Research Article

HEPATOLOGY FORUM

Hepatic HBV DNA in liver transplant recipients

doi: 10.14744/hf.2021.2021.0003

Significance of detectable hepatitis B virus DNA in liver allograft tissue in long-term follow-up of liver transplant recipients

Deniz Mut Surmeli[1], Ilker Turan[2], Sinan Akay[3], Selda Erensoy[4], Galip Ersoz[2], Fulya Gunsar[2], Ulus Akarca[2], Zeki Karasu[2]

[1]Department of Geriatrics, Ankara University School of Medicine, Ankara, Turkey; [2]Department of Gastroenterology, Ege University School of Medicine, Izmir, Turkey; [3]Department of Gastroenterology, Kutahya University of Health Sciences, Kutahya, Turkey; [4]Department of Microbiology and Clinical Microbiology, Ege University School of Medicine, Izmir, Turkey

Abstract

Background and Aim: The objective of this study was to evaluate the long-term presence of hepatitis B virus (HBV) DNA in the liver grafts of liver transplant patients who received hepatitis B immunoglobulin (HBIg) plus oral antiviral hepatitis B virus prophylaxis and had negative HBV serum markers.

Materials and Methods: Patients aged 18 years or older who underwent liver transplantation for HBV-related liver disease, had negative serum viral markers, and had a liver biopsy at least 3 years after liver transplantation were eligible for this study. Clinical, serological, and pathological data were retrospectively obtained from medical records. The HBV DNA of liver biopsy specimens was assessed using the polymerase chain reaction technique.

Results: A total of 150 patients were included. A positive HBV DNA result was seen in 18 (12%) of the liver biopsies. The presence of intrahepatic HBV DNA was not associated with pre-transplantation serum viral markers, type of pre- or post-transplantation antiviral treatment, or post-transplantation immunosuppressive treatment.

Conclusion: The findings suggest that while treatment with HBIg plus oral antiviral as post-transplantation HBV prophylaxis may result in a percentage of patients with persistent HBV DNA in the graft, the presence of HBV DNA in the liver graft may not be related to clinical HBV recurrence.

Keywords: Hepatitis B virus; liver failure; liver transplantation.

Introduction

Hepatitis B virus (HBV) infection is an important public health problem. Chronic HBV infection affects more than 250 million people globally and the inflammation associated with HBV infection is associated with cirrhosis and hepatocellular carcinoma.[1] Antiviral drugs can reduce the long-term complications of chronic HBV infection; however, liver transplantation remains the mainstay of treatment for patients with end-stage liver disease.

HBV reinfection is a significant cause of impaired prognosis after liver transplantation. Reinfection is defined as the reappearance of the hepatitis B surface antigen (HBsAg) and/or HBV DNA in the serum. Immunosuppressive treatment administered after liver transplantation may increase the risk of HBV reinfection.[2–5] The risk of reinfection increases in patients with pre-transplantation hepatitis B e-antigen (HBeAg) positivity or high serum HBV DNA levels, resistance to antiviral drugs before transplantation, or hepatocellular carcinoma at the time of liver transplantation.[6–8] Additionally, extrahepatic reservoirs of HBV in a variety of sites, including peripheral blood mononuclear cells and the spleen, may contribute to graft reinfection.[9–13]

At the same time, negative serum HBsAg and HBV DNA results after liver transplantation may not definitively indicate eradication of HBV. HBV DNA remains detectable in liver tissue in a subset of patients after transplantation.[14–19] The prognostic significance of HBV DNA in graft tissue with no serological evidence of HBV reinfection remains to be determined.[20]

This study was an assessment of the presence of HBV DNA in the liver tissue of patients who underwent liver transplantation for HBV-related liver disease and had negative serological markers of HBV infection. The relationships between the presence of intrahepatic HBV DNA and pre-transplantation serum viral markers, types of pre- and post-transplantation antiviral treatment, and post-transplantation immunosuppressive treatment were also evaluated.

