JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.99609
J Inonu Liver Transpl Inst 2024;2(1):6–10

Original Research

Inonu University Experience in Hepatitis B Recurrence After Liver Transplantation

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Abstract

Objectives: Hepatitis B virus (HBV), one of the biggest health problems of the world and our country, still constitutes the largest cause of liver failure and liver transplantation in the world. Here, we will introduce the HBV virus closely and share the health problems of HBV in the world and in our country in the literature data.

Methods: İnönü University Liver Transplant Institute Patients who underwent liver transplantation due to any reason related to HBV were included in the study. Patients who underwent liver transplantation due to liver diseases caused by HBV in our institute between 2009 and 2023 were included in the study. . A total of 3679 patients underwent liver transplantation between 2002 and 2024. Of these patients, 1275 patients were operated on with the diagnosis of HBV. When 530 patients whose data were not available and 49 patients who were retransplanted were excluded from the study, a total of 695 patients were included in the study.

Results: Treatment is given in combination with antiviral and HBIG. It is available in centers where powerful antivirals are used alone. Although the approaches of the centers vary, patients who have had a liver transplant due to HBV definitely need postoperative medical treatment to prevent HBV recurrence.

Conclusion: Patients who have undergone liver transplantation due to HBV must have their Hbs-ag level checked when they are discharged from the hospital. Informing the patient about HBV recurrence and medical treatment provides a more meticulous medical treatment.

Keywords: Hepatitis B, Recuurence, Liver transplantation

Please cite this article as "Yavuz Baskiran D, Guzel Karahan S, Balikci Cicek I, Yilmaz S. Inonu University Experience in Hepatitis B Recurrence After Liver Transplantation. J Inonu Liver Transpl Inst 2024;2(1):6–10".

Hepatitis B virus (HBV), one of the biggest health problems of the world and our country, still constitutes the largest cause of liver failure and liver transplantation in the world. Here, we will introduce the HBV virus closely and share the health problems of HBV in the world and in our country in the literature data. We will evaluate patients who underwent liver transplantation due to HBV at İnönü University Liver Transplant Institute in terms of HBV recurrence, our results and recommendations. Hepatitis B virus (HBV) is a double-stranded DNA virus with a diameter of 42 nm. It has a spherical appearance. The outermost sheath is HBsAg, which is the surface antigen. Under the HBsAg sheath is the HBcAg core antigen. In the innermost part, there is the genomic structure consisting of DNA. In the inner part is HBeAg, which is the internal coated antigen.[1] Serological tests used in diagnosis; HBsAg, Anti HBc Total, Anti HBcIgM, Anti HBs, HBeAg, Anti HBe, HBV DNA. HBsAg, It is the first indicator . It is the surface antigen of the virus. It is the first antigen to appear in acute infections. It reaches a detectable level 1-2 weeks before symptoms. Positivity

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Submitted Date: 15.04.2024 **Revised Date:** 25.04.2024 **Accepted Date:** 25.04.2024 **Available Online Date:** 13.06.2024

continues for 2-12 weeks. Positivity exceeding 6 months indicates chronicity. HBeAg, It is the internal antigen located at the core of the virus. It is found in dissolved form in the blood. It becomes positive with HBsAg. It becomes negative before HBsAg. It indicates that there is a high level of virus in the blood. It shows that the person is highly contagious. AntiHBs, It is the antibody against HBsAg. HBsAg becomes positive 2-3 months after it becomes negative. It is permanent for a lifetime. Indicates previous infection. It is also positive in vaccinated people. Anti-HBs positivity alone does not always mean that there is an infection. It indicates that the person is immune to hepatitis B infection. AntiHBc Total, It is an antibody against the hepatitis B core antigen. It generally consists of IgG. It becomes positive with clinical findings. Positivity continues throughout life. The positivity of this antibody indicates that the person has encountered the exact virus particle. It is positive in acute infections, chronic infections and carriers. HBV DNA It is the best indicator of the presence of the virus. Allows tracking of active replication. It is safer than HBeAg. It is important in monitoring the treatment. It allows determination of viral load.HBV Genotypes, Genotype A,B,C,D,E,F,G Genotype D is common in our country.

