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SHORT COMMUNICATION

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Self-limited HBV infection of the recipient does not reactivate after liver transplantation: Observations from a 30-year liver transplant program

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Abstract

Background: A self-limited hepatitis B infection can reactivate in patients under immunosuppression or chemotherapy (reappearance of hepatitis B surface antigen (HBsAg) or HBV-DNA). Exact circumstances of HBV reactivation in patients undergoing liver transplantation (LT) for end-stage liver diseases (ESLD) unrelated to HBV are unknown, and recommendations on HBV prophylaxis remain unclear.

Patients and methods: Among 1273 liver transplants, 168 patients with a self-limited HBV hepatitis B infection prior to LT were identified from our prospective liver transplant database. Patients with underlying chronic HBV infection and recipients of an anti-HBc-positive liver were not included in the analysis. Demographic, laboratory, serological, and virological data were analyzed retrospectively. Appearance of HBsAg or HBV-DNA was defined as reactivation.

Results: The median follow-up after LT was 12.0 years (0.6-30.7 years). The rate of HBV reactivation was 0% independent of antiviral prophylaxis (n = 7; 4.2%), the etiology of ESLD, hepatitis C treatment, or the anti-HBs concentration. The overall patient survival with a history of a self-limited HBV infection before LT did not significantly differ from the rest of the cohort.

Conclusion: Antiviral treatment with nucleos(t)ide analogues post-liver transplantation in order to prevent HBV reactivation in patients with a resolved self-limited hepatitis B infection prior to LT seems to be omittable since the main viral reservoir is removed by the hepatectomy. These findings may clarify the current uncertainty in the recommendations regarding the risk of HBV reactivation in patients with self-limited hepatitis B prior to LT.

KEYWORDS

antiviral prophylaxis, graft loss, HBV reactivation, liver transplantation, resolved Hepatitis B infection

Abbreviations: anti-HBc, hepatitis B core antibody; anti-HBe, hepatitis B e antibody; anti-HBs, hepatitis B surface antibody; DAAs, direct-acting antivirals; ESLD, end-stage liver disease; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; NA, nucleos(t)ide analogues.

1 | INTRODUCTION

Hepatitis B virus (HBV) infection is a global health burden and about 2 billion subjects had contact to HBV while 248 million are chronic carriers of hepatitis B surface antigen (HBsAg) leading to liver cirrhosis and hepatocellular carcinoma (HCC).[1,2] An acute self-limited hepatitis B infection represents a recovery state: symptoms have passed, HBsAg is no longer detectable, and the patient is positive for HBc and HBs antibodies.[3] Self-limited acute HBV infection has been reported previously to be associated with abnormal liver histology even a decade after complete recovery because of the persistence of the covalently closed circular DNA (cccDNA) which is made responsible for inflammation and fibrogenesis potentially leading to the end-stage liver disease (ESLD).[4] Hepatitis B core antibody (anti-HBc) carriers may experience HBV reactivation under immunosuppression or cytostatic therapy especially undergoing bone marrow transplantation.[5,6] Transplantation of anti-HBc-positive livers may lead to HBV reactivation in up to 48%, potentially proving the relevance of cccDNA.[7] However, in patients with a history of a self-limited HBV infection and ESLD for other reasons requiring liver transplantation (LT), the main source of HBV is removed by the hepatectomy. According to the literature and current guidelines, there is no evidence that patients who undergo LT for an ESLD not related to chronic HBV infection but with a history of self-limited HBV infection (anti-HBc-positive) may experience HBV reactivation, leading to a wide variation in the clinical management.[5] Furthermore, data on HBV reactivation in patients with hepatitis C virus coinfection undergoing antiviral treatment for HCV after LT are also limited. The aim of our study was to determine the risk for HBV reactivation in patients with self-limited HBV infection prior to LT based on data from our cohort of LT patients from a 30 years LT program in Berlin.