Materials and Methods

Patients

In our clinical practice, a liver biopsy is recommended for all patients who undergo liver transplantation due to HBV-related liver disease 3 years after the transplantation to histologically assess the liver and tissue HBV markers. Patients aged 18 years or older who underwent liver transplantation for HBV-related acute or chronic liver disease between 1998 and 2009, had a minimum post-transplantation follow-up duration of 3 years, negative serological markers of HBV infection (serum HBsAg and HBV DNA) during the follow-up after transplantation, and underwent liver biopsy, were eligible for this study.

Written informed consent was obtained from all of the patients before the liver biopsy. This study was conducted in accordance with the

How to cite this article: Mut Surmeli D, Turan I, Akay S, Erensoy S, Ersoz G, Gunsar F, et al. Significance of detectable hepatitis B virus DNA in liver allograft tissue in long-term follow-up of liver transplant recipients. Hepatology Forum 2021; 2(2):43–48.

Received: February 11, 2021; **Accepted:** March 19, 2021; **Available online:** May 21, 2021

Corresponding author: Deniz Mut Surmeli; Ankara Universitesi Tip Fakultesi, Ibn-i Sina Hastanesi, Geriatri Anabilim Dali, Ankara, Turkey
Phone: +90 312 508 35 91; **e-mail:** denizmut19@yahoo.com

Declaration of Helsinki and was approved by the ethics committee of Ege University (date: 18.08.2014, no: 14-4.1/5).

Antiviral Prophylaxis After Transplantation

In the anhepatic phase of transplantation, 4000 IU hepatitis B immune globulin (HBIg) (2000 IU intramuscular and 2000 IU intravenous) was administered. For the subsequent 5–20 days, 800–1600 IU HBIg intramuscular or 1500 IU HBIg intravenous was provided daily until the serum HBsAg was negative and the serum hepatitis B surface antibody (anti-HBs) level was >200 IU/L. The anti-HBs level was regularly monitored, and 200–1000 IU HBIg was administered intramuscularly every 1–4 weeks in order to maintain a level of serum anti-HBs of >50 IU/L.

Oral antiviral treatment was generally initiated before the liver transplantation. Lamivudine was administered in addition to HBIg after the liver transplantation for the patients who did not receive prior oral antiviral treatment.

Immunosuppressive Treatment After Transplantation

In the absence of contraindications (e.g., renal failure), a prednisolone and calcineurin inhibitor (cyclosporin or tacrolimus) combination was administered. Otherwise, everolimus, rapamycin, mycophenolate mofetil, mycophenolic acid, azathioprine, and basiliximab was administered in different combinations. Steroid treatment was terminated after 6–12 months of treatment. The target serum levels were tacrolimus 5–10 ng/mL, cyclosporin 100–200 ng/mL, and rapamycin 5–15 ng/mL.

Data Collection

This was a retrospective cohort study. Clinical, serological, and pathological data were retrospectively obtained from medical records. The date of liver transplantation, age of the patient at the time of transplantation, status of cadaveric vs. live donor liver transplantation, pre-transplantation antiviral treatment, and pre-transplantation serological markers (HBsAg, anti-HBs, HBeAg, anti-HBe, HBV DNA, anti-delta antibody, delta RNA) were recorded. The Child-Turcotte-Pugh and Model for End Stage Liver Disease (MELD) scores were calculated. The data regarding post-transplantation immunosuppressive and antiviral medications, histopathological findings of the liver explant, date of liver biopsy, presence of HBV DNA in the liver graft biopsy, and serum HBsAg, HBV DNA, and anti-HBs levels at the time of liver biopsy were also recorded. Long-term follow-up data for serum HBsAg and HBV DNA were collected.

