JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2025.42714
J Inonu Liver Transpl Inst 2024;2(3):97–101

Original Research

Early Results of Hepatitis B Recurrence After Postoperative Close Monitoring of Patients Who Have Undergone Liver Transplantation for Hepatitis B

Deniz Yavuz Baskiran,[1] Ipek Balikci Cicek,[2] Murat Harputluoglu,[3] Sezai Yilmaz[1]

[1]Department of General Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye
[2]Department of Biostatistics and Medical Informatics, Faculty of Medicine, Inonu University, Malatya, Türkiye
[3]Department of Gastroenterology and Hepatology, Inonu University Faculty of Medicine, Malatya, Türkiye

Abstract

Objectives: Hepatitis B virus (HBV) is a a frequent cause of liver cirrhosis and hepatocellular carcinoma (HCC), that requires liver transplantation. This study aims to analyze HBV recurrence rates in the early postoperative period. Our second goal was to identify contributing factors of HBV recurrence following liver transplantation.

Methods: This retrospective study included 54 patients who underwent liver transplantation for HBV-related liver diseases at Inonu University Liver Transplant Institute in 2024. Data on demographics, preoperative viral markers, postoperative anti-HBs levels, and immunoglobulin and antiviral therapy regimens were collected from each patient. Statistical analyses were performed to compare outcomes based on risk stratification and anti-HBs levels.

Results: Fifty-four patients (81.48% male; mean age: 52.13±10.54 years were included in the study. In total 1.9% (n=1) experienced HBV recurrence during the early postoperative period. The mean Model for End-Stage Liver Disease (MELD) score was 18.46±6.15, and HBV DNA was negative in 81.48% of patients in the pretransplant period. Anti-HBs titers exceeded 100 IU/L in 79.63% of patients on postoperative day 7. There were no notable differences in demographic or clinical variables between patients with anti-HBs titers exceeding 100 IU/L and those with levels below this threshold.

Conclusion: The combination of hepatitis B immunoglobulin (HBIG) and antiviral therapy effectively prevents HBV recurrence following liver transplantation . Maintaining anti-HBs titers above 100 IU/L is critical. Further studies are needed to optimize prophylactic strategies to improve the outcomes in patients transplanted for HBV-related liver disease.

Keywords: Hepatitis B immunoglobulin, HBV recurrence post-liver transplantation, HBV-related liver diseases

Please cite this article as "Yavuz Baskiran D, Balikci Cicek I, Harputluoglu M, Yilmaz S. Early Results of Hepatitis B Recurrence After Postoperative Close Monitoring of Patients Who Have Undergone Liver Transplantation for Hepatitis B. J Inonu Liver Transpl Inst 2024;2(3):97–101".

Globally, hepatitis B virus (HBV) remains one of the most prevalent viral infections and is a frequent cause of liver cirrhosis and primary indication for liver transplantation in Türkiye. Chronic HBV infection not only leads to liver failure but also increases the risk of hepatocellular carcinoma (HCC) in the individuals . Before the development of effective prophylactic strategies, HBV recurrence following liver transplantation

Address for correspondence: Deniz Yavuz Baskiran, MD. Department of General Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye
Phone: +90 505 853 10 02 **E-mail:** denizbaskiran@gmail.com

Submitted Date: 12.12.2024 **Revised Date:** 13.01.2025 **Accepted Date:** 14.01.2025 **Available Online Date:** 24.01.2025

and immunosuppression was considered unavoidable. Frequently, these recurrences rapidly advanced to graft failure that resembling fulminant hepatitis. These observations emphasize the critical role of effective HBV prophylaxis and treatment protocols in achieving successful liver transplantation outcomes. The introduction of prophylactic therapies including the combination of anti-hepatitis B immunoglobulin (HBIG) and potent antiviral agents has revolutionized the prevention of HBV recurrences in liver transplant recipients. These therapeutic and prophylactic measures have significantly reduced HBV recurrence rates, improving graft and overall survival. Despite necessary precautions, HBV recurrence is can be observed in some cases which raises questions about the limitations of current preventive strategies.[1, 2] The effectiveness of antiviral and HBIG therapies has led to generally superior liver transplantation outcomes for HBV-related liver disease compared to other etiologies.[1, 2] However, persistent or recurrent HBV infection remains a critical concern, particularly because it is closely associated with post-transplant HCC recurrence, significantly complicating clinical management.[3, 4]

