxis available in 719 patients. Qualitative variables are shown as number and percentages and quantitative variables as median values and IQR reported with 25$^{th}$ and 75$^{th}$ percentile values in parenthesis.
In HBV DNA-positive patients, median level of HBV DNA was 70 (24–3458) IU/L.

used NUC (58.9%), followed by TDF (26.1%), LAM (8%), and TAF (3.4%). A smaller group of patients (0.3%) received adefovir or a combination of NUCs. Regarding the mode of administration for HBIG, 38.8% and 36.8% of patients received intramuscular and subcutaneous injections, respectively. A smaller proportion (5.9%) received intravenous HBIG. Types of immunosuppressive therapy were comparable to those used in patients without HCC.

### *Post-transplant survival and HBV recurrence*

Overall patient and graft survival after LT were 94% and 93.3% at 1 year, and 83.5% and 83.1% at 5 years, respectively (Figs S5 and S6). The median follow-up time after LT was 55 [27–93] months.

Rate of HBV-R was 3.1%, with a median time of 5.5[1–13] months after LT (Fig. S7). Data on the type of HBV-R were available for 22 out of 23 patients. HBV-R was defined by HBsAg alone in 47.8% of patients, HBsAg and HBV DNA in 39.1% of patients, and HBV DNA alone in 8.7% of patients. In detail, nine patients experienced both HBsAg and HBV DNA recurrence (five were treated with lifelong HBIG and NUCs, one with a finite course of HBIG and indefinite NUCs and two with NUCs alone from transplantation). Of the patients with available data (8 out of 9), two cleared HBsAg after 0.5 and 3 months from HBV-R, while four cleared HBV DNA (two after 1 month and two after 6 months). Eleven patients had only HBsAg recurrence (nine received a combination of lifelong HBIG and NUCs, one was initially treated with HBIG but later continued with NUCs alone, and one received NUCs alone from transplantation). Five of them, all receiving lifelong HBIG, achieved HBsAg negativization after a median of 6 [3–6.75] months following HBV-R. Finally, two patients, both on lifelong combination of HBIG and NUCs, exhibited only HBV DNA recurrence and remained so thereafter.

Patients with HCC with HBV-R had significantly higher frequency of microvascular invasion (47.8% *vs.* 18.7%, $p = 0.007$), and a number ≥3 of viable nodules (60.9% *vs.* 22.5%, $p < 0.001$) at explant pathology, and they less frequently received HBIG for post-transplant prophylaxis (82.6% *vs.* 92.7%, $p = 0.042$) compared to patients without HBV-R (Table 2).

Notably, patients who received lifelong HBIG in combination with NUCs exhibited relatively lower rates of HBV-R compared to those in whom HBIG was withdrawn, those who received HBIG only at transplant and those who received NUCs alone (2.8% *vs.* 4.3% *vs.* 0% *vs.* 9.1%, respectively) (Fig. 1). No differences in terms of HBV-R rates were observed between patients treated with lamivudine and high-barrier NUCs (2/57 [3.5%] *vs.* 20/638 [3.1%], $p = 0.877$). We did not observe any differences between patients treated with different prophylactic regimens in terms of age, HBV DNA detectability or levels exceeding 2,000 IU/ml at transplantation, and donor anti-HBc status. Additionally, tumor characteristics such as the number and diameter of nodules, grading, TNM score, or microvascular invasion did not influence the selection of antiviral prophylaxis. As with the non-HCC cohort, HDV-coinfected patients had the same rate of HBV-R as HBV-monoinfected patients. However, similarly to the non-HCC cohort, they were more likely to receive lifelong treatment with a combination of HBIG and NUCs (89.6% *vs.* 81%, $p = 0.003$).

At univariate analysis, microvascular invasion and ≥3 viable nodules at explant pathology were the only factors associated with HBV-R (Table 4), whereas no association was found between HBV-R and age, MELD, MELD-Na, Child-Pugh scores, HBV DNA positivity or HBV DNA levels ≥2,000 IU/ml at the time of LT, use of anti-HBc positive donors, HDV coinfection, or other characteristics at explant pathology, *e.g.* diameter of the largest nodule ≥30 mm, TNM (3 *vs.* 1 and 2), and grading (3 *vs.* 1 and 2) (Table 4). Both ≥3 viable nodules and microvascular invasion were independently associated with HBV-R at multivariate analysis (Table 4).

Only two patients required hospital admission, mainly to investigate the cause of elevated ALT levels. One patient, who experienced concomitant HDV recurrence, had ALT levels exceeding 10x ULN. Five patients showed mild-to-moderate elevations (maximum ALT 5x ULN), while 14 patients had no liver test abnormalities. None of the patients experienced any impact on liver synthesis. Among the 10 patients with HDV coinfection, only three had HDV recurrence, with HDV RNA levels of 2,120, 5,180 and 19,000 copies/ml. Only one patient, as stated above, required hospital admission and none of them affect graft or patient survival. Ten patients died after HBV-R, mostly owing to concomitant HCC-R (8/10).

Both patient and graft survival were significantly lower in patients with HCC with HBV-R compared to those without, $p < 0.001$ and $p = 0.002$, respectively (Fig. 3A,B).

