

# Allografts Positive for Hepatitis B Surface Antigen in Liver Transplant for Disease Related to Hepatitis B Virus

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## Abstract

**Objectives:** Liver grafts from hepatitis B surface antigen-negative and anti-core antibody-positive donors are safe for liver transplant. However, the use of hepatitis B surface antigen-positive liver donors in liver transplants is controversial. We assessed the safety and effectiveness of liver transplants using hepatitis B surface antigen-positive liver grafts to patients with diseases related to hepatitis B virus.

**Materials and Methods:** We retrospectively reviewed 23 patients who had a deceased-donor liver transplant using hepatitis B surface antigen-positive liver grafts. All patients had end-stage liver disease secondary to hepatitis B virus infection. Recipients had oral entecavir and intravenous or intramuscular injection of hepatitis B immune globulin for > 1 year after the transplant.

**Results:** Two patients died from severe perioperative pneumonia, and the other 21 patients were followed for 9 to 38 months after transplant. All 21 patients remained hepatitis B surface antigen-positive. A repeat liver transplant was performed in

1 patient at 5 months after the initial transplant because of biliary ischemia. There were 3 patients who died from recurrent liver cancer at 9, 14, and 18 months after transplant. There were 18 patients (78%) who survived and 17 grafts (74%) that survived.

**Conclusions:** Liver transplant using hepatitis B surface antigen-positive liver grafts is safe for patients with end-stage liver disease secondary to hepatitis B virus infection.

**Key words:** *Hepatic failure, Cancer, Immune globulin, Antibody*

## Introduction

Liver transplant currently is the only effective way of treating end-stage liver disease. However, with improved surgical outcomes of liver transplants, live or deceased-donor shortage has become an increasing problem and the death rate of patients with severe liver disease awaiting a liver transplant has increased. To increase the donor pool, some liver transplant specialists have started to use marginal donors, including liver donors positive for hepatitis B core antibody (HBcAb). The safety of HBcAb-positive liver donors has been confirmed,<sup>1</sup> but there are reports citing the effect of using liver donors positive for hepatitis B surface antigen (HBsAg) for a liver transplant in patients with end-stage liver disease. To explore the safety and effectiveness of HBsAg-positive liver donors, we retrospectively analyzed 23 patients with end-stage liver disease related to hepatitis B virus who received HBsAg-positive deceased-donor liver transplants.

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## Materials and Methods

### Patients and liver donors

We reviewed the charts of 23 adult liver transplants with HBsAg-positive donor livers that were performed in the transplant center of First Affiliated Hospital of Sun Yat-Sen University from January 2007 to February 2010. All transplants were approved by the ethics committee of the hospital, and written, informed consent was obtained from every patient and/or his/her guardian. All patients were men (median age, 42.5 y; range, 29 to 61 y). Recipients had severe hepatitis B virus infection (15 patients) or primary hepatocellular carcinoma with liver cirrhosis (8 patients). None of the patients had concomitant infection with hepatitis C or D. All recipients were HBsAg-positive. Hepatitis B virus DNA was detected preoperatively with a polymerase chain reaction kit (Da An Gene Co., Ltd., Sun Yat-Sen University, Guangzhou, China); 15 recipients had  $> 1000$  copies/mL ( $1.33 \times 10^3$  to  $8.75 \times 10^8$  copies/mL) and 8 recipients had  $< 1000$  copies/mL before surgery (Table 1). Patients were tested for hepatitis B core antibody (HBcAb) and antigen (HBcAg) and hepatitis B extracellular core antibody (HBeAb) and antigen (HBeAg). All recipients received preoperative antiviral therapy with adefovir or entecavir (range, 5 to 107 days). All protocols were approved by the ethics committee of the institution before the study began, and the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration.

All deceased-donor liver donors were double checked as being HBsAg-positive with a 1-step test for the qualitative detection of HBsAg in serum, and hepatitis B virus DNA was tested by polymerase chain reaction in liver donor biopsy specimens.

### Patient treatment after transplant

All recipients were treated with a steroid-sparing immunosuppression regimen. Basiliximab (20 mg) for immunosuppressive induction therapy was administered by intravenous infusion once during surgery and again on the fourth postoperative day. Mycophenolate mofetil (750 mg every 12 h) was given orally on the first day after surgery and continued during follow-up. Tacrolimus (0.04 mg/kg/d) was started on the fourth postoperative day, and the dosage of tacrolimus was adjusted to maintain serum levels between 8 and 12 ng/mL; the

goal was to maintain serum tacrolimus levels from 6 to 10 ng/mL at 3 months and 5 to 8 ng/mL at 6 months after transplant.

Antimicrobial prophylaxis included piperacillin-tazobactam (4.5 g intravenously, 3 times daily, starting at surgery and continuing for 5 to 7 days after transplant), fluconazole (400 mg intravenously, once daily for 7 days), and ganciclovir (250 mg intravenously, twice daily for 2 weeks). Oral entecavir (0.5 mg daily, starting at initial admission) and hepatitis B immunoglobulin (HBIG) were used as therapy against hepatitis B virus. The HBIG infusions were given regularly at 10 000 units in the intraoperative anhepatic phase; 2000 units daily during the first postoperative week; and tapered to 2000 units, once weekly, from the second to the fourth postoperative week. After the fourth postoperative week, HBIG (400 units intramuscularly, once a month) was given during the second to sixth postoperative month and then once each 6 months ongoing.

