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ORIGINAL ARTICLE

Characteristics and outcome of anti-hepatitis D virus positive patients with hepatocellular carcinoma

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Abstract

Background & Aims: Chronic hepatitis D virus (HDV) often leads to end-stage liver disease and hepatocellular carcinoma (HCC). Comprehensive data pertaining to large populations with HDV and HCC are missing, therefore we sought to assess the characteristics, management, and outcome of these patients, comparing them to patients with hepatitis B virus (HBV) infection.

Methods: We analysed the Italian Liver Cancer database focusing on patients with positivity for HBV surface antigen and anti-HDV antibodies (HBV/HDV, $n = 107$) and patients with HBV infection alone ($n = 588$). Clinical and oncological characteristics, treatment, and survival were compared in the two groups.

Results: Patients with HBV/HDV had worse liver function [Model for End-stage Liver Disease score: 11 vs. 9, $p < .0001$; Child-Turcotte-Pugh score: 7 vs. 5, $p < .0001$] than patients with HBV. HCC was more frequently diagnosed during surveillance (72.9% vs. 52.4%, $p = .0002$), and the oncological stage was more frequently Milan-in (67.3% vs. 52.7%, $p = .005$) in patients with HBV/HDV. Liver transplantation was more frequently performed in HBV/HDV than in HBV patients (36.4% vs. 9.5%), while the opposite was observed for resection (8.4% vs. 20.1%, $p < .0001$), and in a competing risk analysis, HBV/HDV patients had a higher probability of receiving transplantation, independently of liver function and oncological stage. A trend towards longer survival was observed in patients with HBV/HDV (50.4 vs. 44.4 months, $p = .106$).

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Conclusions: In patients with HBV/HDV, HCC is diagnosed more frequently during surveillance, resulting in a less advanced cancer stage in patients with more deranged liver function than HBV alone. Patients with HBV/HDV have a heightened benefit from liver transplantation, positively influencing survival.

KEYWORDS

liver transplantation, outcome, survival, treatment

1 | INTRODUCTION

Hepatitis D virus (HDV) is a defective virus that requires the presence of hepatitis B virus (HBV) to infect the host.[1] HDV infection can be acquired either concomitantly with HBV (co-infection), often resulting in a self-limited disease, or as a super-infection in patients who are already chronically infected with HBV, in this case frequently leading to a progressive disease with an evolution to cirrhosis in the most cases.[2,3] Chronic infection with HDV has a prevalence of approximately 5% among subjects with HBV, with an estimated worldwide prevalence of 12 million positive subjects, and with a wide geographic variation.[4,5]

Despite a relatively low prevalence in the general population – approximately .16% – chronic infection with HDV is estimated to be responsible for 20% of cases of hepatocellular carcinoma (HCC) associated with HBV infection.[4,5] The mechanisms leading to hepatic carcinogenesis in patients with HBV/HDV infection have not been completely elucidated. The main responsible for the development of HCC in these patients is thought to be the presence of enhanced, ongoing necro-inflammatory and regenerative activities that are present in patients with dual infection.[6,7] Figures regarding HCC associated with positivity for HBV/HDV have not been thoroughly described, as available data mainly derive from single-centre studies that often include a relatively low number of patients.[8,9] Therefore, an updated profile of these patients and of their outcomes is currently lacking.

Chronic HDV infection, unlike infection with HBV or hepatitis C virus (HCV), is unique in the landscape of virus-associated chronic liver diseases since, until recently, treatment with proven efficacy in halting viral replication in patients with cirrhosis and, as a potential result, able to prevent the progression of liver disease and to reduce the risk of HCC development, was unavailable.[10] This drawback offers the opportunity to describe the full picture of patients with positivity for HBV/HDV and HCC without potential modifiers of the disease trajectory related to the cure of the underlying infection.[11] In this regard, a description of a large population of patients with HCC and positivity for HBV/HDV may help better characterise these patients from the clinical and oncological points of view. Moreover, it may provide a potential benchmark against which to test the potential benefit of recently available treatment for HDV infection.[10,12] Therefore, in this study, we exploited the Italian Liver Cancer (ITA.LI.CA) database to describe the main clinical and oncological characteristics and the outcome of a large population of patients with HCC and positivity for HBV/HDV, and compare these figures to those of patients with HBV alone.

Key points

- Patients with hepatitis B virus (HBV)/hepatitis D virus (HDV) and hepatocellular carcinoma (HCC) are younger and with a more deranged liver function than patients with HBV infection alone, and a larger proportion receive a diagnosis of HCC under surveillance, thus resulting in a more favourable oncologic stage.
- Patients with HBV/HDV, due to these liver-related and oncological characteristics, and to the absence in the recent past of effective treatment for HDV, receive the highest benefit from liver transplantation.
- The results of this study provide the background against which, in the future, might be measured the potential benefit on clinical characteristics and oncological outcome of HDV patients treated with bulevirtide antiviral therapy.

2 | METHODS

The current study examined data from the ITA.LI.CA database, including data from more than 10000 patients with HCC. This database has prospectively gathered data on patients diagnosed and treated for HCC in Italian centres and is periodically updated (every 2 years).[13,14] The most recent update was performed in December 2022, including patients from 23 centres.

For this study, patients with HCC were identified based on positivity for anti-HDV antibodies in patients with evidence of chronic HBV infection attested by the positivity of HBV surface antigen (HBsAg/anti-HDV, reported in the text as 'HBV/HDV') as the cause of liver disease in 1992–2022, and as a control group we selected patients with HCC and positivity for HBsAg and negativity for anti-HDV antibodies (reported in the text as 'HBV alone') diagnosed in the same period. We excluded all patients with other causes of chronic liver disease such as those testing positive for anti-HCV antibodies, with alcohol abuse (daily ethanol intake >60 g for women and >80 g for men, for >10 years, in the absence of any other cause

of liver injury), hereditary or acquired liver storage disease, autoimmune liver disease, and patients with human immunodeficiency virus infection.