**Table 2. Characteristics of patients with HBV-R *vs*. those without HBV-R.**

| | Patients without HCC | | | Patients with HCC | | |
|---|---|---|---|---|---|---|
| **Variables** | **HBV-R (n = 10)** | **No HBV-R (n = 462)** | ***p* values** | **HBV-R (n = 23)** | **No HBV-R (n = 710)** | ***p* values** |
| Gender, M | 9 (90) | 280 (60.6) | 0.076 | 22 (95.7) | 790 (9.9) | 0.166 |
| Age | 48 (31.5–56.02) | 53 (45–60) | 0.186 | 57 (53.81–64) | 59 (54–63) | 0.741 |
| Indication for LT | | | 0.661 | | | |
| Decompensated cirrhosis | 9 (90) | 359 (77.7) | | | | |
| ACLF | 0 (0) | 29 (6.3) | | | | |
| ALF | 1 (10) | 58 (12.6) | | | | |
| HDV coinfection | 5 (50) | 235 (50.9) | 0.683 | 10 (43.5) | 257 (36.2) | 0.397 |
| MELD | 23.5 (18–30.5) | 20 (16–28.25) | 0.404 | 10 (9–17) | 12 (9–18) | 0.443 |
| MELD-Na | 19 (18–29.75) | 22 (18–30) | 0.681 | 10 (9–17) | 13 (9–20) | 0.283 |
| Child-Pugh C *vs*. A and B | 7 (70) | 229 (49.6) | 0.137 | 5 (21.7) | 120 (16.9) | 0.606 |
| HBV DNA detectable at LT | 5 (50) | 143 (31) | 0.204 | 6 (26.1) | 140 (19.7) | 0.513 |
| HBV DNA ≥2,000 at LT | 1 (10) | 52 (11.3) | 0.280 | 1 (4.3) | 10 (1.4) | 0.205 |
| Type of antiviral therapy before LT | | | 0.876 | | | 0.577 |
| LAM | 0 (0) | 39 (8.4) | | 1 (4.3) | 52 (7.3) | |
| TDF | 3 (33.3) | 98 (21.2) | | 10 (43.5) | 187 (26.3) | |
| ETV | 6 (66.7) | 235 (50.9) | | 11 (47.8) | 383 (53.9) | |
| TAF | 0 (0) | 6 (1.3) | | 0 (0) | 9 (1.3) | |
| Other | 0 (0) | 9 (1.9) | | 0 (0) | 12 (1.7) | |
| Use of anti-HBc positive donor | 3 (33.3) | 57 (12.3) | 0.089 | 3 (13) | 122 (17.2) | 0.518 |
| Type of post-transplant prophylaxis | | | **0.047** | | | 0.251 |
| NUCs + HBIG long-life | 5 (50) | 372 (80.5) | | 17 (74) | 581 (81.8) | |
| NUCs + HBIG withdrawal | 3 (30) | 32 (6.9) | | 2 (8.7) | 44 (6.2) | |
| NUCs + HBIG at transplant | 1 (10) | 21 (4.5) | | 0 (0) | 31 (4.4) | |
| NUCs alone | 1 (10) | 16 (3.5) | | 3 (13) | 30 (4.2) | |
| HBIG alone | - | 3 (0.6) | | 0 (0) | 2 (0.3) | |
| High-barrier *vs*. low-barrier NUCs | | | 0.430 | | | 0.117 |
| LAM alone | 0 | 2 (0.4) | | 0 (0) | 0 (0) | |
| LAM + HBIG | 0 | 41 (8.9) | | 2 (8.6) | 55 (7.7) | |
| High-barrier NUCs alone | 1 (10) | 12 (2.6) | | 3 (13) | 29 (4.1) | |
| High-barrier NUCs + HBIG | 9 (90) | 382 (82.7) | | 17 (74) | 588 (82.8) | |
| Use of LAM for the post-transplant prophylaxis | 0 (0) | 44 (9.5) | 0.292 | 2 (8.7) | 55 (7.7) | 0.877 |
| Type of immunosuppresive therapy | | | 0.139 | | | 0.638 |
| CNIs | 2 (20) | 228 (49.3) | | 13 (56.5) | 337 (47.5) | |
| mTOR inhibitors | 1 (10) | 24 (5.2) | | 2 (8.6) | 44 (6.2) | |
| Mixed | 7 (70) | 189 (40.9) | | 8 (34.8) | 305 (43) | |
| Use of lifelong HBIG for antiviral prophylaxis | 5 (50) | 375 (81.2) | **0.004** | 17 (74) | 583 (82.1) | 0.341 |
| Use of lifelong/long-term HBIG for antiviral prophylaxis | 8 (80) | 407 (88.1) | 0.193 | 19 (82.6) | 627 (88) | 0.442 |
| Use of HBIG (lifelong/long-term/at transplant) | 9 (90) | 429 (92.6) | 0.291 | 19 (82.6) | 659 (92.7) | **0.042** |
| Microvascular invasion | | | | 11 (47.8) | 133 (18.7) | **0.007** |
| TNM 3 *vs*. TNM 1/2 | | | | 2 (8.7) | 31 (4.4) | 0.481 |
| Grading G3 *vs*. G1/G2 | | | | 8 (34.8) | 162 (22.8) | 0.749 |
| Number of viable nodules ≥3 | | | | 14 (60.9) | 160 (22.5) | **<0.001** |
| Diameter of viable nodule ≥30 mm | | | | 12 (52.2) | 207 (29.2) | 0.095 |
| Downstaging treatment, yes | | | | 15 (65.2) | 397 (55.9) | 0.558 |
| Bridging treatment, yes | | | | 10 (43.5) | 260 (36.6) | 0.681 |

Qualitative variables are shown as number and percentages and quantitative variables as median values and IQR reported with 25$^{th}$ and 75$^{th}$ percentile values in parenthesis. Chi-square test for the comparison of qualitative variables, Student's *t* test for quantitative parametric variables and ANOVA analyses when more than two groups were compared. Differences were considered statistically significant when the *p* value was ≤0.05.