2 | PATIENTS AND METHODS

Demographic, clinical, and laboratory data were extracted from a prospectively organized database of the liver transplant program at Charité, Berlin, Germany existing since 1988. Patients with a complete data set regarding the hepatitis B serology of the donor and recipient (n = 1273) at the moment of LT were followed up regularly (last available clinical information until April 2019) including liver enzymes, parameters of excretion and synthesis, blood cell count, hepatitis serology (HBsAg, anti-HBs, and anti-HBc), HBV-DNA, clotting profile, level of immunosuppression at 3 monthly intervals, and protocol biopsies. Patients were categorized in major diagnosis groups according to the underlying etiology of liver cirrhosis including alcoholic liver disease, chronic hepatitis C infection, chronic hepatitis B infection, hereditary hemochromatosis, alpha 1 antitrypsin deficiency, Wilson's disease, autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), secondary sclerosing cholangitis (SSC), nonalcoholic steatohepatitis (NASH), cryptogenic cirrhosis, and others. Patients with underlying chronic HBV infection, HBV-associated acute liver failure without cirrhosis, and recipients of an anti-HBc-positive liver and incomplete follow-up data were excluded. A highly homogenous cohort of HBsAg-negative, anti-HBc-positive patients was set up in order to determine the risk of HBV reactivation after LT. Demographic, laboratory, serological, and virological data, the indication for LT, immunosuppressive therapy, follow-up duration, incidence of acute rejections, number of retransplantations, prevalence of HCC in the explanted livers as well as the use of antiviral medication to prevent HBV reactivation were analyzed retrospectively. Appearance of HBsAg or HBV-DNA was defined as reactivation.

The immunosuppressive regimen was not standardized because of the different eras reflecting the age of the transplant program. The maintenance immunosuppression regimen was based on calcineurin inhibitors (CNI) in early years cyclosporine-A and later on tacrolimus in individual adaption to patients risk profile for the development of adverse reactions using mycophenolate mofetil (MMF) or everolimus in recent years. A vast majority received tacrolimus mono or a combination with MMF.

Statistical analysis was performed by SPSS (IBM Statistics 24). Continuous variables are presented as medians. Nominal data were tested by cross-tables (univariate, Fisher's exact test). Not normally distributed continuous data were tested by the Mann-Whitney *U* test and if more than one sample was evaluated by Kruskal-Wallis test. Survival was assessed by Kaplan-Meyer analysis. All reported *P*-values are two-sided, and the significance level was .05.

The study was performed retrospectively according to the Professional Code of the German Medical Association (article B.III.§15) based on the World Medical Association´s Declaration of Helsinki.

3 | RESULTS

The cohort (n = 1273) was divided according to the anti-HBc status in anti-HBc-positive and anti-HBc-negative recipients. Among 537 patients positive for anti-HBc, 337 patients were excluded because of HBV-associated ESLD and presented only in the survival analysis, thus leaving 200 patients with an acute self-limited hepatitis B infection prior to LT. There was a significant difference in the distribution of anti-HBc-positivity among the indication groups for LT with HCV patients being the dominant group (35.6%-50.0%; $P < .001$) as presented in Table 1 and Figure 1. After further exclusion of patients with anti-HBc-positive donor organs (n = 10) as a relevant source of HBV reactivation, early postoperative mortality, and patients lost to follow-up (n = 22), a highly homogenous cohort of 168 was set up. Among 168 patients with a history of a self-limited HBV infection prior to LT (Table 2), HBV reactivation was not observed either in 161 (95.8%) patients without HBV prophylaxis or in 7 (4.2%) patients that received a nucleos(t)ide analogue (NA) as HBV reactivation prophylaxis. HBsAg and HBV-DNA were undetectable at any routine patient visit during the whole observation period of 12.0 years (0.6-30.7) with 2159.7 cumulative observed patient years. Characteristics

TABLE 1 Demographic table and prevalence of resolved HBV infection prior to LT according to the main indication groups for LT

		n = 936 (100%)	anti-HBc-positive n = 200 (21.4%)	anti-HBc-negative n = 736 (78.6%)	*P*-value
Median age at LT in years	(min-max)	55.1 (19-74)	54.8 (18-74)		.495
Median follow-up in years	(min-max)	11.2 (0.0-30.7)	7.5 (0.0-30.7)		<.001
Gender; n (%)	male	134 (22.2)	470 (77.8)		.453
	female	66 (19.9)	266 (80.1)		
Etiology; n (%)					
ALD	322 (34.4)	47 (14.6)	275 (85.4)		<.001
HCV	264 (28.2)	94 (35.6)	170 (64.4)		
ALD and HCV	16 (1.7)	8 (50.0)	8 (50.0)		
AIH, PBC, and PSC	86 (9.2)	10 (11.6)	76 (88.4)		
Cryptogenic and NASH	74 (7.9)	14 (18.9)	60 (81.1)		
others	174 (18.6)	27 (15.5)	147 (84.5)		
HCC; n (%)	260 (27.8)	57 (21.9)	203 (78.1)		.790
		143 (21.2)	533 (78.8)		