The presence of cirrhosis was diagnosed through symptoms, medical history, physical examination, and results of laboratory tests together with unequivocal radiological evidence, or based on liver histology, when available.[15,16] Liver function was evaluated using the Child-Turcotte-Pugh classification and the Model for End-stage Liver Disease (MELD) score, while patients' general well-being was assessed by Performance Status (PS) according to Eastern Cooperative Oncology Group (ECOG) and Karnofsky score.[17–19] Clinically significant portal hypertension was considered to be present whenever the presence of oesophageal varices, history of endoscopic band ligation, or a platelet count below 100×10^9L, were detectable.[20]

The diagnosis of HCC was made following International guidelines or with the recommendations of the Italian consensus on HCC available at the time of HCC diagnosis.[21,22] Furthermore, the date of diagnosis, diagnostic modality of HCC (i.e., under periodic ultrasonographic surveillance, incidental or symptomatic), tumour morphology [i.e., single lesion, multi-nodular (<3 nodules, ≥3 nodules), diffuse/infiltrating, and massive HCC] as well as the maximum size of the largest nodule were recorded. The Milan criteria were used to subdivide patients into non-advanced (Milan-in) and advanced (Milan-out) oncological stages[23] Histological tumour grading (grade 1: well-differentiated; grade 2: moderately differentiated; grade 3: poorly differentiated; grade 4: undifferentiated) was recorded in patients undergoing liver biopsy or surgical therapies.[24]

The principal treatment for HCC was recorded and subdivided into: surgical (liver transplantation and liver resection), ablative (radiofrequency ablation, ethanol injection, and other ablative treatments), and trans-arterial (transcatheter arterial chemoembolization, transarterial embolization, transarterial radioembolization), systemic (sorafenib and other palliative treatment), and best supportive care.

Survival was measured in months from the date of HCC diagnosis to the date of death or the last follow-up information. Causes of death were also recorded.

2.1 | Statistical analysis

The Kolmogorov–Smirnov test was used to determine if the variables were normally distributed. The median and 95% confidence interval of the median (95% CI) were used to express the outcomes of continuous variables. Contingency tables were used to show the frequency and proportion of ordinal and nominal variables in the population. When comparing continuous variables between different patient groups, non-parametric Kruskal–Wallis or Mann–Whitney tests were used. Pearson's χ^2-test and Spearman's rank correlation index were applied to analyse the relationship between nominal variables and continuous variables. Variables with missing values were accepted as long as they influenced less than 10% of the sample; otherwise, they were eliminated from the analysis. For variables with missing data <10%, these were imputed by replacing them with a probable value estimated with multivariate imputation regression.[25]

Patients survival was analysed by Kaplan–Maier estimator curves, and the log-rank test was used to compare the survival distribution samples. The Cox proportional hazards model was adjusted for death-related risk factors identified by statistical analysis (the probability value for entering the model was $p = .20$). The association between cumulative survival probability and virological status of patients (i.e., HBV alone vs. HBV/HDV) was evaluated through competing risks survival analysis, accounting for transplant as a competing event. The Fine and Grey methodology was used for competing-risk regressions.[26] Univariate and multivariate hazard ratios and 95% CI were reported, and 2 competing events were investigated: (i) death without liver transplantation, and (ii) receipt of a liver transplant.

The IBM SPSS Statistics, Release Version 25.0 (SPSS, Inc., 2017, Chicago, IL, USA, www.spss.com) and R (the R project, R version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria and EZR: https://github.com/jinkim3/ezr) were used for the statistical analysis.

3 | RESULTS

Figure S1 shows the flow of patients, with a final population of 695 patients with HCC and chronic HBV infection: among them, 588 patients (84.6%) had HBV infection alone while 107 patients (15.4%) had HBV/HDV positivity. During the study period (1992–2022), the newly diagnosed cases of HCC increased every 4-year period until 2014, a trend related to the increase in the number of ITA.LI.CA centres over these years. However, the proportion of cases of HCCs with HBV (HBV *plus* HBV/HDV) remained stable at approximately 6% and similarly, among these cases, the proportion of HCCs attributable to HBV/HDV remained rather stable over the study period, ranging from 12.0% to 20.5% of HBV cases (Figure 1).

3.1 | Patients' characteristics

Table 1 shows the main characteristics of patients subdivided according to the aetiology of liver disease (HBV/HDV vs. HBV alone). Most patients were male with a significantly higher prevalence in HBV than in HBV/HDV patients (86.9% vs. 71.0%, $p < .0001$). Patients with HBV/HDV were significantly younger at the time of diagnosis of HCC than patients with HBV alone [56.3 years (IQR 49.8–63.1) vs. 63.9 years (IQR 56.5–70.8); $p < .0001$]. No significant differences were observed in body mass index and functional status – evaluated by means of ECOG PS and Karnofsky score – between patients with HBV/HDV and those with HBV alone. No statistically significant difference was observed in the prevalence of comorbidities such as diabetes, cardiovascular disease, nephropathy, or respiratory diseases in the two groups of patients (Table S1).

Patients with HBV/HDV had significantly higher aminotransferase levels [ALT 2.0 × ULN (IQR 1.0–3.2) vs. 1.0 × ULN (IQR 1.0–2.0),

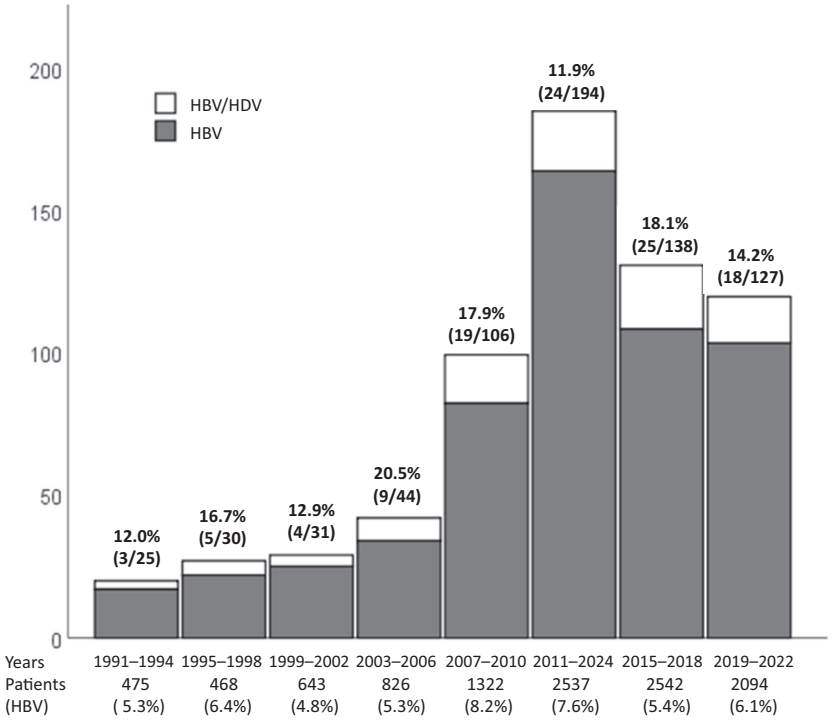


FIGURE 1 Proportion of patients with HBV/HDV infection (white bars) in patients with HBV alone (black bars) across the years. Percentages above the bars refer to the proportion of patients with HBV/HDV, while numbers represent number of HDV/HBV patients on overall patients with HBV.