ACLF, acute-on-chronic liver failure; ALF, acute liver failure; CNIs, calcineurin inhibitors; ETV, entecavir; HBIG, hepatitis B immunoglobulin; HBV-R, hepatitis B recurrence; LAM, lamivudine; LT, liver transplantation; MELD, model for end-stage liver disease; mTORi, mammalian target of rapamycin inhibitors; NUCs, nucleos(t)ide analogues; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil.

### *HCC recurrence*

HCC-R occurred in 10.8% (79/733) of patients. Median time from LT was 18 [10.9–30] months. Twelve LT recipients experienced both HBV- and HCC-R: in 58.3%, HBV-R was documented before HCC-R. The rate of HBV-R was significantly higher in patients with HCC-R than in those without HCC-R (15.2% *vs.* 1.9%; *p* <0.001). Patients with HCC-R exhibited higher levels of AFP at LT, and more frequently had a diameter of the largest viable nodule ≥30 mm, a higher frequency of G3 nodules, a more advanced TNM stage, and a higher microvascular invasion rate at explant pathology. Additionally, they were less frequently treated with lifelong HBIG and had a higher rate of HBV-R after LT, in comparison to patients without HCC-R (Table S1).

Univariate analysis showed that Child-Pugh C, microvascular invasion, diameter of the largest viable nodule ≥30 mm, grading G3, TNM 3, and HBV-R were associated with HCC-R (Table 5), whereas other variables, such as age, sex, MELD/MELD-Na score, HBV DNA detectable or ≥2,000 IU/ml at the time of LT, HDV coinfection, AFP, downstaging and bridging treatment, anti-HBc-positive donors, and number of viable nodules at explant pathology were not associated with HCC-R (Table 5). At the multivariate analysis, Child-Pugh C, microvascular invasion, diameter of the largest viable nodule ≥30 mm

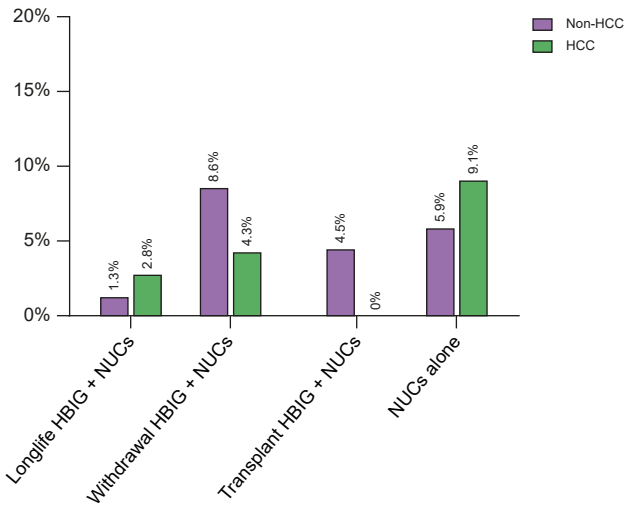



**Fig. 1. Risk of HBV recurrence after LT according to the type of antiviral prophylaxis after LT in patients without and with HCC.** HBIG, hepatitis B immunoglobulins; HCC, hepatocellular carcinoma; NUCs, nuclos(t)ide analogues.

and HBV-R remained independently associated with HCC-R (Table 5). HCC-R was associated with a significantly reduced survival after LT, with a 5-year survival rate of 32.5% compared to 92.4% for patients without HCC-R ($p$ <0.001) (Fig. S8). Fifty-seven patients died after HCC-R, the vast majority for HCC-related causes (53/57).

## Discussion

There is an ongoing debate on the optimal prophylactic strategy to prevent HBV-R after LT, especially in patients transplanted for HCC.[6,7,22] Antiviral prophylaxis with the combination of HBIG and high-barrier NUCs is currently considered the gold standard.[6] However, high costs, limited availability, patient compliance, and the need for parenteral administration of HBIG have led to the implementation of alternative strategies.

Fung *et al.*[23] showed that ETV monotherapy is effective in preventing HBV-R after LT. Recently, Rodríguez-Tajes *et al.*[24] analyzed real-life data from 173 HDV-coinfected recipients who underwent HBIG withdrawal after LT. Despite HBIG being

**Table 3. Univariate analysis for HBV recurrence in patients transplanted without HCC. Linear regression analysis.**

| Covariates | OR | 95% CI | *p* value |
|---|---|---|---|
| Male gender | 0.186 | 0.023-1.484 | 0.112 |
| Age | 0.961 | 0.911-1.014 | 0.147 |
| HDV coinfection | 1.298 | 0.370-4.553 | 0.683 |
| MELD | 1.028 | 0.956-1.106 | 0.459 |
| MELD-Na | 0.983 | 0.897-1.076 | 0.706 |
| Child-Pugh C vs A/B | 3.133 | 0.644-15.253 | 0.157 |
| HBV DNA detectable at LT | 2.091 | 0.596-7.338 | 0.250 |
| HBV DNA ≥2,000 IU/ml | 0.313 | 0.034-2.881 | 0.305 |
| Anti-HBc-positive donor | 3.202 | 0.779-13.163 | 0.107 |
| Use of lifelong HBIG for post-transplant prophylaxis | 0.184 | 0.052-0.653 | **0.009** |

Level of significance: p <0.05.
ACLF, acute-on-chronic liver failure; HBIG, hepatitis B immunoglobulins; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease.