The challenges of managing HBV in the context of liver transplantation extend beyond recurrence prevention. HBV-related HCC requires strict oncologic surveillance and antiviral therapy to prevent HBV recurrence and subsequent HCC recurrence after liver transplantation. Factors such as pre-transplant viral load, adherence to prophylactic regimens, and potential drug resistance requires continuous evaluation and refinement of the treatment protocols.[4] Evoluating the efficacy of prophylactic therapies and assessing risk factors for recurrence are important for preventing HBV recurrence after liver transplantation.. In this study, we aimed to investigate early postoperative HBV recurrence rates. Furthermore, we aimed to evaluate the underlying factors contributing to recurrence in patients who underwent liver transplantation for HBV-related cirrhosis and HCC in 2024. We hope to provide insights into optimizing prophylactic strategies and improving post-transplant care for HBV-infected patients.

Methods

This study included patients who underwent liver transplantation at our institute in 2024 due to liver diseases associated with HBV infection. The analyzed data included demographic details, MELD scores, transplant dates, and preoperative ELISA test results, which encompassed HBsAg, HBeAg, HBcAg, anti-HBc, anti-HBs, delta Ag, delta Ab, HBV DNA, and HDV RNA. Postoperative data such as administered immunoglobulin doses, initial HBsAg levels, and follow-up HBsAg levels were also analyzed.This study was approved by the Inonu University Scientific Research Publication Ethics Board (approval number: 2024/6685).

We performed a risk stratification to taper the protocol for immunoglobulin administration. Several factors influenced risk stratification for HBV recurrence after liver transplantation. Patients with pre-transplant HBV-DNA, HBe antigen positivity, HIV or HDV coinfection, antiviral non-compliance or resistance, or hepatocellular carcinoma were considered high-risk. Otherwise, they were considered to have low-risk. High-risk patients received an intraoperative dose of 10,000 IU of immunoglobulin. Low-risk patients received 5,000 IU. Both groups then received a daily dose of 2,000 IU for the first postoperative week. The goal of this therapy was to maintain an anti-HBs antibody titer of at least 100 IU/mL. If, at the end of the first postoperative week, antibody titers were below this target, immunoglobulin therapy was continued for another week in both groups. In 2024, our institute performed a total of 257 liver transplants, with 54 of these were due to HBV-related liver diseases. HBV recurrence was observed in only one patient, indicating a recurrence rate of 1.9% with the prophylaxis protocol that used.

Statistical Analysis

Categorical variables were and expressed as number of affected individuals and th percentage of the study population (percentages), while continuous variables were tested for normality using the Shapiro-Wilk test. Continuous data were expressed as median (minimum-maximum) and mean±standard deviation. Comparisons of categorical variables between groups were performed using Fisher's exact chi-square test. For continuous variables, comparisons between two independent groups were performed using the Mann-Whitney U test. A p-value of <0.05 was considered as statistically significant. All statistical analyses were performed using IBM SPSS Statistics 26.0 for Windows (New York, USA).