Abbreviations: AIH, autoimmune hepatitis; ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; HCV, ESLD associate with hepatitis C virus; NASH, nonalcoholic liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

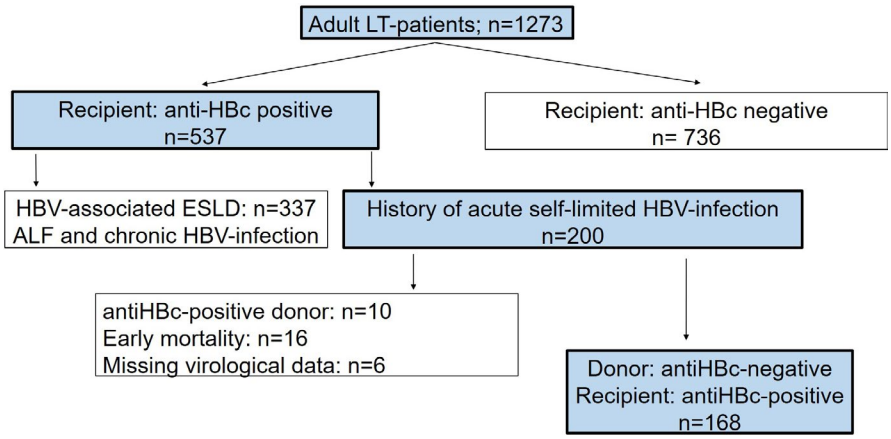


FIGURE 1 Schematic presentation of the study population. Exclusion criteria were patients with chronic HBV infection, recipients of an anti-HBc-positive liver, and early mortality (<6 mo). ALF, acute liver failure

of 168 patients with a history of resolved HBV infection prior to LT are summarized in Table 2.

The leading indication for LT was HCV-induced liver cirrhosis with or without HCC (n = 88; 52.4%). All 88 patients developed HCV recurrence after LT as an inevitable phenomenon after LT if not pre-emptively treated and the majority of patients were treated with pegylated interferon and ribavirin (n = 36; 40.9%). Non-responders underwent a successful antiviral therapy with direct-acting antivirals (DAAs) (n = 24; 27.3%) after 2013, while 28 (31.8%) patients were not treated at all. Four of 60 patients in the HCV subgroup received an NA as HBV prophylaxis due to anti-HBc-positivity and no one developed an HBV reactivation disregarding the prophylaxis and the mode of HCV treatment.

The prevalence of anti-HBc was as high as 21.4% among all patients excluding chronic HBV infection as underlying disease. Among our 168 patients, HBc antibodies were assessed after LT in 133 patients with 21 (15.8%) becoming negative (Figure 2A) over a median of 5 years (0-16.0 years). 47 (29.2%) patients were positive for HBe antibody at the beginning and 33 (24.4%) at the end of observation. Anti-HBe-negativity at LT was significantly ($P = .01$) associated with anti-HBc-loss later (Figure 2B). After the exclusion of patients being negative for hepatitis B surface antibody (anti-HBs) at the moment of LT, median anti-HBs sank significantly after LT (208.5 (11-1000) vs 122.0 (11-1000) U/mL; $P < .001$).

Survival analysis was performed for all patients with a history of acute self-limited HBV infection (n = 200) including 168 patients with known long-term virological status, 10 patients who received an anti-HBc-positive liver transplant and 16 patients with early mortality and 6 patients with missing data. Thus, survival of 200 patients was compared with the rest of the cohort (n = 1073). No

TABLE 2 Demographic table of LT patients with a history of self-limited HBV infection