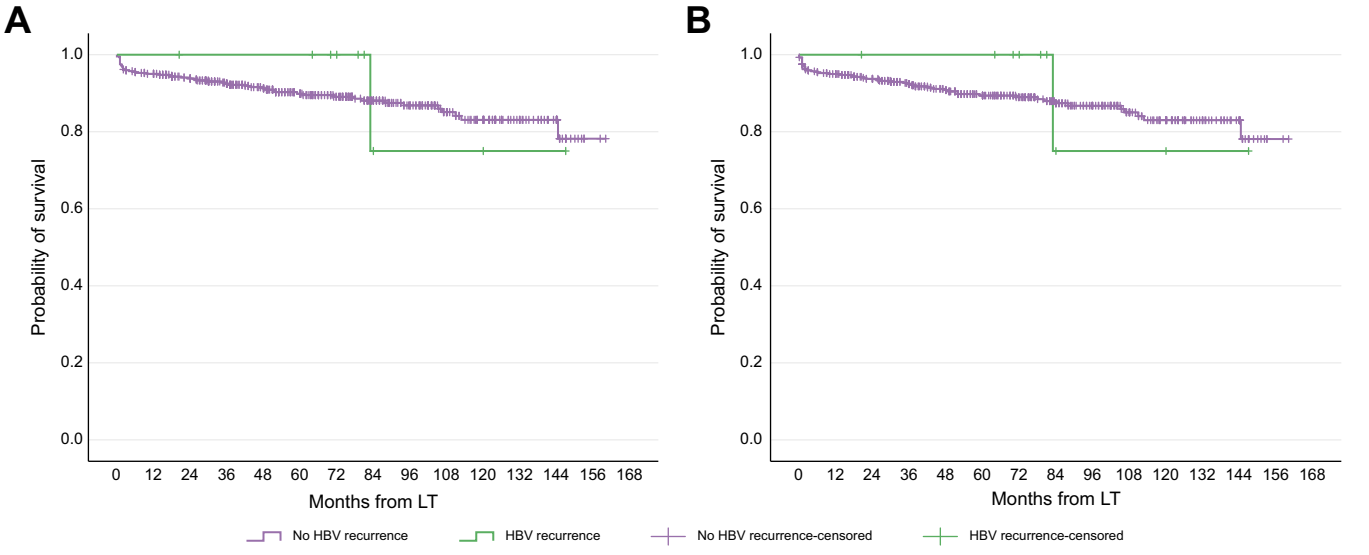



**Fig. 2. Patient and graft survival of patients without HCC with or without HBV recurrence.** (A) Survival of patients without HCC with HBV recurrence *vs.* those without. (B) Graft survival of patients without HCC with HBV recurrence *vs.* those without. HCC, hepatocellular carcinoma. Kaplan-Meyer analysis.

**Table 4. Univariate and multivariate analyses for HBV recurrence in patients transplanted with HCC. Linear regression analysis.**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| **Covariates** | **OR** | **95% CI** | ***p* values** | **OR** | **95% CI** | ***p* values** |
| Male gender | 0.266 | 0.035-1.992 | 0.197 | | | |
| Age | 1.003 | 0.953-1.056 | 0.900 | | | |
| HDV coinfection | 0.682 | 0.280-1.661 | 0.399 | | | |
| MELD | 0.974 | 0.913-1.040 | 0.435 | | | |
| MELD-Na | 0.971 | 0.912-1.033 | 0.351 | | | |
| Child-Pugh C *vs.* A/B | 1.303 | 0.475-3.579 | 0.607 | | | |
| HBV DNA detectable at LT | 1.371 | 0.531-3.543 | 0.514 | | | |
| HBV DNA ≥2,000 IU/ml | 4.400 | 0.366-52.962 | 0.243 | | | |
| AFP | 0.999 | 0.995-1.002 | 0.470 | | | |
| Grading G3 *vs.* G1/2 at explant | 1.159 | 0.471-2.853 | 0.749 | | | |
| TNM 3 *vs.* TNM 1/2 at explant | 1.705 | 0.380-7.651 | 0.486 | | | |
| Diameter of largest viable nodule at explant, ≥30 mm | 2.087 | 0.864-5.040 | 0.102 | | | |
| Anti-HBc-positive donor | 0.668 | 0.195-2.293 | 0.521 | | | |
| Use of LAM for antiviral prophylaxis | 0.890 | 0.230-3.908 | 0.877 | | | |
| Use of lifelong HBIG for post-transplant prophylaxis | 0.612 | 0.221-1.696 | 0.345 | | | |
| Number of viable nodules at explant, ≥3 | 4.627 | 1.905-11.238 | <0.001 | 5.071 | 1.867-13.775 | 0.001 |
| Microvascular invasion at explant | 3.253 | 1.318-8.027 | 0.010 | 2.320 | 0.911-5.904 | 0.078 |

Level of significance: p <0.05.
AFP, alpha-fetoprotein; HBIG, hepatitis B immunoglobulins; LAM, lamivudine; LT, liver transplantation; MELD, model for end-stage liver disease; OR, odds ratio.

withdrawn in 60% of patients, at a median follow-up of 7.8 years after LT, only 7% of patients had detectable HBV DNA, and less than 1.7% experienced HDV recurrence.

Although NUC monotherapy appears promising in preventing clinically significant HBV-R, it may not entirely prevent graft reinfection,[25] which may be implicated in HCC-R after LT.[18] Moreover, the proliferation of residual, circulating HCC cells with integrated HBV DNA may predispose recipients to both HBV-R and HCC-R.[26] Hence, it could be that patients with HCC should be preferably treated with the combination of lifelong HBIG and NUCs to prevent the establishment of cccDNA (covalently closed circular DNA) in the graft, though tissue cccDNA has been documented in post-LT HBsAg-negative recipients receiving combined HBV prophylaxis.[25] However, some studies suggested that the use of HBIG might be associated with a lower risk of HCC-R after LT.[27,28]

Recognizing the lack of a clear consensus on this important topic, the "Permanent Transplant Commission" of the Italian Association for the Study of the Liver (AISF) initiated this study to investigate the current practices for preventing HBV-R after LT in Italy and assessing the impact of HBV and HCC-R after LT.