Results

In total 54 patients included in this study. Fourty-four (81.48%) were male and 10 (18.52%) were female. The mean age of the patients was 52.13±10.54 years (median: 54, range: 20-72). Of these patients, 28 (51.85%) had HBV-related liver disease, while 26 (48.15%) were diagnosed with HBV+HCC. The mean MELD score was 18.46±6.15 (median: 17, range: 6-32), and the mean body mass index (BMI) was 26.93±5.33 kg/m^2 (median: 25.86, range: 18.94-40.86). HBV DNA was negative in 44 patients (81.48%) and positive in 10 patients (18.52%). HDV RNA was negative in 39 patients (72.22%) and positive in 15 patients (27.78%). On

postoperative 7th day , anti-HBs levels exceeded 100 IU/L in 43 patients (79.63%) and were below 100 IU/L in 11 patients (20.37 %). HBV recurrence was observed in only one patient (1.85%) during our follow-up period. The mean survival time was 128.04±89.85 days (median: 114, range: 10-296). The clinical and demographic data are summarized in Table 1.

Patients with postoperative day-7 anti-HBs levels below and above 100 were compared based on their demographic and clinical characteristics. there were no statistically significant differences between the two groups in terms of age (p=0.581), recipient height (p=0.755), recipient weight (p=0.874), BMI (p=0.632), MELD score (p=0.274), or survival duration (p=0.499). Similarly, there was no significant difference between the groups in terms of gender distribution (p=1.0), diagnosis distribution (HBV and HBV+HCC) (p=0.224), HBV DNA status (p=0.408), or HDV RNA status (p=1.0). These findings suggest demographic and cinical variables have no effect on the postoperative day-7 anti-HBs antibody titers. The results of our evaluation are summarized in Table 2.

Table 1. Demographic and Clinical Characteristics of the patients included in the study.

Variables	n	%	Mean±SD
Gender (Female/Male)	10/44	18.52/81.48	
Diagnosis			
HBV	28	51.85	
HBV+HCC	26	48.15	
HBV DNA			
Negative	44	81.48	
Positive	10	18.52	
HDV RNA			
Negative	39	72.22	
Positive	15	27.78	
Anti-HBs Day 7			
Below 100	11	20.37	
Above 100	43	79.63	
HBsAg Recurrence			
Negative	53	98.15	
Positive	1	1.85	
Age (Years)			52.13±10.54
Recipient Height (m)			1.71±0.09
Recipient Weight (kg)			78.39±15.27
BMI (kg/m^2)			26.93±5.33
Survival (Days)			128.04±89.85
MELD Score			18.46±6.15

SD: Standard Deviation; Min: Minimum; Max: Maximum; HBV: Hepatitis B; HCC: Hepatocellular Carcinoma; BMI: Body Mass Index; MELD: Model for End-Stage Liver Disease.

Discussion

In our study, the recurrence rate of hepatitis B virus (HBV) after liver transplantation in patients with HBV-related liver disease was remarkably low (1.92%, n=1). This finding emphasizes the effectiveness combination of hepatitis B immunoglobulin (HBIG) and antiviral agents to prevent HBV recurrence post-transplantation. Prophylactic HBV therapy has been shown to effectively reduce HBV recurrence after liver transplantation, thereby enhancing the positive impact of immunosuppression management in the post-transplant period.There are studies that report HBV recurrence rates less than 5% following prophylactic therapy with HBIG and antiviral agents.[7] For instance, a the study by Roche et al.,[8] a combination of immunoglobulin and antiviral agents reduced the recurrence rate of HBV to as low as 3.5%, effectively. These findings are consistent with our study, suggesting that the combination of these prophylactic measures is highly effective in reducing the recurrence of HBV in transplant recipients.Most of the patients who did not experience HBV recurrence (82.35%) had anti-HBs levels over 100 IU/L on postoperative 7th day. Our observation is supported by previous research suggesting that high anti-HBs titers play a key protective role in preventing HBV recurrence.[9] Higher levels of anti-HBs are often associated with better immunological control of the virus and reduced risk of reinfection, making it a critical marker for predicting the success of prophylactic therapy. The findings of our study emphasize the importance of maintaining high anti-HBs antibody titers in the immediate postoperative period. However, it is noteworthy that even in patients with anti-HBs antibody titers below 100 IU/L, HBV recurrence rates remained low (p>0.05). This observation suggests that factors other than anti-HBs antibody titers may play a role in the prevention of HBV recurrence. The role of immunosuppression treatment, the patient's immune response, and the genetic or viral factors that influence the susceptibility to HBV reinfection remain areas that need further research. It is well documented that the immune status of the patient, as well as the degree of immunosuppression, have a significant impact on the outcome of post-transplant HBV management.[10]