$p < .0001$; AST 2.2 × ULN (IQR 1.5–4) vs. 1.1 × ULN (IQR 1.0–2.0), $p < .0001$] and worse liver function – as evaluated by both the Child-Pugh-Turcotte score [7 (IQR 5–8) vs. 5 (IQR 5–6), $p < .0001$] and the MELD score [11 (IQR 9–14) vs. 9 (IQR 8–11), $p < .0001$] – as compared to patients with HBV alone. Lastly, both oesophageal varices (63.6% vs. 42.1%, $p < .0001$) and ascites (43.0% vs. 22.9%, $p < .0001$) were more prevalent among patients with HBV/HDV. In patients with oesophageal varices, these were large in 48.5% of HBV/HDV patients and in 41.9% of HBV alone patients.

3.2 | Diagnosis and characteristics of HCC

Overall, the diagnosis of HCC was made during surveillance in 55.5% ($n = 386/695$) of patients, incidentally in 24.9% ($n = 173/695$), and due to symptoms in 15.0% ($n = 104/695$). In detail, the diagnosis of HCC was more frequently made during surveillance in patients with HBV/HDV (72.9% vs. 52.4%, $p = .0002$), in whom both an incidental diagnosis (17.8% vs. 26.2%) and a diagnosis due to symptoms (4.7% vs. 16.8%) were significantly less frequent than in patients with HBV alone ($p < .0001$ for both comparisons). In patients whose diagnosis of HCC was made under surveillance, the median length of surveillance before HCC detection did not significantly differ between patients with HBV/HDV and those with HBV alone [54 months (IQR 21–110) vs. 60 months (IQR 24–120)]. Diagnosis of HCC was made on a histological basis in 10.3% of patients with HBV/HDV ($n = 11/107$) and in 13.3% of patients with HBV alone ($n = 78/588$).

Table 2 shows the characteristics of HCC in the two groups of patients: while the number of HCC nodules was similarly distributed in the two groups of patients (uni-nodular vs. ≤3 nodules vs. >3 nodules, $p = .310$), patients with HBV/HDV less frequently harboured tumours with diffuse/infiltrating or massive behaviour than patients with HBV alone ($p = .023$). The median diameter of the largest lesion was smaller in HBV/HDV than in HBV patients [2.2 cm (IQR 1.5–3.1) vs. 3 cm (IQR 2–5), $p < .0001$], and patients with HBV/HDV were more frequently classified as Milan-in (67.3% vs. 53.7%, $p = .005$). Lastly, we observed no difference in the proportion of patients with macro-vascular invasion or extra-hepatic spread between the two groups.

Tumour histology was available in 21 (19.6%) patients with HBV/HDV and in 135 (23.0%) patients with HBV alone, and no difference in tumour grading was observed between the two aetiological groups (data not shown).

3.3 | Treatment and outcome

In the whole cohort, the most frequent principal treatments for HCC were those potentially curative (surgical and ablative procedures: $n = 380/695$, 54.7%), with no significant difference between patients with HBV/HDV (60.7%, $n = 65/107$) and those with HBV alone (53.6%, $n = 315/588$). Considering surgical therapies, liver transplantation was more frequently carried out in patients with HBV/HDV than in those with HBV alone (36.4% vs. 9.5%), while the opposite occurred for surgical resection (8.4% vs. 20.1%, $p < .0001$). The proportion of patients who received ablative, or transarterial, therapies was similar to the two groups, as well as the proportion of patients who received the best supportive care alone (Table 3).

TABLE 1 Clinical characteristics of the 695 patients, subdivided according to aetiology of liver disease.

Characteristics	HBV ($n=588$)	HBV/HDV ($n=107$)	p
Sex, male	511 (86.9)	76 (71.0)	<.0001
Age, years	63.9 (56.5–70.8)	56.3 (49.8–63.1)	<.0001
Body mass index, kg/m^2	24.4 (22.6–26.6)	24.7 (21.8–28.4)	.657
Smoker, active	119 (23.2)	29 (32.6)	.101
ECOG performance status, score			
0	461 (78.4)	83 (77.6)	.914
1–2	106 (18.0)	20 (18.7)	
3–4	21 (3.6)	4 (3.7)	
Karnofsky performance status, %	90 (75–100)	90 (80–100)	.531
Alanine aminotransferase, $n\times$ULN	1 (1–2)	2 (1–3.2)	<.0001
Aspartate aminotransferase, $n\times$ULN	1.1 (1–2)	2.2 (1.5–4)	<.0001
Platelet count, $\times10^9$/L	135 (86–189)	81 (56–115)	<.0001
MELD score	9 (8–11)	11 (8–14)	<.0001
Child-Turcotte-Pugh score	5 (5–6)	7 (5–8)	<.0001
Clinically significant portal hypertension	275 (46.8)	85 (79.4)	<.0001
Oesophageal varices[a]			
Absent	272 (57.9)	28 (26.2)	<.0001
Present	198 (42.1)	68 (63.6)	

Note: Data are shown as absolute value and percentage or median and interquartile range.

Abbreviations: HBV, hepatitis B virus; HDV, hepatitis D virus; ECOG, Eastern Cooperative Oncology Group; MELD, Model for End-stage Liver Disease.

[a]The total numbers of patients who underwent screening for varices were 470/588 (79.9%) HBV patients and 96/107 (89.7%) HBV/HDV patients.

TABLE 2 Main characteristics and staging of hepatocellular carcinoma subdivided according to aetiology of liver disease.