We found that approximately all recipients received HBV prophylaxis, mostly with the lifelong combination of HBIG and NUCs (83.9%). Hence, the recent proposal to consider HBIG withdrawal in clinically stable patients after LT[22] has not been translated into clinical practice in Italy yet. Interestingly, we found that HBIG-free regimens were more frequently used in the Southern regions ($p$ <0.001), thus indicating that heterogeneity among transplant centers within the same country exists.

With this prophylaxis, in patients transplanted without HCC, the overall, cumulative rate of HBV-R was low (2.1%). Lifelong HBIG with NUCs was associated with a lower risk of HBV-R than HBIG withdrawal, HBIG only at transplant, and NUCs alone. Use of lifelong HBIG was the only factor associated with

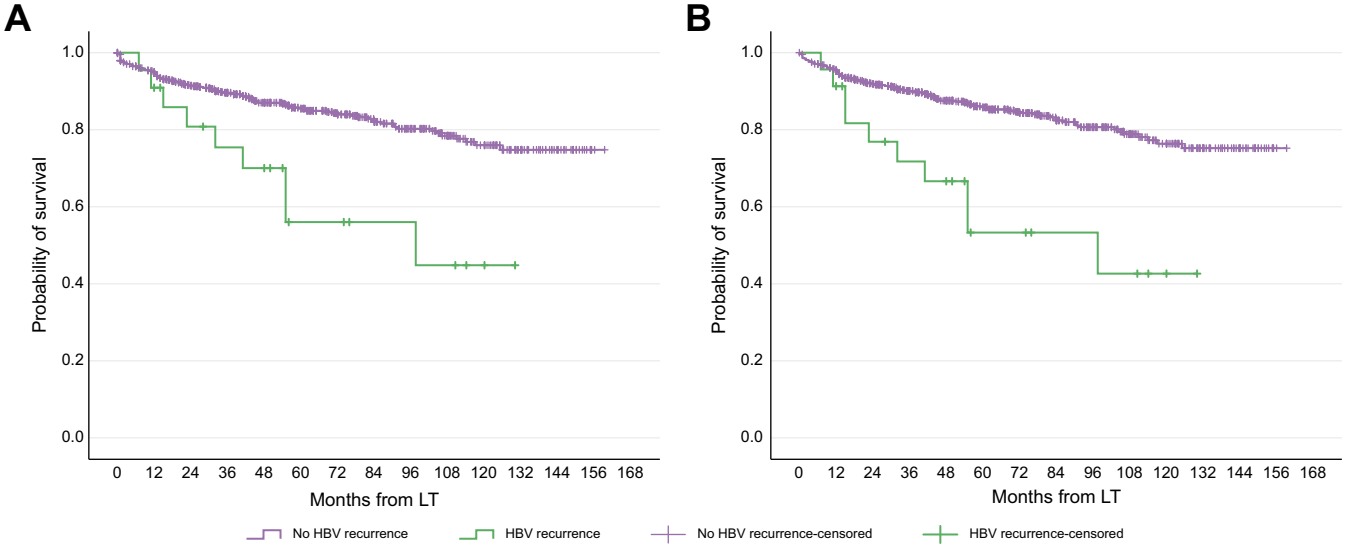



**Fig. 3. Patient and graft survival of patients with HCC with or without HBV recurrence.** (A) Survival of patients with HCC with HBV recurrence *vs.* those without. (B) Graft survival of patients with HCC with HBV recurrence *vs.* those without. HCC, hepatocellular carcinoma. Kaplan-Meyer analysis.

**Table 5. Univariate and multivariate analyses for HCC recurrence. Linear regression analysis.**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| **Covariates** | **OR** | **95% CI** | ***p* values** | **OR** | **95% CI** | ***p* values** |
| Male gender | 0.546 | 0.243-1.227 | 0.143 | | | |
| Age | 1.017 | 0.986-1.048 | 0.288 | | | |
| MELD | 1.006 | 0.974-1.040 | 0.719 | | | |
| MELD-Na | 1.008 | 0.975-1.042 | 0.646 | | | |
| aFP | 1 | 1-1 | 0.998 | | | |
| HBV DNA detectable at LT | 0.865 | 0.469-1.598 | 0.644 | | | |
| HBV DNA ≥2,000 IU/ml | 1.296 | 0.140-12.030 | 0.819 | | | |
| Downstaging treatment | 1.033 | 0.616-1.733 | 0.901 | | | |
| Bridging treatment | 1.185 | 0.731-1.921 | 0.490 | | | |
| Anti-HBc donor | 0.558 | 0.269-1.158 | 0.117 | | | |
| Number of viable nodules at explant, ≥3 | 1.356 | 0.815-2.256 | 0.242 | | | |
| Use of lifelong HBIG for post-transplant prophylaxis | 0.637 | 0.355-1.141 | 0.130 | | | |
| TNM 3 *vs*. TNM 1/2 at explant | 3.347 | 1.497-7.483 | 0.003 | | | |
| Grading G3 *vs*. G1/G2 at explant | 2.550 | 1.490-4.365 | <0.001 | | | |
| HDV coinfection | 1.598 | 0.941-2.714 | 0.083 | 1.362 | 0.707-2.625 | 0.356 |
| Child-Pugh C *vs*. A/B | 2.287 | 1.068-5.334 | 0.034 | 3.519 | 1.305-9.484 | 0.013 |
| Microvascular invasion | 4.129 | 2.409-7.078 | <0.001 | 3.088 | 1.692-5.634 | <0.001 |
| Diameter of largest viable nodule at explant, ≥30 mm | 2.397 | 1.443-3.983 | <0.001 | 1.998 | 1.092-3.656 | 0.025 |
| HBV recurrence | 9.085 | 3.858-21.395 | <0.001 | 10.329 | 3.665-29.110 | <0.001 |

HBIG, hepatitis B immunoglobulins; MELD, model for end-stage liver disease; OR, odds ratio.

a lower risk of HBV-R during follow-up at univariate analysis. Therefore, we could not perform a multivariate model, also because the total number of events was low. It is worth noting, however, that the development of HBV-R was not associated with reduced survival (5-year survival 91.4% *vs.* 89.9%).

