Risk factors for recurrent hepatitis B after liver transplantation: a systematic review and meta-analysis

Min Liu[1,2], Li-Ying Sun[1,2,3], Zhi-Jun Zhu[1,2], Shan-Shan Wu[4]

[1]Liver Transplantation Center, National Clinical Research Center for Digestive Diseases, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China;
[2]Clinical Center for Pediatric Liver Transplantation, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China;
[3]Intensive Care Unit, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China;
[4]Clinical Epidemiology and EBM Unit, National Clinical Research Center for Digestive Diseases, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China.

To the Editor: Hepatitis B virus (HBV) infection is a major global health problem associated with liver-related morbidity and mortality. Chronic HBV infection, defined as hepatitis B surface antigen (HBsAg) positivity, affecting approximately 257 million people worldwide. Chronic infection with HBV may result in the development of cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Liver transplantation (LT) remains the only curative treatment for HBV-related end-stage liver diseases.[1]

Unfortunately, before the advent of hepatitis B immunoglobulin (HBIG) and nucleos(t)ide analog (NA) therapy, the HBV recurrence after LT was almost universal.[2] The introduction of HBIG in the early 1990s was an important milestone in the prevention of post-LT hepatitis B recurrence. NA therapy in combination with or without HBIG has markedly reduced the risk of HBV reinfection.[3] However, <10% of transplanted patients still develop HBV recurrence. Recurrent HBV infection is associated with increased allograft dysfunction, cirrhosis of the allograft, and graft failure. The consequences of HBV recurrence after LT are serious with an early occurrence and rapid progression of liver diseases, which significantly decreased overall survival. The etiology of recurrent HBV infection remains largely indefinite, so evaluating the risk of HBV recurrence is crucial in devising an effective strategy against post-LT reactivation. However, the identification of the risk factors has failed to reach a consensus, and to date, there has been no adequate attempt to assess the risk factors for recurrent HBV. This study was conducted to summarize the available data to define the risk factors for recurrent HBV after LT.

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Relevant studies that described risk factors for recurrent HBV after LT were selected. We searched PubMed, EmBase, Web of Science, and Cochrane Library for studies published up to March 25, 2020. The search terms were "hepatitis B virus" and "recurrence" and "liver transplantation" or "hepatic transplant" and "risk factor" or "risk." The detailed search strategy in EmBase is presented in the Supplementary Material, http://links.lww.com/CM9/A621. We also searched the reference lists of key articles to identify additional relevant studies. Original articles were included if they met the following criteria: (1) reporting risk factors for HBV recurrence after LT; and (2) offering the hazard ratio (HR), risk ratio, relative risk, odds ratio, and its 95% confidence intervals (CI) of the risk factors for HBV recurrence. The exclusion criteria were: (1) duplicate publications; and (2) case reports, reviews, editorials, letters, and comments. When multiple articles involved the same population, the articles reporting the most complete data would be used. Recurrence of HBV infection after LT was defined as the reappearance of HBsAg in the sera of patients with or without detectable HBV deoxyribonucleic acid (DNA). However, only the patients who developed persistently detectable HBV DNA were shown to be at risk for clinical disease and graft loss. Two independent investigators reviewed the titles and abstracts, and consulted full text when abstracts did not provide sufficient information about the study. The quality of selected studies was evaluated by two reviewers with the Newcastle-Ottawa scale (NOS) for cohort studies and the risk for bias was assessed according to the PRISMA recommendations. We used Cochrane Review Manager (RevMan5.3, Microsoft, Redmond, WA, USA) for all statistical analyses.

Twenty-six studies enrolling a total of 11,925 patients (692 with HBV recurrence and 11,233 without HBV

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001580

Correspondence to: Li-Ying Sun, Liver Transplantation Center, National Clinical Research Center for Digestive Diseases, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong-an Road, Xi-Cheng District, Beijing 100050, China
E-Mail: sunxlx@outlook.com

Chinese Medical Journal 2021;134(19)
Received: 21-01-2021 **Edited by:** Li-Shao Guo

recurrence) were included in the meta-analysis. The flow diagram is shown in Supplementary Figure 1, http://links.lww.com/CM9/A622. There are 24 cohorts and two case-control studies. All the included studies had NOS scores ≥5, which were considered to be of high quality. Basic characteristics and quality assessment of the included research are shown in Supplementary Table 1, http://links.lww.com/CM9/A620. Risk factors for the recurrent HBV after LT included: pre-transplant HCC, HCC recurrence, serum HBV DNA $\geq 10^5$ copies/mL, hepatitis B e antigen (HBeAg) positivity, and HBIG monoprophylaxis.