Hepatocellular carcinoma characteristics	HBV ($n=588$)	HBV/HDV ($n=107$)	p
Number of nodules			
1	273 (46.4)	47 (43.9)	.310
≤3	93 (15.8)	23 (21.2)	
>3	60 (10.2)	15 (14.0)	
Diffuse/infiltrating type	47 (8.0)	3 (2.8)	.023
Massive type	26 (4.4)	2 (1.9)	
Median maximum diameter (cm)	3 (2.0–5.0)	2.2 (1.5–3.1)	<.0001
Median alpha fetoprotein level (ng/mL)	14.2 (4.3–236)	16.0 (6.9–83.5)	.532
Macro-vascular invasion (present)	93 (15.8)	16 (15.0)	.802
Extra-hepatic spread (present)	36 (6.1)	5 (4.5)	.590
Milan criteria (in)	310 (52.7)	72 (67.3)	.005

Note: Data are shown as absolute value and percentage or median and interquartile range.

Abbreviations: HBV, hepatitis B virus; HDV, hepatitis D virus.

After a median follow-up of 26.4 months, 406 patients died (54 HBV/HDV and 352 HBV alone), without difference between the two groups. Overall, most patients (55.6%) died due to HCC progression, followed by end-stage liver disease (15.5%). Notably, the proportion of patients who died due to liver failure was higher in those with HBV/HDV compared with patients with HBV alone (27.5% vs. 14.2%), while the opposite was observed for mortality attributable to HCC progression (41.2% vs. 59.0%, $p=.006$).

The median overall survival was 44.4 months (95% CI: 36.5–52.2), with a trend ($p=.106$) towards longer survival in patients with

TABLE 3 Principal modality of hepatocellular carcinoma treatment subdivided according to aetiology of liver disease.

Treatment	HBV ($n=588$)	HBV/HDV ($n=107$)
Surgical therapies		
Liver transplantation	56 (9.5)	39 (36.4)
Liver resection	118 (20.1)	9 (8.4)
Ablative therapies		
Radiofrequency ablation	108 (18.4)	12 (11.2)
Ethanol injection	27 (4.6)	5 (4.7)
Other ablative treatments	6 (1.1)	0 (0)
Trans-arterial therapies		
TACE	100 (17.0)	11 (10.3)
TARE	7 (1.2)	0 (0)
TAE	2 (.3)	1 (.9)
Systemic therapies		
Sorafenib	52 (8.8)	8 (7.5)
Others	52 (8.8)	8 (7.5)
Best supportive care, n (%)	60 (10.2)	14 (13.1)

Note: Data are shown as absolute value and percentage.

Abbreviations: HBV, hepatitis B virus; HDV, hepatitis D virus; TACE, transcatheter arterial chemoembolization; TAE, transarterial embolization; TARE, transarterial Radioembolization.

HBV/HDV (50.7 months, 95% CI: 24.5–76.9) as compared to patients with HBV alone (43.9 months, 95% CI: 34.9–52.8, Figure 2).

Cox multivariate analysis showed that lower BMI, higher ECOG PS, higher MELD score, presence of clinically significant portal hypertension, high alpha-fetoprotein levels, advanced tumour stage (according to Milan criteria), and not undergoing surgical treatments (liver transplantation and liver resection) were independently associated with worse survival, while HBV/HDV status was not (Table 4).

In a sub-analysis that excluded patients who underwent liver transplantation, patients with HBV/HDV had a significantly shorter survival as compared to patients with HBV alone (21.7 months, 95% CI: 15.7–27.8 vs. 35.5 months, 95% CI: 28.4–42.6; $p=.008$, Figure 3A), while the opposite was observed when we performed a sub-analysis that excluded patients who underwent liver resection (46.7 months, 95% CI: 0–116.8 vs. 31.4, 95% CI: 24.6–38.2; $p=.023$, Figure 3B).

In a competing risk model, the cumulative incidence of death was 55.8% (44.8–65.4) in HBV/HDV patients and 70.5% (65.7–74.7) in HBV alone ($p=.025$), while the competing probability of receiving a liver transplant over a 10-year time-span was 19.7 (12.0–28.8) in patients with HBV/HDV and 6.1% (4.0–8.8) in HBV alone ($p<.0001$) (Figure 4).

A multivariate analysis focused on *receiving a liver transplant* and *risk of death* as competing events showed a significant independent association of *receiving a liver transplant* with lower age (HR: .966, 95% CI: .951–.982), presence of clinically significant portal hypertension (HR: 2.093, 95% CI: 1.274–3.439), Milan-in tumour stage (HR: 3.197, 95% CI: 1.693–6.039), and HBV/HDV coinfection (HR: 2.142, 95% CI: 1.310–3.503), while a higher *risk of death* was associated with lower BMI (HR: .954, 95% CI: .921–.988), higher ECOG-PS (HR: 1.207, 95% CI: 1.033–1.410), higher MELD score (HR: 1.036, 95% CI: 1.007–1.066), higher alpha-fetoprotein level (HR: 1.106, 95% CI: 1.065–1.148), Milan-out tumour stage (HR: 2.241, 95% CI:

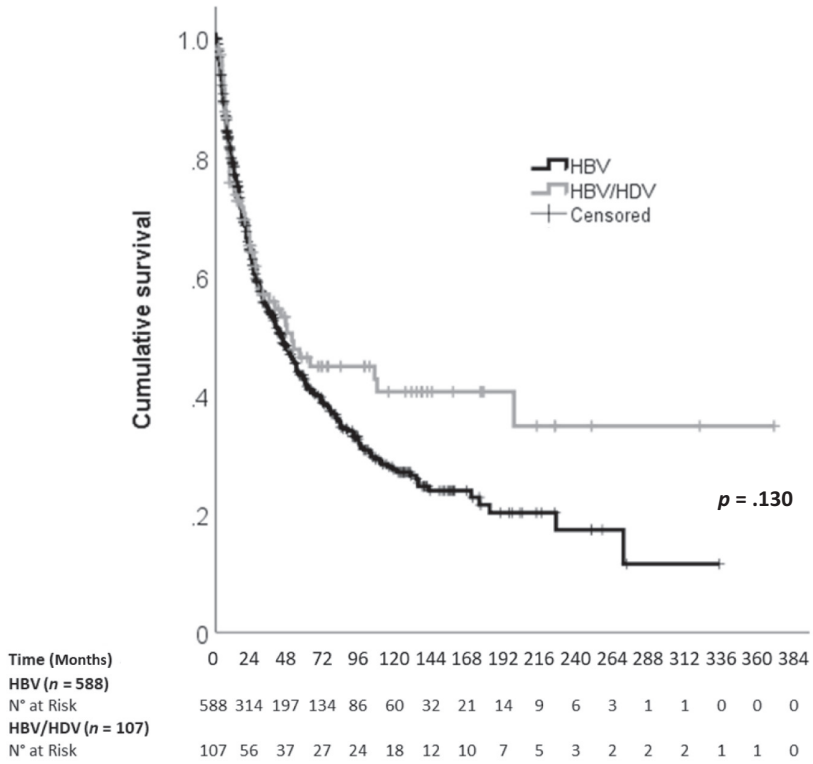


FIGURE 2 Kaplan–Meier survival curves of all patients sub-divided according to virological status (black line: HBV alone patients; grey line: HBV/HDV patients).

TABLE 4 Univariate and multivariate Cox regression analysis of predictors of mortality.

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Sex (Female = ref)	1.14	.865–1.530	.351			
Age (+1 year)	1.005	.996–1.014	.308			
Body mass index (+1 kg/m^2)	.954	.921–.988	**.009**	.955	.924–.987	**.006**
ECOG performace status (+1 point)	1.553	1.339–1.724	**<.0001**	1.209	1.092–1.339	**<.0001**
HBV status (HBV alone = ref)	.790	.593–1.052	.107	1.084	.798–1.474	.605
MELD score (+1 point)	1.036	1.018–1.055	**<.0001**	1.035	1.014–1.056	**<.0001**
Clinically significant portal hypertension (absent = ref)	1.460	1.199–1.778	**.0001**	1.303	1.058–1.603	**.039**
Alpha-fetoprotein level [+1 × ln(ng/nL)]	1.155	1.115–1.197	**<.0001**	1.107	1.067–1.148	**<.0001**
Milan criteria (OUT = ref)	.364	.298–.444	**<.0001**	.448	.363–.552	**<.0001**
Surgery (No = ref)	.236	.183–.306	**<.0001**	.272	.209–.356	**<.0001**

Abbreviations: 95% CI, 95% confidence interval; ECOG, Eastern Cooperative Oncology Group; HBV, Hepatitis B Virus; HR, hazard ratios; MELD, Model for End-stage Liver Disease. Statistically significant differences are highlighted in bold.

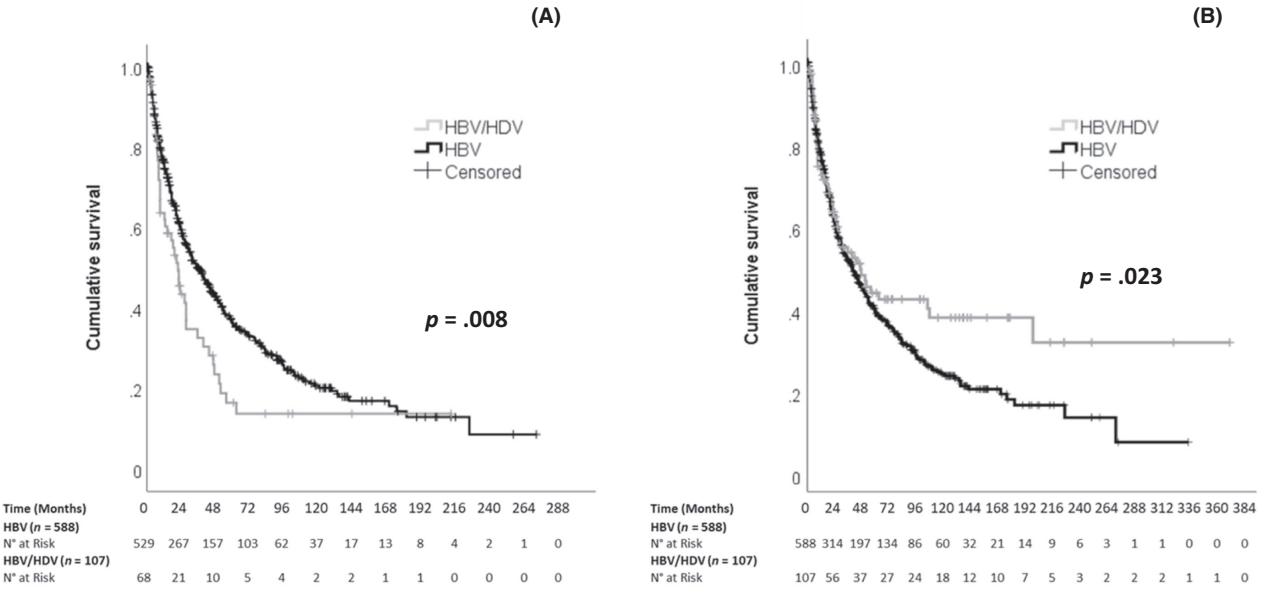


FIGURE 3 Kaplan–Meier survival curves of patients sub-divided according to virological status (black line: HBV alone patients; grey line: HBV/HDV patients) excluding patients who underwent liver transplantation (A) or liver resection (B).

1.815–2.774) and treatments different from surgery (HR: 4.238, 95% CI: 3.174–5.646) (Table S2).