Notably, in patients transplanted without HCC, the rate of HBV-R was numerically lower in those treated with HBIG only at the time of transplantation than in those in whom HBIG was withdrawn during post-transplant follow-up (4.5% *vs.* 8.9%, respectively). The same trend was observed in patients transplanted with HCC with a recurrence rate of 0% and 4.3%, respectively, in the two groups. These differences seem not biologically plausible and should not be interpreted as evidence indicating a lower risk of HBV-R in patients receiving HBIG only at transplantation. Instead, they might be related to the retrospective design that – together with the low number of events – limits meaningful comparisons between subgroups.

The rate of HBV-R in patients transplanted with HCC was also low (3.1%). Development of HBV-R, however, was the strongest, independent predictor of HCC-R after adjusting for liver disease severity and HCC-related characteristics reflecting tumor behavior and aggressiveness (odds ratio 10.329). Our data confirm previous results from comparatively smaller series from Asia wherein HBV relapse was linked to HCC-R.[29,30] Since HCC-R was associated with a significant reduction in patient survival (34.2% *vs.* 92.4% at 5 years in patients with *vs.* without HCC-R), strategies to prevent HBV-R in patients transplanted with HCC seem advisable once a direct pathogenic effect is demonstrated. Interestingly, in our cohort, the combination of lifelong HBIG and NUCs emerged as the strategy associated with the lowest risk of HBV-R after LT, in comparison to HBIG for a finite period or NUCs alone (2.8% *vs.* 6.5% *vs.* 9.1%, respectively). However, the association between HBV-R and HCC-R should not be interpreted as evidence of direct causality. Other authors have suggested that HBV-R may simply be an epiphenomenon of HCC-R,[31] without implying a pathophysiological role. Moreover, the clinical significance of HBV reappearance after LT, in the absence active replication, has yet to be determined.

In patients transplanted for HCC, the rate of HBV-R was significantly higher in those who experienced HCC-R compared to those who did not (15.2% *vs.* 1.9%; $p$ <0.001). Among the 12 patients who experienced both HBV-R and HCC-R, the HBV-R was documented prior to HCC-R in 58.3% of the cases, thus leading to the hypothesis that in some recipients the reactivation of HBV may play a role in the recurrence of HCC. However, it should be highlighted that an expert consensus[22] hypothesizes that HBV-R occurring within 6 months before or after HCC-R may simply reflect an epiphenomenon of HCC-R, rather than a true causative factor. Additionally, HCC-R implies that neoplastic cells likely spread beyond the liver removed during transplantation. While these cancerous cells may remain undetectable until radiological evidence appears, they could still produce viral particles and be responsible for earlier HBV.[26] Further prospective studies are still required to better characterize the complex relationship between HBV and HCC in the setting of LT.[26] Awaiting these studies, patients transplanted for HCC should be considered a relatively higher risk group in which the decision to simplify prophylaxis should be taken with caution, considering time from transplantation, clinical conditions, viral-related factors, and HCC phenotype.[32]

We found a significant number of patients with positive HBV DNA at the time of transplantation. This finding extends previous results regarding LT for HBV-related disease in Europe.[8] In the ELTR (European Liver Transplant Registry) study,[8] among patients transplanted for decompensated cirrhosis, the percentage of patients transplanted with positive HBV DNA increased from 19.8% (between 1988-1995) to 49% (between 2006-2010). The same trend was observed in patients transplanted for HCC (from 18% to 42.6%). These trends reflect the increasing efficacy and availability of HBV antiviral therapies after transplantation. In the current Italian experience including patients from 2010, ∼32% of patients without HCC and ∼21% of patients with HCC had

positive HBV DNA at transplantation. On the one hand, these lower percentages, compared with the last period (2006-2010) included in the ELTR study,[8] indirectly indicate more effective and widespread HBV treatment with high-barrier NUCs prior to LT. On the other hand, they highlight the importance of a proactive, aggressive treatment of HBV. Another potential factor that could explain the presence of patients with positive HBV DNA is the inclusion of those with HBV-related ALF (*i.e.*, difficult to treat). In fact, in our non-HCC cohort, excluding patients transplanted for ALF, the percentage of viremic patients decreases from 32% to 25%, while the proportion of those with levels exceeding 2,000 IU/ml drops from 36% to 18.6%.

In our study, 43.5% of HBsAg-positive transplant recipients were HDV coinfected. This elevated proportion of HDV coinfection in HBV-transplanted patients, compared with lower rate of HDV in the non-transplant HBsAg-positive population,[2–4] might be explained by the limited and ineffective therapeutic options to treat HDV infection. The recent introduction of bulevirtide may change, at least partly, this scenario.[33] We could not retrieve data on the HDV RNA at the time of transplantation, thus limiting definitive conclusions. Based on our preliminary data, it seems that HDV infection is not associated with the risk of HBV and HCC-R after LT, thus suggesting that HDV status may not be useful to stratify individual patient's risk. However, prospective data are required to confirm our results and provide further insights regarding the clinical impact of HDV in the LT setting.