Details of the Serological Tests and the Serum and Liver HBV DNA Measurements

Serological tests were performed with the Abbott AxSYM System (Abbott Diagnostics Inc., Lake Forest, IL, USA) immunochemical automated analyzer. Serum HBV DNA evaluation was performed using different methods at different periods, based on availability: Digene Hybrid Capture Assay (Digene Corp., Gaithersburg, MD, USA; detection limit 5 pg/mL), Versant HBV DNA (bDNA; Siemens Healthineers GmbH, Erlangen, Germany; detection limit 2000 IU/mL), COBAS AmpliPrep TaqMan (real-time PCR; F. Hoffmann-La Roche Ltd., Basel, Switzerland; detection limit 20 IU/mL), or the Abbott m2000sp, m2000rt (real-time PCR; Abbott Laboratories, Chicago, IL, USA; detection limit 10 IU/mL). HBV DNA in the liver tissue was evaluated with polymerase chain reaction (PCR) (HBV S primers, HBV P7-P8 primers, LIPA primers) and gel electrophoresis (Innogenetics N. V., Ghent, Belgium). Anti-delta antibodies were assessed using a microenzyme immunoassay (Murex Biotech Ltd., Dartford, UK).

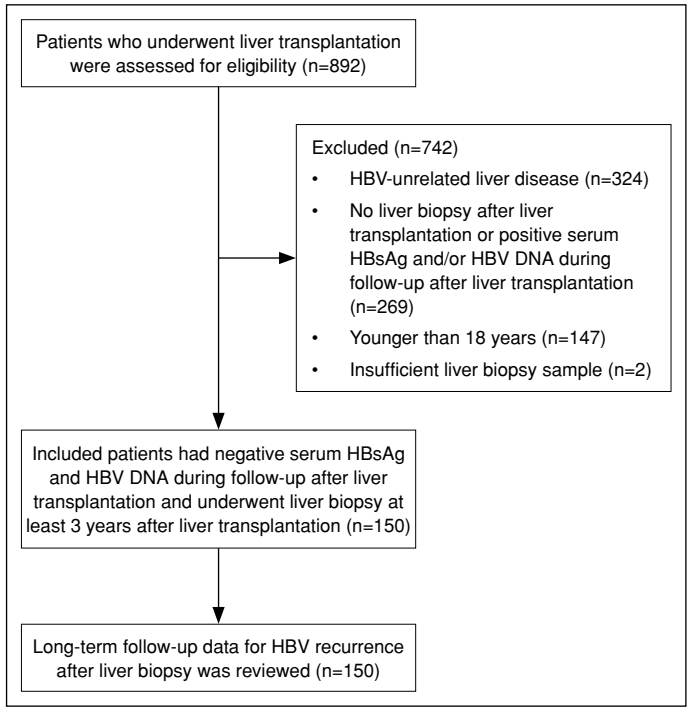

Figure 1. Flowchart of the study population.

HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

Statistical Analysis

The statistical analyses were performed with IBM SPSS Statistics for Windows, Version 20.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median and range. Categorical variables were summarized as count and percentage. Between group comparisons were performed using the Mann-Whitney U test for continuous variables and a chi-squared test (or Fisher's exact test where appropriate) for categorical variables. A p value <0.05 was considered to indicate statistical significance. All of the statistical tests were 2-sided.

Results

Between January 1998 and November 2009, a total of 892 study patients underwent liver transplantation, 745 of whom were adults. Of these, 421 (57%) required liver transplantation due to HBV-related liver disease. A liver biopsy after transplantation was performed in 152 patients. Two patients were excluded because the liver biopsy sample was insufficient. A total of 150 patients were included in this study (Fig. 1).

Patient Characteristics

The median age at the time of the liver transplantation was 47 years (range: 18–64 years). All of the patients had HBV-related cirrhosis. Thirty-four (22.7%) of the patients were female, and 116 (77.3%) patients were male. The median MELD score before transplantation was 16.5 (range: 6–39). The pre-transplantation HBeAg result was positive in 11 of 121 (9.1%) patients. The pre-transplantation HBV DNA result

Table 1. Patient characteristics (n=150)