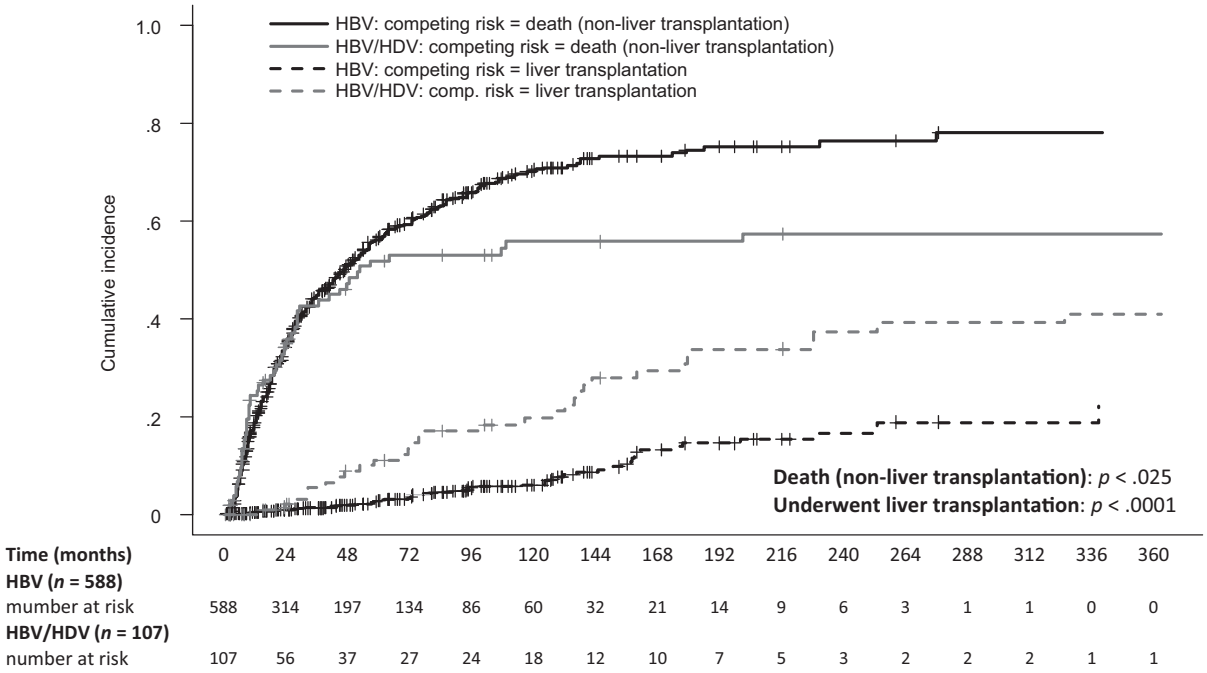
3.4 | Determinants of survival in patients with HBV/HDV

A multivariate Cox regression analysis focused on the 107 patients with HBV/HDV and including demographic, clinical, and oncological characteristics showed that the only independent determinants of survival were Milan-in tumour stage [HR: .226 (95% CI: .116–.442), $p < .0001$] and surgical treatment, either liver transplantation [HR: .069 (95% CI: .028–.173), $p < .0001$] or liver resection [HR: .334 (95% CI: .115–.971), $p = .044$].

4 | DISCUSSION

The presence of concomitant positivity for HBV and HDV infection is associated with a 3-fold increase in the risk of developing HCC as compared to HBV alone, and persistent HDV replication leads to a yearly incidence of HCC of 2.8%, with the greatest influence of elevated HDV viraemia in patients who have not yet developed cirrhosis.[27–29] Until recently, HDV was considered an orphan disease with few – if any – aetiological treatments available able to modify the natural course of disease towards end-stage liver disease and HCC, leading to high liver-related mortality in these patients.[8–11,30]

Due to the relatively low prevalence of HDV positivity in patients with HBV – approximately 5% – and therefore to the low



Time (months)	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336	360
HBV (*n* = 588)																
number at risk	588	314	197	134	86	60	32	21	14	9	6	3	1	1	0	0
HBV/HDV (*n* = 107)																
number at risk	107	56	37	27	24	18	12	10	7	5	3	2	2	2	1	1

FIGURE 4 Competing risk analysis curves showing cumulative incidence of receiving liver transplant or death without liver transplantation in patients with HBV alone or HBV/HDV infection.

number of patients in the general population, a thorough description of large cohorts of patients with positivity for HBsAg/anti-HDV and HCC was missing. The current study, which included one of the largest populations of patients with positivity for HBsAg/anti-HDV and HCC described so far, was designed and conducted in the belief that reporting data on the clinical and oncological characteristics, treatment and outcome of these patients, compared to those with HBV infection alone, not only may help better understand this peculiar disease but also provide a comparative clinical benchmark for bulevirtide-treated patients who might develop HCC despite positive viral outcome.[31,32]

This study shows that, in Italy, patients with positivity for HBsAg/anti-HDV account for approximately 15% of individuals with HBV-related HCC. These patients are significantly younger – by about 10 years – than patients with HBV alone, and develop this tumour at a median age approximately 20 years lower than the median age at which HCC is diagnosed in our country, findings are consistent with evidence from longitudinal studies in patients with HDV.[13,14,33] These data may suggest that the presence of HDV might accelerate the progression of disease towards the development of HCC, and is in keeping with data on the same subject collected in other countries, although they do not represent data on the natural history of patients with chronic HDV infection, and therefore need to be interpreted with caution.[34] This notwithstanding, we feel that this piece of information is of particular relevance for establishing appropriate surveillance programs specific to patients with HDV. Furthermore, at the time of HCC diagnosis, patients with HBV/HDV had greater liver disease activity and worse liver function as compared to patients with HBV, likely due to the absence of an effective treatment for the combined infections. This finding, together with an increased mortality rate from end-stage liver disease and no significant difference in the prevalence of comorbidities, highlights the enhanced role played by the deterioration of liver function in the natural history of HBV/HDV patients with HCC, and consequently the great utility in this setting of liver transplantation, the only treatment able to counteract the natural course of both liver dysfunction and HCC.

HCC was prevalently detected under surveillance in both patients with HBV/HDV and HBV alone. Nevertheless, this type of diagnosis was more common in the former group, likely due to the particular attention given to these patients, who are usually followed in expert liver centres. As a fact, the increased prevalence of surveyed patients led to a significantly smaller tumour size and a greater percentage of Milan-in tumours in patients with HBV/HDV, oncological features that increased the amenability to liver transplantation as compared to patients with HBV alone. As previously emphasised, our results did not allow us to draw a definite conclusion on a potentially heightened carcinogenic risk in patients with HBV/HDV as compared to patients with HBV alone, since despite a numerically shorter overall duration of surveillance in patients with the former condition, this difference was not statistically significant.

Despite the prevalence of surgical treatments being similar in the 2 groups, liver transplantation and resection had a different distribution in the two aetiological groups. This difference can be attributed to different distributions of relevant characteristics, such as age, liver function, and oncological stage. Indeed, patients with HBV alone – who were older, with a well-preserved liver function, and with a slightly worse oncological stage – more frequently underwent surgical resection, while HBV/HDV patients – who were younger, with a more deranged liver function yet with a more permissive oncological stage – more frequently underwent liver transplantation.