LT cohort with a history of resolved HBV infection; n = 168		
Median age at LT in years (min-max)		55.7 (19.0-73.0)
Median follow-up in years (min-max)		12.0 (0.6-30.7)
Re-LT-rate; n(%)		18 (10.7)
Gender; n (%)	male/female	114 (67.9)/54 (32.1)
TX-mode; n (%)	whole organ/split	163 (97.0)/5 (3.0)
Indication for LT; n (%)	ALD	39 (23.2)
	HCV	80 (47.6)
	AIH, PBC, PSC	10 (6.0)
	cryptogenic	11 (6.5)
	others	20 (11.9)
	HCV and ALD	8 (4.8)
HBsAg; n(%)	positive/negative	0 (0)/168 (100)
HBeAg; n(%)	positive/negative	0 (0)/168 (100)
Anti-HBc; n(%)	positive/negative	168 (100)/0 (0)
Anti-HBe; n(%)	positive/negative	47 (29.2)/114 (70.8)
Anti-HBs; n(%)	positive/negative	73 (43.5)/95 (56.5)
Median anti-HBs at LT; (min-max)		56 (0-1000) IU/L
HCV recurrence; n(%)	yes/no	88 (52.4)/80 (47.6)
HCC; n (%)	yes/no	50 (29.8)/118 (70.2)
NA prophylaxis; n (%)	yes/no	7 (4.2%)/161 (95.8%)
HCV treatment; n (%)	yes/no	60 (68.2)/28 (31.8)
	IFN-based	36 (40.9)
	DAAs	24 (27.3)
Immunosuppression; n (%)	CNI-mono	85 (50.6)
	CNI/MMF or mTOR	69 (41.1)
	MMF-mono	12 (7.1)
	others	2 (1.2)
Acute rejection; n (%)	none	114 (67.9)
	one	40 (23.8)
	more than one	14 (8.3)

Note: HBV reactivation; n (%).

Abbreviations: AIH, autoimmune hepatitis; ALD, alcoholic liver disease; CNI, calcineurin inhibitor; HCC, hepatocellular carcinoma; HCV, ESLD associated with hepatitis C virus; IFN, interferon; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; NA, nucleos(t)ide analogues; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

statistical significant difference was detected ($P = .681$) as displayed in Figure 3. There was no survival differences regarding NA prophylaxis as well ($P = .818$).

Eighteen (10.7%) patients had to undergo a retransplantation. 7 patients were retransplanted early because of vascular complications (mainly hepatic artery thrombosis; n = 5) and initial non-function (n = 2) while 11 patients had to be retransplanted because of late complications: ischemic type biliary lesions (n = 4), HCV-associated graft cirrhosis (n = 4), and chronic rejection (n = 3).

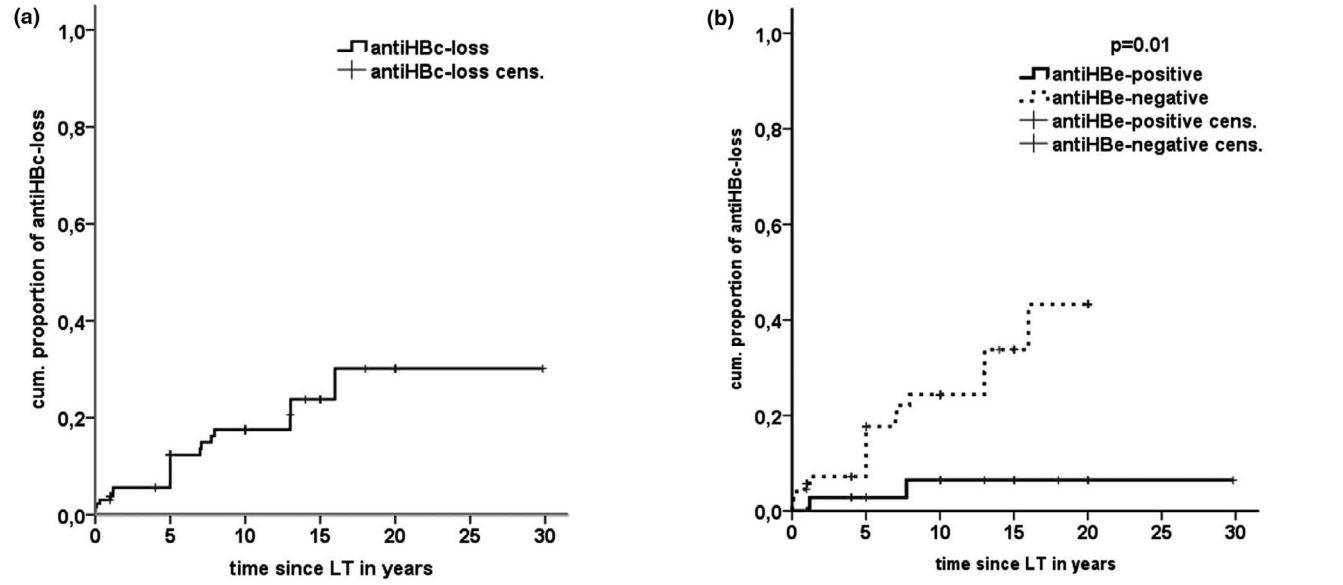
Among 168 patients, the induction therapy was performed in 42 (25%) patients according to the standard protocol of our clinic favoring the approach of induction either with thymoglobuline or with IL2 receptor blocker (antiCD-25) in patients with autoimmune compound of ESLD or in patients undergoing retransplantation in a standard dose and duration. The mode and extent of the immunosuppressive regimen were not adapted specifically to the anti-HBc status. However, patients with viral cirrhosis and malignancies tended to receive less of immunosuppressive medication than patients with an autoimmune compound of the underlying disease in an individual manner.