	All patients*	Intrahepatic HBV DNA		p
		Positive	Negative	
Age, median (range), years	47 (18–64)	48.5 (39–53)	47 (39–51)	0.670
Gender, n (%)				
Female	34 (22.7)	4 (22.2)	30 (22.7)	0.962
Male	116 (77.3)	14 (77.8)	102 (77.3)	
Child-Turcotte-Pugh score, n (%)				
A	9 (6.0)	0 (0.0)	9 (6.8)	0.324
B	24 (16.0)	3 (16.7)	21 (15.9)	
C	48 (32.0)	9 (50.0)	39 (29.5)	
Unknown	69 (46.0)	6 (33.3)	63 (47.7)	
MELD score, median (range)	16.5 (6–39)	19 (14–23)	16 (13–22)	0.392
Pre-transplantation serum HBV DNA, n (%)				
Positive	49 (32.7)	9 (50.0)	40 (30.3)	0.167
Negative	73 (48.7)	7 (38.9)	66 (50.0)	
Unknown	28 (18.7)	2 (11.1)	26 (19.7)	
Pre-transplantation serum HBeAg, n (%)				
Positive	11 (7.3)	2 (11.1)	9 (6.8)	0.611
Negative	110 (73.3)	14 (77.8)	96 (72.7)	
Unknown	29 (19.3)	2 (11.1)	27 (20.5)	
Pre-transplantation serum anti-delta, n (%)				
Positive	64 (42.7)	7 (38.9)	57 (43.2)	0.592
Negative	49 (32.7)	7 (38.9)	42 (31.8)	
Unknown	37 (24.7)	4 (22.2)	33 (25.0)	
Donor type, n (%)				
Live	108 (72)	16 (88.9)	92 (69.7)	0.089
Cadaveric	42 (28)	2 (11.1)	40 (30.3)	
Histopathology of explant liver, n (%)				
Liver cirrhosis	59 (39.3)	10 (55.6)	49 (37.1)	0.400
Hepatocellular carcinoma†	41 (27.3)	4 (22.2)	37 (28.0)	
Dysplastic nodules†	35 (23.3)	3 (16.7)	32 (24.2)	
Unknown	15 (10.0)	1 (5.6)	14 (10.6)	

P values were calculated using the Mann-Whitney U test for continuous variables and a chi-squared test for categorical variables. P values <0.05 were considered statistically significant. *: Percentages may not sum up to 100 due to rounding; †: Findings in addition to liver cirrhosis; HBV: Hepatitis B virus; HBeAg; Hepatitis B e-antigen: MELD: Model for End Stage Liver Disease.

was positive in 49 of 122 (40.2%) patients. The pre-transplantation anti-delta result was positive in 64 of 113 (56.6%) patients. Liver grafts were obtained from live donors for 108 (72%) patients, and cadaveric donors were used for 42 (28%) patients (Table 1).

The following drugs were used (alone or sequentially) in the pre-transplantation period: 57 (38%) patients received lamivudine, 13 (8.7%) patients received adefovir dipivoxil, 4 (2.7%) patients received entecavir, and 8 patients received interferon (5.3%). In this study group, 21 (14%) patients did not receive any pre-transplantation antiviral treatment, and no data were available for 65 (43.3%) patients.

Presence of Intrahepatic HBV DNA and Associated Factors

The median length of time between the liver transplantation and the liver biopsy in this study was 4.4 years (range: 3–12.4 years). Intrahepatic HBV DNA test findings were positive in the liver biopsies of 18 (12%) patients. The presence of liver HBV DNA was not associated with gender (p=0.962) or the type of donor (live or cadaveric) (p=0.089). The pre-transplantation serum HBeAg (p=0.611), HBV DNA (p=0.167), and anti-delta (p=0.592) status was not associated with post-transplantation liver HBV DNA positivity (Table 1). The type of pre-transplantation antiviral treatment was not related to the presence of post-transplantation hepatic HBV DNA (Table 2). Furthermore, the type of post-transplantation antiviral drugs and immunosuppressive treatments were not related to the presence of intrahepatic HBV DNA (Table 2 and Table 3). At the time of the liver biopsy, 19 patients had no measurable anti-HBs in the serum and 2 had positive results for hepatic HBV DNA. The absence of serum anti-HBs was not associated with the presence of hepatic HBV DNA (p=1.000).