All in all, liver transplantation represented the strongest independent prognostic determinant in patients with HBV/HDV. Furthermore, in a competing risk analysis with a 10-year horizon, patients with HBV/HDV had a higher probability of receiving liver transplantation, and, in a multivariate competing risk analysis that included oncological stage and liver function, HBV/HDV coinfection maintained an independent association with the probability of being transplanted. Taken together, these findings underscore how patients with HBV/HDV receive a heightened benefit from liver transplantation that includes not only the 'double benefit' of curing both liver failure and HCC – as occurs for other aetiologies of liver disease – but also the 'cure' of the cause of liver disease that could not rely on an effective antiviral therapy until very recently.[1,2,10] It is worth noting that this preference for liver transplantation underscores how, in clinical practice, limited resources are adequately allocated, respecting the principle of transplant benefit, and taking into account all the additional benefits that may derive from liver transplantation in particular situations.[35–37] This finding is also in keeping with data reported from an analysis carried out in a liver transplant centre in Italy, showing how the ratio of HDV to total HBsAg transplants increased from 38.5% in the period 2000–2009 to 50.2% in the period 2010–2019.[38] Lastly, it has to be emphasised that HBV/HDV infection, per se, does not increase – nor reduces – the risk of death independently of liver function, oncological stage, and treatment received.

Due to the elevated proportion of patients whose tumour was detected under surveillance, in this cohort, many patients had access to curative treatments and few patients were treated with systemic therapies or underwent best supportive care alone. These findings were likely the main determinants of a long median overall survival – approximately 4 years– we observed in the whole population. In fact, multivariate analysis results attested that liver function, tumour burden, and curative treatments were fundamental prognostic determinants. Noteworthy, also body mass index turned out to be an independent, and positive, predictor of survival in the whole cohort, highlighting the prognostic importance – in a population of mainly non-obese patients – of maintaining a good overall nutritional status. Lastly, the presence of clinically significant portal hypertension was confirmed to be an independent prognostic marker also in patients with HCC, once again emphasising the fundamental role of screening for varices and prompt institution of primary prophylaxis as a standard of care so as to improve the prognosis of these patients.[39–41]

This study, due to its real-world setting, has several limitations. In particular, patients were labelled as HBV/HDV due to the presence of positivity for HBsAg and anti-HDV antibodies, and since HDV-RNA is detectable in approximately 70% of anti-HDV positive patients some patients might have had a resolved infection at the time of HCC detection; moreover, in the course of the disease, and in particular one cirrhosis ensues, in a relevant part of patients with cirrhosis HDV viraemia tends to be undetectable, and therefore assessment of viraemia at the time of HCC development might have underestimated a long course of active disease in a significant proportion of patients.[38,42] Notwithstanding these limitations, which are inherent to large databases accrued in clinical practice, the finding that patients with HBV alone had normal aminotransferase activity and better-preserved liver function, while HBV/HDV patients had an altered aminotransferase profile and a more deranged liver function suggests that in the majority of patients identified as HBV/HDV, there was an ongoing activity of liver disease. Moreover, the absence of data regarding HDV-RNA serum levels prevented the possibility to obtain an in-depth characterisation of viral activity and to provide an information on the potential association between viraemia and patients' outcome. In this regard, it has to be emphasised that – also for the reasons outlined above – the association between viraemia and HCC development in patients with positivity for HDV is still debated, and accrual of data over a long period of time would have prevented, anyway, to provide solid data regarding HDV RNA levels due to the absence of standardised techniques.[29,43,44]

To conclude, this study provided a comprehensive picture of patients who developed HCC in the context of HBV/HDV infection. In the absence of effective treatment for the underlying liver disease, these patients, compared to those with the sole HBV infection, develop HCC at a younger age and in a background of more deranged liver function. Noteworthy, due to viral, liver disease, and oncological characteristics, patients with HBV/HDV derive the greatest benefit from liver transplantation, whose access is favoured by a higher proportion of early-stage tumours diagnosed thanks to the very frequent use of surveillance.

AUTHOR CONTRIBUTIONS

E.G.G. and A.P. contributed to conceptualization, literature search, figures, study design, data collection, data analysis, writing the first draft, and had access to and verified data. G.P., M.C.P.T., L.B., A.V., F.T., M.M., F.P., A.S., G.C., G.G., M.D.M., F.G.F., M.G., E.B., C.S., C.C., G.S-B., A.G., M.R.B., D.M., F.A., A.M., R.S., G.N., D.S., A.M., and G.V. contributed for resources, investigation, data collection, data analyses, writing-review and editing. All the authors approved the final draft submitted.

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CONFLICT OF INTEREST STATEMENT

Edoardo G. Giannini advises and is on the speakers' bureau for AbbVie, Gilead, MSD, EISAI, Roche. Franco Trevisani is on the speakers' bureau for AbbVie, AstraZeneca, Gilead, MSD, EISAI, Roche. Giuseppe Cabibbo advises for Bayer, Eisai, Ipsen, AstraZeneca, MSD, and Roche. Andrea Pasta, Giulia Pieri, Maria Corina Plaz Torres, Mariarosaria Marseglia, Filippo Pelizzaro, Angelo Sangiovanni, Giorgia Ghittoni, Mariella Di Marco, Francesco Giuseppe Foschi, Maria Guarino, Elisabetta Biasini, Carlo Saitta, Claudia Campani, Gianluca Svegliati-Baroni, Antonio Gasbarrini, Maurizia Rossana Brunetto, Donatella Magalotti, Francesco Azzaroli, Andrea Mega, Rodolfo Sacco, Gerardo Nardone, David Sacerdoti, Alberto Masotto, Gianpaolo Vidili, Alessandro Vitale, Laura Bucci: nothing to disclose.