4 | DISCUSSION

In the present analysis with a long follow-up period of up to 30 years, we observed that HBV reactivation after LT in patients with a history of a self-limited HBV infection prior to LT did not occur; neither in the group with NA prophylaxis (n = 7) nor in the group without (n = 161). Anti-HBc-positivity in the recipient with the absence of HBV replication markers does not require any further actions than usual monitoring long-term. This indicates that NA prophylaxis is not necessary in this selected group of patients.

The prevalence of anti-HBc as a serologic marker for resolved hepatitis B infection was 5 times higher in presented LT patients than it is reported in the general population according to the literature (21.4% vs 4.1%).[8] The course of HBV infection ranges from a self-limited infection to acute liver failure requiring LT, and chronic HBV infection with the risk of cirrhosis and HCC.[9] A resolved HBV infection describes the state when all symptoms have disappeared, HBsAg and HBV-DNA are no longer detectable, and a seroconversion has taken place. Patients are then positive for anti-HBc and mostly for anti-HBs.[3] However, HBs antibodies may disappear later, thus leaving an isolated anti-HBc.[9] Chronic HBV infection is characterized by HBsAg persistence over at least 6 months. In contrast to self-limited HBV infection, seroconversion does not take place.[9,10] LT patients with chronic HBV infection before LT were not included into the analysis: All of them demonstrated a 100%-positive anti-HBc status. In patients with a previously resolved HBV infection, though being robust, anti-HBc may slowly disappear as observed in 15.8% of patients during the follow-up, predominantly in females and anti-HBe-negative patients.

The course of HBV infection is an interaction of viral replication and the immune system. HBV may persist in spite of HBV-specific cytotoxic T cells in the liver and serum even for years after transmission.[11-13] Active HBV replicates had been detected in extrahepatic reservoirs such as lymph nodes, spleen, pancreas, and even brain,

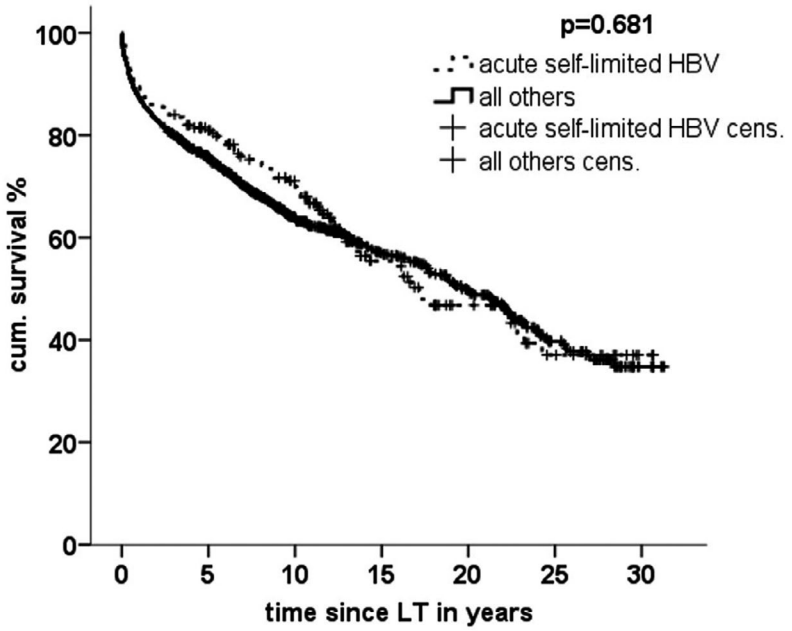


N at risk	0	5	10	15	20	25	30
Acute self-limited HBV	133	95	62	22	9	1	0

N at risk	0	5	10	15	20	25	30
antiHBe-positive	40	30	25	9	3	1	0
antiHBe-negative	87	59	33	12	5	0	0