Additionally, the analysis of demographic and clinical variables, such as age, gender, BMI, MELD score, and liver function, revealed no significant differences between the groups with different anti-HBs antibody titter on postoperative day-7 (p>0.05). This suggests that factors such as age, sex, and MELD score did not affect anti-HBs antibody titters in the early post-transplant period. These findings are valuable as they help highlight the factors that have various influences on the success of prophylactic treatment. It is particularly

Table 2. Comparison of Demographic and Clinical Characteristics Based on Anti-HBS Level

Variables	Anti HBS 7. Day		p
	<100 ıu/ml	>100 ıu/ml	
Age	50.55±14.81	52.53±9.34	0.581*
Recipient Height	1.7 (1.6-1.82)	1.72(1.5-1.85)	0.755**
Recipient Weight	77.73±15.94	78.56±15.28	0.874*
BMI	26.23±6.16	27.11±5.16	0.632*
MELD Score	16.64±5.03	18.93±6.37	0.274*
Survival Duration (Days)	157(11-287)	114(10-296)	0.499**

Variables are presented as mean±standard deviation or median (minimum-maximum) according to the normality of the distribution.

	n (%)	n (%)	p
Gender			
Female	2 (18.18)	8 (18.60)	1.0****
Man	9 (81.82)	35 (81.40)	
Diagnosis			
HBV	8 (72.73)	20 (46.51)	0.224***
HBV+HCC	3 (27.27)	23 (53.49)	
HBV DNA			
Negative	8 (72.73)	36 (83.72)	0.408****
Positive	3 (27.27)	7 (16.28)	
HDV RNA			
Negative	8 (72.73)	31 (72.09)	1.0****
Positive	3 (27.27)	12 (27.91)	

*: Mann Whitney U test; **: Independent sample t-test; ***: Yates's correction chi-square test; ****: Fisher's exact chi square; BMI: Body mass Index; MELD: The Model for End-Stage Liver Disease.

noteworthy that even in patients with HDV co-infection, the recurrence rates of HBV remained low. This emphasizes the fact that prophylactic treatment including combination of immunoglobulin and antiviral agents is effective even in the presence of HDV, which is known to complicate HBV infection and may alter its clinical course.[11] The importance of this lies in the fact that HDV coinfection is associated with a more severe clinical course of HBV infection, including a higher incidence of liver failure, thus posing greater challenges for disease management.The demonstrated efficacy of prophylactic therapies in these cases affirms the robustness of current therapeutic strategies.

Maintaining anti-HBs antibody titters above a protective threshold in most patients (above 100 IU/L) supports the surveillance strategy that is essential to ensure the success of the transplant. However, the study also suggests that more individualized approaches may be beneficial in further reducing recurrence rates. This may involve tailoring immunosuppression therapies and antiviral regimens based on the patient's baseline immunological status, viral load, and other genetic or environmental factors that influence the immune response.

The results of our study highlight the need for long-term follow-up to understand the persistence of HBV control and the long-term risks of recurrence. While the early results in this cohort are promising, ongoing surveillance of HBV DNA, anti-HBs levels, and liver function will be crucial in assessing the durability of the treatment and in identifying any delayed recurrences of HBV infection. Future studies are need that incorporates more diverse patient populations, longer follow-up periods, and the evaluation of alternative treatment regimens, including newer antiviral agents or personalized immunosuppression strategies, to optimize the prevention of HBV recurrence. Limitations of the study include patients who received liver transplantation after 2024, patients who received liver transplantation only due to hepatitis B, and only adult patients.