Regardless of the situation of a person who has encountered HBV, the disease rates that this HBV will cause in the person are as follows. After HBV is detected in the blood, a 90% recovery rate is observed. 1% has fulminant hepatitis and the remaining 9% remains HBs-Ag positive. 50% of this 9% rate recovers within 6 months. The remaining 50% progresses as asymptomatic carrier, chronic resistant carrier, and chronic active hepatitis, which in the future will emerge as a liver transplant candidate in the form of cirrhosis or hepatocellular cancer (HCC) (Fig. 1, Table 1).[2]

In the 1980s, cirrhosis due to HBV was considered a relative contraindication for liver transplantation.[5] Because without antiviral prophylaxis, the recurrence rate of HBV after liver transplantation was close to 100% and the mortality rate in the first year after transplantation was approximately 50%. With the discovery of hepatitis B immunoglobulin (HBIG), a polyclonal antibody developed against HBV surface antigen, in the early 1990s, HBV recurrence after liver transplantation decreased significantly and survival increased.[6] HBIG has a polycolonal immunoglobulin G (IgG) structure and is in the IgG subclass. Its distribution is very close to the rates in human plasma. HBIG has been shown to neutralize circulating virions, facilitate the lysis of infected hepatocytes through antibody-dependent cellular cytotoxicity, and block HBV receptors on hapatocytes. HBIG half-life is on average 22 days. The dose and frequency of HBIG use after liver transplantation, the method of application and the duration of application vary from center to center.[7] Both high and low risk groups have been defined in terms of HBV recurrence. The groups are as follows. High Risk Groups for HBV Recurrence; Pre-Transplant Hbv DNA + • Pre-Transplant Hbe-ag + • Presence of HCC , Low compliance with antiviral treatment • Resistance to antiviral treatment• Concomitant HIV or HDV infection[8,9] Low Risk Group for HBV Recurrence, Pre-Transplant HBV DNA negativity • Pre-Transplant Hbe-ag negativity • No HCC• High compli-

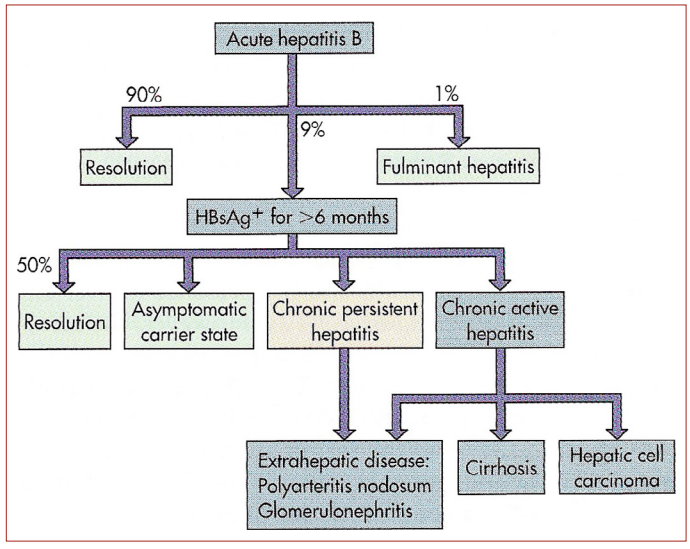

Figure 1. A patient exposed to HBV.