The meta-analysis showed that the pre-LT HCC was a significant risk factor for HBV recurrence with a pooled HR of 3.56 (95% CI: 2.27–5.60, $P < 0.001$) [Supplementary Figure 2A, http://links.lww.com/CM9/A623]. The heterogeneity between the groups was high in the random-effects model, which disappeared when Shen 2015 trial was excluded; the HR ranged from 3.56 (95% CI: 2.27–5.60) to 4.08 (95% CI: 2.73–6.10), with a pooled HR of 7.89 (95% CI: 5.00–12.43, $P < 0.001$), which indicates that HCC recurrence after LT may increase the risk of developing recurrent HBV. Sensitivity analysis revealed that the Kiyici 2008 study was the source of statistical heterogeneity. The heterogeneity between the groups was high in the random-effects model [Supplementary Figure 2B, http://links.lww.com/CM9/A623], which was reduced when Kiyici 2008 trial was excluded; the HR ranged from 7.89 (95% CI: 5.00–12.43) to 6.02 (95% CI: 4.52–8.02). This heterogeneity may have been due to the different study designs. The Kiyici 2008 study is a case-control study, which is different from other studies. The pooled HR for HBV recurrence in patients with pre-operative serum HBV DNA levels $\geq 10^5$ copies/mL in comparison with those with serum HBV DNA levels $< 10^5$ copies/mL was 3.11 (95% CI: 1.91–5.06, $P < 0.001$). Sensitivity analysis revealed that Shen 2015 study was the source of statistical heterogeneity. The heterogeneity between the groups was high in the random-effects model [Supplementary Figure 2C, http://links.lww.com/CM9/A623], which disappeared when Shen 2015 trial was excluded; the HR ranged from 3.11 (95% CI: 1.91–5.06) to 3.51 (95% CI: 2.46–5.03). This heterogeneity may have been caused by the designing differences among the studies, involving the origin of the samples and the sample size. The pooled HR for HBV recurrence in patients with positive pre-transplant HBeAg in comparison with those with negative pre-transplant HBeAg was 2.61 (95% CI: 1.28–5.29) [Supplementary Figure 2D, http://links.lww.com/CM9/A623]. The meta-analysis showed that patients with HBIG monoprophylaxis were at a higher risk of HBV recurrence (HR = 6.86, 95% CI: 2.45–19.22) [Supplementary Figure 2E, http://links.lww.com/CM9/A623].

The objective of the current study was to assess the risk factors for HBV recurrence after LT using a meta-analysis to provide the best evidence for clinical strategies. We found that HCC before LT, HCC recurrence, HBV DNA $\geq 10^5$ copies/mL before LT, HBeAg positivity, and HBIG monoprophylaxis were risk factors for HBV recurrence. HBIG monoprophylaxis was a significant risk factor for developing HBV recurrence. Our findings are consistent with the included studies. However, more work is required to confirm the effect of HBeAg positivity on HBV recurrence. The American Association for the Study of Liver Diseases 2018 hepatitis B guidance recommended that all HBsAg-positive patients undergoing LT should receive prophylactic therapy with NAs with or without HBIG after LT regardless of pre-LT HBeAg status or HBV-DNA level. Nevertheless, HBIG monotherapy should not be used.[4] However, this conclusion was drawn based on only three studies, and more studies are required to validate this conclusion.

Pre-transplant HCC was a significant risk factor for HBV recurrence after LT.[5] Indeed, HBV covalently closed circular DNA has been detected in HCC, suggesting that HBV replication in tumor cells contributes to HBV recurrence after LT. The current meta-analysis showed pre-transplant HCC to be a significant risk factor for recurrent HBV. However, significant statistical heterogeneity was shown for this risk factor. This heterogeneity may have been due to designing differences among the studies, including the origin of the samples. Our meta-analysis also showed that HCC recurrence after LT was significantly related to HBV recurrence. Thus, HBV-related HCC patients who have recurrent HCC after LT require close virological monitoring.

HBV DNA $\geq 10^5$ copies/mL at the time of LT was another significant risk factor for HBV reinfection after LT. Considering the impact of HBV viral load at transplantation on the rate of HBV recurrence, antivirals should be used pre-transplant in all patients to achieve undetectable HBV DNA levels to reduce the risk of HBV recurrence. In addition, to reduce the impact of this risk factor for those on antiviral therapy who are awaiting LT, HBV DNA should be monitored regularly to observe antiviral efficacy and the development of viral resistance. Furthermore, rapid and sustained suppression of pre-transplant HBV DNA results in improved survival rates. However, in practice, the duration of pre-transplant antiviral therapy varies among patients because it largely depends on the predictability of transplant timing. Therefore, the goal of sufficiently reducing the HBV DNA level before LT may not be achieved in every recipient.

To conclude, our meta-analysis identified some risk factors for HBV recurrence after LT and may provide a basis for clinical prevention. Due to the limitations in this meta-analysis, more well-designed studies are needed to verify our findings. These findings may aid clinical practice in optimizing monitoring strategies.

Conflicts of interest

None.

References

1. Verna EC. Updated hepatitis B guidance: implications for liver transplant patients. Liver Transpl 2018;24:465–469. doi: 10.1002/lt.25037.
2. Yang JM, Chen LP, Wang YJ, Lyu B, Zhao H, Shang ZY, *et al*. Entecavir add-on Peg-interferon therapy plays a positive role in reversing hepatic fibrosis in treatment-naive chronic hepatitis B patients: a prospective and randomized controlled trial. Chin Med J 2020;133:1639–1648. doi: 10.1097/CM9.0000000000000857.

3. Yin XR, Liu ZH, Liu J, Liu YY, Xie L, Tao LB, *et al*. First line nucleos (t)ide analog monotherapy is more cost-effective than combination strategies in hepatitis B e antigen-positive chronic hepatitis B patients in China. Chin Med J 2019;132:2315–2324. doi: 10.1097/CM9.0000000000000445.
4. Terrault NA, Lok A, McMahon BJ, Chang KM, Hwang JP, Jonas MM, *et al*. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560–1599. doi: 10.1002/hep.29800.
5. Yu J, Ye Y, Liu J, Xu Y, Lou B, Zhu J, *et al*. The role of hepatitis B core-related antigen in predicting hepatitis B virus recurrence after liver transplantation. Aliment Pharmacol Ther 2019;50:1025–1036. doi: 10.1111/apt.15429.

How to cite this article: Liu M, Sun LY, Zhu ZJ, Wu SS. Risk factors for recurrent hepatitis B after liver transplantation: a systematic review and meta-analysis. Chin Med J 2021;134:2388–2390. doi: 10.1097/CM9.0000000000001580