In conclusion, the results of this study demonstrate that the combination of HBIG and antiviral therapy can effectively control HBV recurrences in the post-transplant period. We observed low recurrence rates in the early postoperative period. These findings support the current prophylactic protocols for HBV management in liver transplant patients and suggest that further refinements and personalized

treatment strategies may hold the potential reduce the recurrence rates further. However, multi-center studies with high patient volumes and long-term follow-up are needed to confirm the findings and to optimize management strategies for patients with HBV-related liver disease undergoing transplantation.

Disclosures

Ethics Committee Approval: This study was approved by the Inonu University Scientific Research Publication Ethics Board (approval number: 2024/6685).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

References

1. Z. F. Xi and Q. Xia, "Recent advances in prevention of hepatitis B recurrence after liver transplantation," World Journal of Gastroenterology, vol. 21, no. 3, pp. 829–835, 2015.
2. C. Buchanan and T. T. Tran, "Current status of liver transplantation for hepatitis B virus," Clinics in Liver Disease, vol. 15, no. 4, pp. 753–764, 2011.
3. S. Hwang, C. S. Ahn, G. W. Song, K. H. Kim, D. B. Moon, H. B. Oh, et al., "Posttransplantation prophylaxis with primary high-dose hepatitis B immunoglobulin monotherapy and complementary preemptive antiviral add-on," Liver Transplantation, vol. 17, no. 4, pp. 456–465, 2011.
4. J. Chun, W. Kim, B. G. Kim, K. L. Lee, K. S. Suh, N. J. Yi, et al., "High viremia, prolonged Lamivudine therapy and recurrent hepatocellular carcinoma predict posttransplant hepatitis B recurrence," American Journal of Transplantation, vol. 10, no. 7, pp. 1649–1659, 2010.
5. A. N. Fox and N. A. Terrault, "The option of HBIG-free prophylaxis against recurrent HBV," Journal of Hepatology, vol. 56, no. 5, pp. 1189–1197, May 2012, doi: 10.1016/j.jhep.2011.08.026.
6. I. Fernández, C. Loinaz, O. Hernández, M. Abradelo, A. Manrique, J. Calvo, et al., "Tenofovir/entecavir monotherapy after hepatitis B immunoglobulin withdrawal is safe and effective in the prevention of hepatitis B in liver transplant recipients," Transplant Infectious Disease, vol. 17, no. 5, pp. 695–701, Oct. 2015, doi: 10.1111/tid.12434.
7. N. A. Terrault, et al., "Prophylaxis against hepatitis B recurrence in liver transplantation recipients," Liver Transplantation, vol. 21, no. 5, pp. 580–590, 2015.
8. B. Roche, et al., "Efficacy of anti-hepatitis B immunoglobulin and antiviral therapy in liver transplantation," Journal of Hepatology, vol. 62, no. 5, pp. 984–993, 2015.
9. J. Fung, et al., "Prevention of hepatitis B recurrence post-liver transplantation with oral nucleos(t)ide analogues," Hepatology, vol. 46, no. 1, pp. 106–112, 2007.
10. E. Gane, et al., "Long-term outcomes of anti-HBs immunoglobulin and lamivudine combination therapy in preventing hepatitis B recurrence post-transplant," Liver International, vol. 34, no. 5, pp. 666–676, 2014.
11. Y. F. Liaw, et al., "Management of hepatitis B in patients with coinfections, including HIV, HCV, or HDV," Journal of Hepatology, vol. 61, no. 1, pp. 423–432, 2014.
12. Baskiran, D. Y et al."Inonu University Experience in Hepatitis B Recurrence After Liver Transplantation".DOI:10.14744/jilti.2024.99609 J Inonu Liver Transpl Inst 2024;2(1):6–10