Table 1. Laboratory findings can be used to determine whether the patient has encountered HBV, early HBV infection, acute HBV infection, chronic HBV infection, acute HBV infection window period, previous HBV infection, and HBV vaccine response.[3,4]

HBs Ag	Hbe Ag	Anti HBe	AntiHBc IgM	Anti HBc	Anti HBs	Comment
-	-	-	-	-	-	Not exposed to HBV.
+	+/-	-	-	-	-	* Early HBV infection?
+	+/-	+/-	+	+	-	Acute HBV infection
+	+/-	+/-	-	+	-	Chronic HBV infection
-	-	+/-	+	+	-	* Acute HBV infection (window period)
-	-	-	-	+	-	AntiHBc positivity only
-	-	+/-	-	+	+	Previous HBV infection
-	-	-	-	-	+	HBV vaccine response

ance with antiviral treatment• Lack of resistance to antiviral treatment• No accompanying HIV or HDV infection.[8,9]

In a center where more than 300 liver transplants are performed annually, HBV constitutes the largest part of the indications for liver transplantation. More than 3000 liver transplants have been performed so far. We will evaluate patients who underwent liver transplantation due to HBV at İnönü University Liver Transplant Institute in terms of HBV recurrence, our results and recommendations.

Methods

İnönü University Liver Transplant Institute Patients who underwent liver transplantation due to any reason related to HBV were included in the study.

Patients who underwent liver transplantation due to liver diseases caused by HBV in our institute between 2009 and 2023 were included in the study. Demographic data of the patients, Meld score, operation date, preop eliza tests (hbs-ag. hbe-ag,hbc-ag, anti-hbc, anti-hbs delta ag, delta ab, hbv dna, hdvrna), postop 1. Monthly Hbs-ag level and follow-up Hbs-ag levels were examined. A total of 3679 patients underwent liver transplantation between 2002 and 2024. Of these patients, 1275 patients were operated on with the diagnosis of HBV. When 530 patients whose data were not available and 49 patients who were retransplanted were excluded from the study, a total of 695 patients were included in the study. Of these patients, no HBV recurrence was observed in 599 patients. HBV recurrence was observed in 96 of these patients (13.8%).

Table 2. Demographic Data of Patients, 74% of the patients were male and 26% were female. Their average age is 64, their average MELD score is 16, and their average follow-up period is 65 months.

Variables	n	%
Gender (female/male)	178/517	25.6/74.4
	Mean±SS	**Median**
Age (Years)	53.45±15.08	58
Tracking Period (Months)	81.17±52.02	65
MELD Score	18.52±4.969	16

Findings

Laboratory findings can be used to determine whether the patient has encountered HBV, early HBV infection, acute HBV infection, chronic HBV infection, acute HBV infection window period, previous HBV infection, and HBV vaccine response.[3,4]

When the Hbs-ag levels of the patients are examined at the first month after surgery, Hepatitis B recurrence is observed in a total of 112 patients (16.1%) and when the Hbs-ag levels after the long follow-up are examined, 96 patients (13.8%) are observed to have Hepatitis B recurrence (Tables 1-5).

Discussion

In a study, subcutaneous HBIG was given to patients who had completed 1 year after liver transplantation, with an anti-HBS titer of >150 Iu/L. After 48 weeks, the average anti-HBs titer was found to be 232 Iu/L, and no HBV recurrence was observed in any of the patients.[10]

In our clinic, HBIG treatment is given for life. In the unhepatic phase, HBIG is given for 7 days postoperatively and every month, depending on the AntiHbs level. Anti-HBS level is tried to be kept above 100 IU/L. The HBV recurrence rate seen in our clinic shows that patients are not fully compliant with medical treatment and that patients must receive postoperative education.

In another study involving 176 patients, the combination of HBIG and potent antivirals was targeted to have an anti-HBS titer of 100-250 Iu/l in the post-transplant period. It was reported that only 2 patients developed relapse during an average follow-up of 43 months and one of these patients did not use the treatment.[11]

Table 3. We see that there is no significant difference in the demographic and follow-up period data of the two groups with and without HBV recurrence.