This study is subject to several, significant limitations. Firstly, the retrospective design is associated with multiple potential biases and confounding factors. This includes non-standardized follow-up, potential differences in the HBIG titration between centers, lack of substantial virological data, such as HDV RNA or quantitative HBsAg, at the time of transplantation, lack of data regarding the reasons for prescription of LAM *vs.* high-barrier NUCs pre-transplantation, and lack of data regarding the resistance profile to LAM. Most patients received lifelong HBIG, thus limiting meaningful comparison with other groups. However, this is the current picture of LT for HBV-related liver disease in a nationwide study from Italy. Therefore, we had to accept these results when performing the analyses. Furthermore, we could not collect robust data on non-liver-related comorbidities, which may affect morbidity and mortality after transplantation.[34] Secondly, despite this being a nationwide study thoroughly collecting clinical, laboratory, and explant data from 20 liver transplant centers over 12 years, HBV-R was rare. The multicentric nature also introduces the possibility of data heterogeneity across different centers, as also suggested by the different uses of HBV prophylaxis. Furthermore, data regarding donor-recipient matching were not available from all centers. However, no differences were observed in the allocation of anti-HBc-positive grafts between patients with detectable and undetectable HBV DNA at the time of LT and among those patients, between those with HBV DNA below or above >2,000 IU/ml. Additionally, in the univariate analysis, receiving an anti-HBc-positive graft was not associated with HBV-R in either patients with or without HCC, and among the latter, it was not associated with HCC-R. Finally, numerous changes have occurred in the landscape of LT, including improvement in patient assessment criteria for waiting list inclusion, changing of the epidemiological trends, advances in transplant techniques and post-transplant management.[35] These factors may have influenced our results and should be considered when interpreting our findings. Yet, this study represents the first comprehensive, multicenter study thoroughly describing liver transplant outcomes for HBV-related liver disease in Italy, which was never analyzed before.

However, due to the retrospective nature of the study and the fact that most of our patients were receiving HBIG post-transplant, our findings should not be interpreted as evidence supporting the indiscriminate use of long-term HBIG after LT for HBV-related liver disease. Prospective trials will ultimately tell us whether our historical data and clinical management are still valid or need to be refined.

In conclusion, our multicenter study shows that, in Italy, the combination of lifelong HBIG and NUCs remains the most used strategy for preventing HBV-R after LT. HBIG withdrawal was associated with a 4% increase of HBV-R without any impact on graft survival. However, in patients transplanted with HCC, HBV-R was associated with HCC-R, independently of HCC-related factors. Further studies are required to clarify the relationship between HBV and HCC-R in the setting of LT, creating potential opportunities for a more individualized management of antiviral prophylaxis after LT.

**Affiliations**

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## Abbreviations

ACLF, acute-on-chronic liver failure; AFP, alpha-fetoprotein; ALF, acute liver failure; anti-HBc, antibodies anti-hepatitis B core antigen; anti-HBe, antibodies anti-hepatitis e antigen; ETV, entecavir; G3, grade 3; HBIG, hepatitis B immunoglobulins; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV-R, HBV recurrence; HCC, hepatocellular carcinoma; HCC-R, HCC recurrence; LAM, lamivudine; LT, liver transplantation; MELD, model for end-stage liver disease; NUCs, nucleos(t)ide analogues; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil.

## Financial support

The authors did not receive any financial support to produce this manuscript.

## Conflict of interest

SP: Consultant: Plasma Protein Therapeutics Association, Boehringer Ingelheim, Resolution Therapeutics; Speaking fees: Grifols, MEDSCAPE. PB has received lecture and consulting fees from Biotest, Chiesi Farmaceutici and Sandoz. The other authors have nothing to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

PB; FPR; AZ: research idea and design, interpretation of the data, critical revision of the manuscript and final approval. SB: acquisition and interpretation of the data, statistical analysis, and writing of the manuscript. LT, MCM, GF, NDM, LP, SF, CDB, MFD, BM, DP, SB, VM, AL, LDC, DF, MR, DA, AGL, GS, GSB, SP, PA, CM, SM, PDE, PGV, DG, RL, VG, LM, EF, PT, MB, FRP, IL, AF, NP, SM, EG, FF, ST, PG, AA: acquisition of the data, interpretation of the data, critical revision of the manuscript.

## Data availability statement

Data sharing will not be available due to Ethical restriction. For further information, please contact Dr. Alberto Zanetto (alberto.zanetto@unipd.it) or the Ethics Committee of Padua University Hospital (prc.unitaricercaclinica@aopd.veneto.it).

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## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101278.