Table 2. Association between pre- and post-transplantation antiviral use and post-transplantation intrahepatic HBV DNA status

	Liver HBV DNA (-)		Liver HBV DNA (+)		Total*	p†
	n	%	n	%		
Pre-transplantation antiviral use						
Interferon	7	87.5	1	12.5	8	1.000
Lamivudine	47	82.5	10	17.5	57	0.323
Adefovir	13	100	0	0.0	13	0.198
Entecavir	4	100	0	0.0	4	1.000
None	19	90.5	2	9.5	21	
Unknown	58	89.2	7	10.8	65	
Post-transplantation antiviral use						
Lamivudine	126	88.1	17	11.9	143	0.545
Adefovir	11	78.6	3	21.4	14	0.379
Telbivudine	14	87.5	2	12.5	16	1.000
Entecavir	12	92.3	1	7.7	13	1.000
Tenofovir	27	87.1	4	12.9	31	1.000

*: Some patients received more than 1 type of antiviral drug; therefore, the total count exceeds the total number of patients; †: P values were calculated using a chi-squared test based on contingency tables of the number of patients who were or were not treated for each drug. P values <0.05 were considered statistically significant. HBV: Hepatitis B virus.

Table 3. Association between the type of post-transplantation immunosuppressive drugs and the presence of post-transplantation intrahepatic HBV DNA

	Liver HBV DNA (-)		Liver HBV DNA (+)		Total	p†
	n	%*	n	%*		
Methylprednisolone	130	88.4	17	11.6	147	0.228
Tacrolimus	110	87.3	16	12.7	126	0.741
Cyclosporin A	24	92.3	2	7.7	26	0.740
Rapamycin	35	85.4	6	14.6	41	0.579
Everolimus	9	69.2	4	30.8	13	0.054
Basiliximab	9	90.0	1	10.0	10	1.000
Mycophenolat mofetil	46	86.8	7	13.2	53	0.754
Mycophenolic acid	9	100	0	0.0	9	0.601
Azathioprine	2	100	0	0.0	2	1.000
Unknown	1		0		1	

*: Row percentages; †: P values were calculated using a chi-squared test based on contingency tables of the number of patients who were or were not treated for each drug. P values <0.05 were considered statistically significant. HBV: Hepatitis B virus.

Long-Term Serological Outcomes

After a median post-transplant follow-up of 7.5 years (range: 4–15.2 years), 4 patients (2.7%) had a positive serum HBsAg level. Only 1 of these 4 patients was found to have a positive finding of intrahepatic HBV DNA; there was no association between intrahepatic HBV DNA and long-term HBsAg positivity (p=0.417). All 4 of these patients had negative serum HBV DNA results.

Discussion

We investigated the presence of intrahepatic HBV DNA in a cohort of long-term survivors who underwent liver transplantation for HBV-related liver disease. To the best of our knowledge, no previous study of this subject has described a cohort of liver transplant recipients of this size, and we were able to provide long-term follow-up results. The primary conclusion of our study is the observation that after a median post-transplantation follow-up of 4.4 years, the majority of patients who were given combination prophylaxis with HBIg and an oral antiviral did not have intrahepatic HBV DNA. The long-term follow-up revealed that a positive intrahepatic HBV DNA finding was not associated with clinical HBV recurrence.

The presence of intrahepatic HBV DNA in patients who underwent liver transplantation for hepatitis B-associated liver disease has been investigated in previous studies. Hussain et al.[21] reported a higher rate of positive hepatic HBV DNA in post-transplantation liver biopsies (total HBV DNA was positive in 83% of 47 liver biopsy samples from

25 patients). The differences between our study and this one are the pre-transplantation HBV DNA levels and the length of follow-up after liver transplantation. Most of the patients included in our study were HBeAg-negative, and had the pre-transplantation serum level of HBV DNA undetectable. Additionally, the post-transplantation duration of follow-up in our study (median: 4.4 years, range: 3–12.4 years) was longer than that of Hussain et al.[21] (range: 7 days–48 months). Hussain et al.[21] proposed that intrahepatic HBV DNA had no predictive value for HBV recurrence, but there were 2 HBV recurrences in 25 patients, which could be considered a high recurrence rate and might have been related to the high rate of liver HBV DNA positivity. Our patients were classified as a low risk group with regard to HBV recurrence and represent the majority of the hepatitis B patient population to undergo transplantation at most centers. The antiviral prophylaxis regimen applied in the cited earlier study was primarily HBIg and lamivudine, which was similar to our findings.