	HBSAG			
	Negative, n (%)		**Positive (Relapse), n (%)**	
Gender				
Female	157 (26.48)		19 (19.79)	
Male	436 (73.52)		77 (80.21)	
	Mean±SS	**Median (Min-Max)**	**Mean±SS**	**Median**
Age	53.55±14.73	58 (5-83)	53.14±16.53	58
Tracking Period (Months)	79.61±52.04	64 (5-177)	89.28±50.98	75.5
MELD	18.57±5.02	16 (15-40)	18.1±4.58	16

Table 4. When the Hbs-ag levels of the patients are examined at the first month after surgery, Hepatitis B recurrence is observed in a total of 112 patients (16.1%) and when the Hbs-ag levels after the long follow-up are examined, 96 patients (13.8%) are observed to have Hepatitis B recurrence

Variables	n	(%)
Diagnosis		
HBV	454	65.3
HBV+HCC	151	21.7
HBV+HDV	61	8.8
HBV+HDV+HCC	24	3.5
HBV+HCV	3	0.4
HBV+HDV+HCV+HCC	1	0.1
HBV+HCV+HCC	1	0.1
HBSAG 1st month after liver transplantation		
Negative	583	83.9
Positive	112	16.1
Last chech HBSAG		
Negative	599	86.2
Positive	96	13.8

Treatment is given in combination with antiviral and HBIG. It is available in centers where powerful antivirals are used alone. Although the approaches of the centers vary, patients who have had a liver transplant due to HBV definitely need postoperative medical treatment to prevent HBV recurrence.

In another study where HBIG + Antiviral treatment was used, the anti-HBS level was 500 IU/L for the first 6 months and 100 IU/L for the follow-up, and no recurrence was observed during an average follow-up of 25 months.[12]

Anti-HBS level differences may be required in the follow-up of high-risk and low-risk groups. However, monitoring this requires detailed information about the patient discharged from the hospital.

In a study conducted by Fung et al., a 91% HBsAg negativity rate was reported at the end of 10 years with antiviral monotherapy in liver transplant patients with chronic hepatitis B who were previously resistant to Lamivudine.[13,14]

Combination therapy is recommended in our clinic. Comparative studies are needed in our high-volume center.

In the same study, while 72% of the patients had positive HBV DNA before surgery, HBV DNA was found to be negative in 91% of the patients at the end of the first year, and this rate was found to be 100% in the 5th and 8th years.[15]

When the effect of high-risk patient group on postoperative HBV recurrence was examined, it was seen that noncompliance with medical treatment was effective.

Despite all these findings, it has been reported that the use of HBIG has additional contributions such as reducing rejection and HCC recurrence rates after liver transplantation.[16]

Table 5. HBIG treatment algorithm, In the high risk group, 10,000 IU per day in the anhepatic phase, 2000 IU HBIG per day for the next week, and 2000 IU per day for 14 days if AntiHBS is <100 IU/L. In the low risk group, 5000 IU per day in the anhepatic phase, 500 IU HBIG per day for the next week, and 2000 IU per day for 14 days if AntiHbs is <100 Iu/l. Monthly anti-HBS levels are tried to be kept above 100 for life.

	High risk	Low risk
Anhepatic phase	10000 ıu	5000
First 7 days	2000	500
14 days	2000	500
Long term	2000	2000

If the anti-HBS level is < 100 IU/L in the first 7 days, the treatment is completed in 14 days.

Conclusion

Patients who have undergone liver transplantation due to HBV must have their Hbs-ag level checked when they are discharged from the hospital. Informing the patient about HBV recurrence and medical treatment provides a more meticulous medical treatment. In particular, antiviral treatment and access to HBIG should be provided, and a prospective study should be started in our liver transplantation institute to investigate HBV recurrence. The shortcomings of the study are that it is a retrospective study, not all patient data can be accessed in the study (Hospital automation system change), and the HBIG doses taken by the patient cannot be determined.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – D.Y.B., S.G.K., S.Y.; Design – D.Y.B., S.G.K., S.Y.; Supervision – D.Y.B., S.Y.; Materials D.Y.B., I.B.C., S.Y.; Data collection &/or processing – D.Y.B., I.B.C., S.Y.; Analysis and/or interpretation – D.Y.B., I.B.C., S.Y.; Literature search – D.Y.B., S.Y.; Writing – D.Y.B., S.G.K., I.B.C., S.Y.; Critical review – D.Y.B., S.G.K., I.B.C., S.Y.