## References

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[1] WHO - data from. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b. 07/02/2024.
[2] Miao Z, Zhang S, Ou X, et al. Estimating the global prevalence, disease progression, and clinical outcome of hepatitis delta virus infection. J Infect Dis 2020;221:1677–1687.
[3] Chen H-Y, Shen D-T, Ji D-Z, et al. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. Gut 2019;68:512–521.
[4] 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.
[5] Buti M, Gonzalez A, Riveiro-Barciela M, et al. Management of chronic HBV-HDV patients chronic HBV-HDV infection: a review on new management options. UEG J 2023;ueg2.12494.
[6] Lampertico P, Agarwal K, Berg T, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–398.
[7] EASL clinical practice guidelines: liver transplantation. J Hepatol 2016;64:433–485.
[8] 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.
[9] Demetris AJ, Todo S, Van Thiel DH, et al. Evolution of hepatitis B virus liver disease after hepatic replacement. Practical and theoretical considerations. Am J Pathol 1990;137:667–676.
[10] Perrillo R, Buti M, Durand F, et al. Entecavir and hepatitis B immune globulin in patients undergoing liver transplantation for chronic hepatitis B. Liver Transpl 2013;19:887–895.
[11] Nasir M, Wu GY. Prevention of HBV recurrence after liver transplant: a review. J Clin Translational Hepatol 2020;8:150–160.
[12] Adam R, Karam V, Cailliez V, et al. 2018 annual report of the European liver transplant Registry (ELTR) - 50-year evolution of liver transplantation. Transpl Int 2018;31:1293–1317.
[13] Cholongitas E, Papatheodoridis GV. High genetic barrier nucleos(t)ide analogue(s) for prophylaxis from hepatitis B virus recurrence after liver transplantation: a systematic review. Am J Transplant 2013;13:353–362.
[14] Fung J, Chan S-C, 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.
[15] Chen J, Li L, Yin Q, Shen T. A review of epidemiology and clinical relevance of Hepatitis B virus genotypes and subgenotypes. Clin Res Hepatol Gastroenterol 2023;47:102180.
[16] Russo FP, Viganò M, Stock P, et al. HBV-positive and HIV-positive organs in transplantation: a clinical guide for the hepatologist. J Hepatol 2022;77:503–515.
[17] Battistella S, Zanetto A, Gambato M, et al. The role of antiviral prophylaxis in preventing HBV and HDV recurrence in the setting of liver transplantation. Viruses 2023;15:1037.
[18] Faria LC, Gigou M, Roque–Afonso AM, et al. Hepatocellular carcinoma is associated with an increased risk of hepatitis B virus recurrence after liver transplantation. Gastroenterology 2008;134:1890–1899.
[19] Saab S, Yeganeh M, Nguyen K, et al. Recurrence of hepatocellular carcinoma and hepatitis B reinfection in hepatitis B surface antigen-positive patients after liver transplantation: recurrence of Hepatocellular Carcinoma. Liver Transpl 2009;15:1525–1534.
[20] Wendon J, Cordoba J, Dhawan A, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol 2017;66:1047–1081.
[21] Moreau R, Jalan R, Gines P, et al. Acute-on-Chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–1437.e9.
[22] **Duvoux C**, **Belli LS**, **Fung J**, et al. 2020 position statement and recommendations of the European Liver and Intestine Transplantation Association (ELITA): management of hepatitis B virus-related infection before and after liver transplantation. Aliment Pharmacol Ther 2021;54:583–605.
[23] Fung J, Wong T, Chok K, et al. Long-term outcomes of entecavir monotherapy for chronic hepatitis B after liver transplantation: results up to 8 years. Hepatology 2017;66:1036–1044.
[24] Rodríguez-Tajes S, García-Eliz M, Marcos AC, et al. The role of HBIG in real life for patients undergoing liver transplantation due to HDV -related cirrhosis. Liver Int 2024;44:279–285.
[25] Villeret F, Lebossé F, Radenne S, et al. Early intrahepatic recurrence of HBV infection in liver transplant recipients despite antiviral prophylaxis. JHEP Rep 2023;5:100728.
[26] Schemmer P, Burra P, Hu R, et al. State of the art treatment of hepatitis B virus hepatocellular carcinoma and the role of hepatitis B surface antigen post-liver transplantation and resection. Liver Int 2022;42:288–298.
[27] Lee EC, Kim SH, Lee SD, et al. High-dose hepatitis B immunoglobulin therapy in hepatocellular carcinoma with hepatitis B virus-DNA/hepatitis B e antigen-positive patients after living donor liver transplantation. WJG 2016;22:3803.
[28] Beckebaum S, Herzer K, Bauhofer A, et al. Recurrence of hepatitis B infection in liver transplant patients receiving long-term hepatitis B immunoglobulin prophylaxis. Ann Transpl 2018;23:789–801.

[29] Li M, Chen G, Cai C, et al. High hepatitis B virus DNA level in serum before liver transplantation increases the risk of hepatocellular carcinoma recurrence. Digestion 2011;84:134–141.
[30] Wu T-J, Chan K-M, Chou H-S, et al. Liver transplantation in patients with hepatitis B virus-related hepatocellular carcinoma: the influence of viral characteristics on clinical outcome. Ann Surg Oncol 2013;20:3582–3590.
[31] Li H, Lu D, Chen J, et al. Post-transplant HBV reactivation impacts the prognosis of patients with hepatitis B-related hepatocellular carcinoma: a dual-center retrospective cohort study in China. Int J Surg 2024;110(4):2263–2274.
[32] Pelizzaro F, Gambato M, Gringeri E, et al. Management of hepatocellular carcinoma recurrence after liver transplantation. Cancers 2021;13:4882.
[33] Wedemeyer H, Aleman S, Brunetto MR, et al. A phase 3, randomized trial of bulevirtide in chronic hepatitis D. N Engl J Med 2023;389:22–32.
[34] Palaniyappan N, Peach E, Pearce F, et al. Long-term outcomes (beyond 5 years) of liver transplant recipients—a transatlantic multicenter study. Liver Transplant 2024;30:170–181.
[35] Terrault NA, Francoz C, Berenguer M, et al. Liver transplantation 2023: status report, current and future challenges. Clin Gastroenterol Hepatol 2023;21:2150–2166.

Keywords: HBV; HCC; HDV; liver transplantation; HBV recurrence; HCC recurrence.
*Received 3 July 2024; received in revised form 14 November 2024; accepted 14 November 2024; Available online 23 November 2024*