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REFERENCES

1. Asselah T, Rizzetto M. Hepatitis D virus infection. *N Engl J Med*. 2023;389:58-70.
2. Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. *Lancet*. 2011;378:73-85.
3. Stroffolini T, Morisco F, Ferrigno L, et al. Acute Delta hepatitis in Italy spanning three decades (1991–2019): evidence for the effectiveness of the hepatitis B vaccination campaign. *J Viral Hepat*. 2022;29:78-86.
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. Vlachogiannakos J, Papatheodoridis GV. New epidemiology of hepatitis delta. *Liver Int*. 2020;40(Suppl 1):48-53.
6. Puigvehí M, Moctezuma-Velázquez C, Villanueva A, Llovet JM. The oncogenic role of hepatitis delta virus in hepatocellular carcinoma. *JHEP Rep*. 2019;1:120-130.
7. Papatheodoridi A, Papatheodoridis G. Hepatocellular carcinoma: the virus or the liver? *Liver Int*. 2023;43(Suppl 1):22-30.
8. Romeo R, Petruzziello A, Pecheur EI, et al. Hepatitis delta virus and hepatocellular carcinoma: an update. *Epidemiol Infect*. 2018;146:1612-1618.
9. Farci P, Niro GA, Zamboni F, Diaz G. Hepatitis D virus and hepatocellular carcinoma. *Viruses*. 2021;13:830.
10. 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.
11. Cabibbo G, Petta S, Barbara M, et al. Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma. *J Hepatol*. 2017;67:65-71.
12. European Association for the Study of the Liver. EASL clinical practice guidelines on hepatitis delta virus. European Association for the Study of the liver. *J Hepatol*. 2023;79:433-460.
13. Bucci L, Garuti F, Lenzi B, et al. The evolutionary scenario of hepatocellular carcinoma in Italy: an update. *Liver Int*. 2017;37:259-270.
14. Garuti F, Neri A, Avanzato F, et al. The changing scenario of hepatocellular carcinoma in Italy: an update. *Liver Int*. 2021;41:585-597.
15. Udell JA, Wang CS, Tinmouth J, et al. Does this patient with liver disease have cirrhosis? *JAMA*. 2012;307:832-842.
16. European Association for the Study of the Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. European Association for the Study of the liver. *J Hepatol*. 2018;69:406-460.
17. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646-649.
18. Giannini E, Botta F, Testa E, et al. The 1-year and 3-month prognostic utility of the AST/ALT ratio and model for end-stage liver disease score in patients with viral liver cirrhosis. *Am J Gastroenterol*. 2002;97:2855-2860.
19. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol*. 1982;5:649-655.
20. Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology*. 1996;111:1018-1022.
21. Italian Association for the Study of the Liver (AISF); AISF Expert Panel; AISF Coordinating Committee; et al. Position paper of the Italian Association for the Study of the liver (AISF): the multidisciplinary clinical approach to hepatocellular carcinoma. *Dig Liver Dis*. 2013;45:712-723.
22. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. European Association for the Study of the liver. *J Hepatol*. 2018;69:182-236.
23. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334:693-699.
24. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer*. 1954;7:462-503.
25. Kang H. The prevention and handling of the missing data. *Korean J Anesthesiol*. 2013;64:402-406.
26. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509.
27. Fattovich G, Giustina G, Christensen E, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. The European Concerted Action on Viral Hepatitis (Eurohep). *Gut*. 2000;46:420-426.
28. Romeo R, Del Ninno E, Rumi M, et al. A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. *Gastroenterology*. 2009;136:1629-1638.
29. Romeo R, Foglieni B, Casazza G, Spreafico M, Colombo M, Prati D. High serum levels of HDV RNA are predictors of cirrhosis and liver cancer in patients with chronic hepatitis delta. *PLoS One*. 2014;9:e92062.
30. Ghany MG. A glimmer of Hope for an orphan disease. *N Engl J Med*. 2023;389:81-82.
31. Anolli MP, Degasperi E, Allweiss L, et al. A 3-year course of bulevirtide monotherapy may cure HDV infection in cirrhotics. *J Hepatol*. 2023. doi:10.1016/j.jhep.2022.12.023
32. Dietz-Fricke C, Tacke F, Zöllner C, et al. Treating hepatitis D with bulevirtide – real-world experience from 114 patients. *JHEP Rep*. 2023;5:100686.
33. Verme G, Brunetto MR, Oliveri F, et al. Role of hepatitis delta virus infection in hepatocellular carcinoma. *Dig Dis Sci*. 1991;36:1134-1136.
34. Costante F, Stella L, Santopaolo F. Molecular and clinical features of hepatocellular carcinoma in patients with HBV-HDV infection. *J Hepatocell Carcinoma*. 2023;10:713-724.
35. Vitale A, Morales RR, Zanus G, et al. Barcelona clinic liver cancer staging and transplant survival benefit for patients with hepatocellular carcinoma: a multicentre, cohort study. *Lancet Oncol*. 2011;12:654-662.
36. Vitale A, Burra P, Frigo AC, et al. Survival benefit of liver resection for patients with hepatocellular carcinoma across different

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37. Vitale A, Cabibbo G, Iavarone M, et al. Personalised management of patients with hepatocellular carcinoma: a multiparametric therapeutic hierarchy concept. *Lancet Oncol*. 2023;24:e312-e322.
38. Caviglia GP, Martini S, Ciancio A, et al. The hepatitis D virus in Italy. A vanishing infection, not yet a vanished disease. *J Adv Res*. 2021;33:183-187.
39. Giannini EG, Risso D, Testa R, et al. Prevalence and prognostic significance of the presence of esophageal varices in patients with hepatocellular carcinoma. *Clin Gastroenterol Hepatol*. 2006;4:1378-1384.
40. Giannini EG, Trevisani F. Improving survival of cirrhosis patients with hepatocellular carcinoma through application of standard of care. *Hepatology*. 2014;60:1446-1447.
41. Reggidori N, Bucci L, Santi V, et al. Landscape of alcohol-related hepatocellular carcinoma in the last 15 years highlights the need to expand surveillance programs. *JHEP Rep*. 2023;5:100784.
42. Vieira Barbosa J, Sahli R, Aubert V, Chaouch A, Moradpour D, Fraga M. Demographics and outcomes of hepatitis B and D: a 10-year retrospective analysis in a Swiss tertiary referral center. *PLoS One*. 2021;16(4):e0250347.
43. Da BL, Rahman F, Lai WC, et al. Risk factors for Delta hepatitis in a north American cohort: who should be screened? *Am J Gastroenterol*. 2021;116:206-209.
44. Jang TY, Wei YJ, Liu TW, et al. Role of hepatitis D virus infection in development of hepatocellular carcinoma among chronic hepatitis B patients treated with nucleotide/nucleoside analogues. *Sci Rep*. 2021;11:8184.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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