Another study reported that among 18 patients with positive serum HBV DNA results, 9 were found to have positive intrahepatic HBV DNA.[17] The proportion of liver HBV DNA positivity was considerably higher than that of our study, most likely because all of the patients in our group had undetectable serum HBV DNA levels. Furthermore, the antiviral prophylaxis regimen consisted of only HBIg rather than a combination of HBIg and oral antiviral treatment in most patients, which could be considered a less effective treatment compared to the regimen used in our study.

As we also found, Lenci et al.[22] reported that about 7% of post-transplantation patients with negative serum HBV DNA findings had positive liver HBV DNA results detected within a mean follow-up period of 88.3 months. One patient had HBV recurrence in the follow-up period and a positive liver HBV DNA result.

The mechanism of post-transplantation HBV recurrence is not clearly understood, but the immunosuppressive treatment administered after the transplantation may play a role.[2] There were not enough data on the effects of different immunosuppressive medications on HBV recurrence in previous studies, most probably because there were too few patients included in these studies. Our results suggest that the type of immunosuppressive regimen had no effect on post-transplantation HBV recurrence.

The retrospective design and missing data for various parameters, including baseline characteristics, medications, and treatment durations, constitute limitations of this research. We were not able to obtain data about the histopathological findings of the liver biopsy specimens. Additionally, the data reflect a long period of treatment, and during that time different measurement methods of serum HBV DNA with different thresholds were used.

In conclusion, intrahepatic HBV DNA was rarely detectable in long-term survivors among liver transplant recipients who had combination prophylaxis with HBIg and an oral antiviral drug after transplantation, especially those patients with a low risk of HBV recurrence. The presence of intrahepatic HBV DNA was not associated with pre-transplantation serum viral markers, the type of pre- and post-transplantation antiviral treatment, or the type of immunosuppressive treatment. Our results suggest that the presence of intrahepatic HBV DNA is not a reliable indicator of HBV recurrence after liver transplantation. The presence of HBV DNA in liver grafts may not indicate clinical recurrence. Further studies are needed to assess the prognostic value of the detection of intrahepatic HBV DNA and its role in guiding further treatment options.

Acknowledgement: We would like to thank Dr. Timur Kose (Ege University, Department of Biostatistics) for his valuable contribution to the statistical analysis.