References

1. Turkish Clinical Microbiology and Infectious Diseases Association https://www.idcmjournal.org/idcm.
2. Viral Hepatitis Fight Association https://www.worldhepatitisalliance.org/
3. Hepatitis Viruses and Infection Forming Mechanisms; Prof. Dr. Ömer POYRAZ https://www.gtu.edu.tr/Files/UserFiles/161/1-H
4. Viral Hepatitis; Prof. Dr. Fehmi TABAK https://www.kitapyurdu.com/kitap/viral-hepatit-2013/456648.html
5. Teegen EM, Maurer MM, Globke B, Pratschke J, Eurich D. Liver transplantation for Hepatitis-B-associated liver disease - Three decades of experience. Transpl Infect Dis. 2019 Feb;21(1):e12997.

6. Lens S, García-Eliz M, Fernández I, Castells L, Bonacci M, Mas A, et al. Shorter hepatitis B immunoglobulin administration is not associated to hepatitis B virus recurrence when receiving combined prophylaxis after liver transplantation. Liver Int 2018;38(11):1940-1950.
7. Schilling R, Ijaz S, Davidoff M, Lee JY, Locarnini S, Williams R, et al. Endocytosis of hepatitis B immune globulin into hepatocytes inhibits the secretion of hepatitis B virus surface antigen and virions. J Virol 2003;77(16):8882-92.
8. Fox AN, Terrault NA. The option of HBIG-free prophylaxis against recurrent HBV. J Hepatol 2012;56(5):1189-1197.
9. Fernández I, Loinaz C, Hernández O, Abradelo M, Manrique A, Calvo J, et alTenofovir/entecavir monotherapy after hepatitis B immunoglobulin withdrawal is safe and effective in the prevention of hepatitis B in liver transplant recipients. Transpl Infect Dis 2015;17(5):695-701.
10. Di Costanzo GG, Lanza AG, Picciotto FP, Imparato M, Migliaccio C, De Luca et all. Safety and efficacy of subcutaneous hepatitis B immunoglobulin after liver transplantation: an open single-arm prospective study. Am J Transplant 2013;13(2):348-52.
11. Choudhary NS, Saraf N, Saigal S, Soin AS. Long-term Management of the Adult Liver Transplantation Recipients. J Clin Exp Hepatol 2021;11(2):239-253.
12. Ueda Y, Marusawa H, Kaido T, Ogura Y, Ogawa K, Yoshizawa A,et al. Efficacy and safety of prophylaxis with entecavir and hepatitis B immunoglobulin in preventing hepatitis B recurrence after living-donor liver transplantation. Hepatol Res 2013;43(1):67-71.
13. Fung J, Wong T, Chok K, Chan A, Sin SL, Cheung TT, et al. Oral Nucleos(t)ide Analogs Alone After Liver Transplantation in Chronic Hepatitis B With Preexisting rt204 Mutation. Transplantation 2017;101(10):2391-2398.
14. 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.
15. Couto CA, Bittencourt PL, Farias AQ, Lallee MP, Cançado EL, Massarollo PC, et al. Human polyclonal anti-hepatitis B surface antigen immunoglobulin reduces the frequency of acute rejection after liver transplantation for chronic hepatitis B. Rev Inst Med Trop Sao Paulo 2001;43(6):335-7
16. Lee EC, Kim SH, Lee SD, Park H, Lee SA, Park SJ. High-dose hepatitis B immunoglobulin therapy in hepatocellular carcinoma with hepatitis B virus-DNA/hepatitis B e antigen-positive patients after living donor liver transplantation. World J Gastroenterol 2016;22(14):3803-12.