FIGURE 2 Overall loss of anti-HBc (a) and loss of anti-HBc depending on the anti-HBe-status (b) at the moment of transplantation in patients with acute self-limited HBV infection prior to LT

FIGURE 3 Survival of patients with the history of a self-limited HBV infection prior to LT compared to all other LT patients



N at risk	0	5	10	15	20	25	30
Acute self-limited HBV	200	149	112	54	32	14	1
All others	1073	739	481	244	160	62	8

thus providing an extrahepatic source for a potential HBV reactivation.[4,14] However, the main source for HBV reactivation is the covalently linked cccDNA of HBV in the infected liver, which is removed at LT, thus explaining the difference in the HBV reactivation rate of 2.9% in a recently published study in 70 HBsAg-negative/anti-HBc-positive kidney transplant recipients.[15] The median follow-up time was comparable (12.0 vs 12.5 years), and no NA prophylaxis was administered in the analysis. The role of the extrahepatic reservoir remained unclear especially after LT and under immunosuppression.[11,12] According to the present analysis, it may be neglected. NA prophylaxis in LT patients with a history of an acute self-limited HBV infection does not seem to be necessary and might expose patients

to the adverse effects of the medication. This observation forced us to stop antiviral prophylaxis in the remaining patients with resolved HBV infection pre-transplant. Previously published series of patients in the same situation did not recommend performing NA prophylaxis. However, the number of patients in these studies was low to definitely answer the question (n = 27 and n = 55).[16,17] To our best knowledge, this is the largest study that accurately determines the risk of HBV reactivation in a homogenous cohort of LT patients and gives a clear answer that NA prophylaxis is unnecessary in these patients.

HBV reactivation in anti-HBc-positive patients is occasionally reported after HCV treatment with DAAs.[18] HBV may of course exacerbate, if HBV-DNA is still present, when the dominant virus (HCV) is removed. As recently published, DAA treatment of 848 patients (HBsAg-negative/anti-HBc-positive) including 8 post-transplant patients did not lead to HBV reactivation.[19] Interestingly, HBV reactivation did not occur even regarding a nearly total loss of anti-HBs during the follow-up period in our patients.

There are two different situations demanding the use of NA after liver transplantation. A potent NA with a high barrier to resistance should be used with or without hepatitis B immunoglobulin in patients undergoing LT for a HBV-associated liver disease ranging from acute liver failure to HBV-associated cirrhosis or HCC.[20] Transplantation of an anti-HBc-positive liver is the second situation requiring an NA prophylaxis, for example, lamivudine being sufficient to control the reactivation of HBV in the most cases. A rather rare case of a de novo HBV infection requires treatment of HBV infection according to the guidelines with a potent NA with a high barrier to resistance.[5] A resolved HBV infection before LT does not require any antiviral treatment post-transplant, since the reservoir of a potential HBV reactivation has been removed by the hepatectomy and risk of reactivation does not exist according to the present results. Still, we suggest monitoring HBsAg and HBV-DNA as part of routine clinical follow-up for example once a year or upon suspicion of viral hepatitis.

5 | CONCLUSION

In the present analysis, we could not confirm a risk for HBV reactivation after LT in patients with a history of a self-limited HBV infection prior to LT. Since an HBV reactivation has not been observed during the long follow-up period in a large group of patients without prophylactic NA use, our study confirms that a prophylactic use of NA is not necessary.

CONFLICT OF INTEREST

All authors declare no conflict of interest related to the presented work.

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AUTHOR CONTRIBUTIONS

All authors contributed to the study conception. Data were collected by RROS, PN, and DE. Statistical analysis was performed by DE, RROS, and MD. Figures were created by DE. Manuscript´s first draft was written by RROS, DE, and EMD. Thorough revision was done by RO, WS, and JP. All authors contributed on the intellectual content of the manuscript during its revision, and all authors read and approved the final version of the manuscript.

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