Ethics Committee Approval: The Ege University Clinical Research Ethics Committee granted approval for this study (date: 18.08.2014, number: 14-4.1/5).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ZK; Design – DMS, ZK; Supervision – ZK, IT; Materials – SE, IT, FG, UA, GE, ZK; Data Collection and/or Processing – DMS, IT, SE, FG, UA, GE; Analysis and/or Interpretation – DMS, ZK, IT, SA; Literature Search – DMS, SA; Writing – DMS, SA; Critical Reviews – SE, IT, ZK, DMS, FG, UA, GE, SA.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. World Health Organization. Global Hepatitis Report 2017. Geneva: World Health Organization; 2017.
2. McMillan JS, Shaw T, Angus PW, Locarnini SA. Effect of immunosuppressive and antiviral agents on hepatitis B virus replication in vitro. Hepatology 1995;22(1):36-43. [CrossRef]
3. Degos F, Lugassy C, Degott C, Debure A, Carnot F, Theirs V, et al. Hepatitis B virus and hepatitis B-related viral infection in renal transplant recipients. A prospective study of 90 patients. Gastroenterology 1988;94:151-156.
4. Demetris AJ, Jaffe R, Sheahan DG, Burnham J, Spero J, Iwatsuki S, et al. Recurrent hepatitis B in liver allograft recipients. Differentiation between viral hepatitis B and rejection. Am J Pathol 1986;125:161-172.
5. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148(1):221-244.e3. [CrossRef]
6. Marzano A, Gaia S, Ghisetti V, Carenzi S, Premoli A, Debernardi-Venon W, et al. Viral load at the time of liver transplantation and risk of hepatitis B virus recurrence. Liver Transpl 2005;11(4):402-409. [CrossRef]
7. Faria LC, Gigou M, Roque-Afonso AM, Sebagh M, Roche B, Fallot G, et al. Hepatocellular carcinoma is associated with an increased risk of hepatitis B virus recurrence after liver transplantation. Gastroenterology 2008;134(7):1890-1899. [CrossRef]
8. Mutimer D, Pillay D, Dragon E, Tang H, Ahmed M, O'Donnell K, et al. High pre-treatment serum hepatitis B virus titre predicts failure of lamivudine prophylaxis and graft re-infection after liver transplantation. J Hepatol 1999;30(4):715-721. [CrossRef]
9. Omata M. Significance of extrahepatic replication of hepatitis B virus. Hepatology 1990;12(2):364-366. [CrossRef]
10. Michalak TI. Occult persistence and lymphotropism of hepadnaviral infection: insights from the woodchuck viral hepatitis model. Immunol Rev 2000;174:98-111. [CrossRef]
11. Pontisso P, Poon MC, Tiollais P, Brechot C. Detection of hepatitis B virus DNA in mononuclear blood cells. Br Med J (Clin Res Ed) 1984;288(6430):1563-1566. [CrossRef]
12. Bouffard P, Lamelin JP, Zoulim F, Pichoud C, Trepo C. Different forms of hepatitis B virus DNA and expression of HBV antigens in peripheral blood mononuclear cells in chronic hepatitis B. J Med Virol 1990;31(4):312-317.
13. Mason A, Wick M, White H, Perrillo R. Hepatitis B virus replication in diverse cell types during chronic hepatitis B virus infection. Hepatology 1993;18(4):781-789. [CrossRef]
14. Terrault NA, Zhou S, Combs C, Hahn JA, Lake JR, Roberts JP, et al. Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. Hepatology 1996;24(6):1327-1333. [CrossRef]

15. Féray C, Zignego AL, Samuel D, Bismuth A, Reynes M, Tiollais P, et al. Persistent hepatitis B virus infection of mononuclear blood cells without concomitant liver infection. The liver transplantation model. Transplantation 1990;49(6):1155-1158. [CrossRef]
16. Marzano A, Salizzoni M, Debernardi-Venon W, Smedile A, Franchello A, Ciancio A, et al. Prevention of hepatitis B virus recurrence after liver transplantation in cirrhotic patients treated with lamivudine and passive immunoprophylaxis. J Hepatol 2001;34(6):903-910. [CrossRef]
17. Roche B, Feray C, Gigou M, Roque-Afonso AM, Arulnaden JL, Delvart V, et al. HBV DNA persistence 10 years after liver transplantation despite successful anti-HBS passive immunoprophylaxis. Hepatology 2003;38(1):86-95.
18. Fox AN, Terrault NA. The option of HBIG-free prophylaxis against recurrent HBV. J Hepatol 2012;56(5):1189-1197. [CrossRef]
19. Maiwall R, Kumar M. Prevention and treatment of recurrent hepatitis b after liver transplantation. J Clin Transl Hepatol 2016;4(1):54-65. [CrossRef]
20. Chauhan R, Lingala S, Gadiparthi C, Lahiri N, Mohanty SR, Wu J, et al. Reactivation of hepatitis B after liver transplantation: Current knowledge, molecular mechanisms and implications in management. World J Hepatol 2018;10(3):352-370. [CrossRef]
21. Hussain M, Soldevila-Pico C, Emre S, Luketic V, Lok AS. Presence of intrahepatic (total and ccc) HBV DNA is not predictive of HBV recurrence after liver transplantation. Liver Transpl 2007;13(8):1137-1144. [CrossRef]
22. Lenci I, Marcuccilli F, Tisone G, Di Paolo D, Tariciotti L, Ciotti M, et al. Total and covalently closed circular DNA detection in liver tissue of long-term survivors transplanted for HBV-related cirrhosis. Dig Liver Dis 2010;42(8):578-584. [CrossRef]