### Follow-up monitoring indicators

Patients were monitored on postoperative day 1, 7, 14, 21, and 30 with serum hepatitis B antigen and hepatitis B virus DNA quantitative tests. We assessed the hemodynamics of the donor liver using color Doppler ultrasonography. These tests were performed once each month after the patients were discharged. All patients were followed up after discharge. Patients were asked to return for follow-up visits monthly for the first year after surgery, every 2 months during the second year after surgery, and every 3 months during the third year after surgery. By 6 years after surgery, follow-up interval was decreased to 6 months indefinitely. At follow-up visits, patients were evaluated for liver and renal function, acute rejection, infection, vascular complications, biliary complications, recurrence of hepatitis B virus infection, tumor recurrence, and patient survival. Survival curves were estimated using the Kaplan-Meier method.

## Results

After surgery, 2 patients died of multiple organ failure caused by severe fungal pneumonia. The other 21 patients recovered well at the time of discharge (follow-up, 9 to 38 months after surgery). All 21 alive patients remained positive for HBsAg

and HBcAb when this was reported. Among of them, 8 patients were positive for HBeAg, as they had been before surgery; 9 of patients were positive for HBeAb; the rest of the 4 patients remained negative for HBeAg and HBeAb. The hepatitis B virus DNA test showed that 8 patients had < 1000 copies/mL and 13 cases had > 1000 copies/mL (Table 1). At 1 month after liver transplant, there were 2 patients positive for HBsAg, HBeAg, and HBcAb that converted positive for HBsAg, HBeAb, and HBcAb. The serum level of hepatitis B virus DNA in all 21 patients was < 1000 copies/mL by the end of the first postoperative month.

Acute transplant rejection occurred in 1 patient at 2 weeks after transplant surgery, and this patient responded well to steroid pulse therapy with normalization of liver enzymes. Another patient required revision liver transplant (using a liver donor that was HBsAg-negative) because of biliary ischemia at 5 months after initial transplant; this patient was alive and maintained negative HBsAg serology to date. Three of 8 patients with hepatocellular cancer died of tumor recurrence at 9, 14, and 18 months after transplant; the other 5 patients with hepatocellular cancer survived tumor-free with normal donor liver function and low levels of serum hepatitis B virus DNA (< 1000 copies/mL).

At the most recent follow-up, 18 of 23 patients survived. Liver graft survival at 1 year after

transplant was 19 grafts (83%) and at 2 years after transplant it was 17 grafts (74%). Patient survival rate at 1 year after transplant was 87% and at 2 years after transplant was 78% (Figure 1). There was 1 patient that underwent revision liver transplant that converted from positive to negative HBsAg after transplant, and the other 17 patients remained HBsAg-positive. Among the 18 surviving patients, 5 patients remained positive for HBsAg, HBeAg, and HBcAb; 9 patients were positive for HBsAg, HBeAb, and HBcAb; and 3 patients were positive for HBsAg and HBcAb. The hepatitis B virus test showed that all 18 patients had < 1000 copies/mL. There was no occurrence of liver dysfunction, graft loss, or death attributed to recurrence of hepatitis B infection.

## Discussion

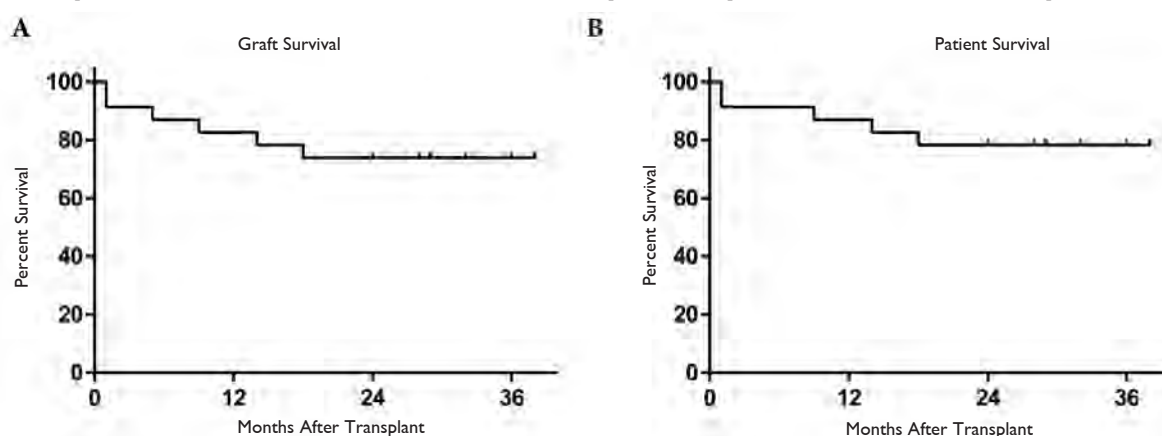
The results showed that the short-term survival was not diminished using HBsAg-positive liver grafts. However, further investigations are needed to evaluate the long-term effects of using HBsAg-positive liver grafts in liver transplant. With the large imbalance of available donor organs and necessary recipients, it is difficult to expand donor sources, including HBsAg-positive liver donors. China has a high incidence of hepatitis B, with 57.6% infection frequency according to national epidemiologic data, and the HBsAg carrier frequency is 9.8%. Thus, the

**Table 1.** Preoperative Clinical Characteristics of Liver Transplant Recipients\*

| Case No. | Age (y) | HBsAg | HBeAb | Hepatitis B Virus DNA Level<br>(Copies/mL) | ALT (U/L) | Bilirubin, Total<br>( $\mu$ mol/L) | PT (s) | INR  | Cr ( $\mu$ mol/L) |
|----------|---------|-------|-------|--------------------------------------------|-----------|------------------------------------|--------|------|-------------------|
| 1        | 53      | +     |       | $6.32 \times 10^5$                         | 237       | 254                                | 22     | 1.24 | 96                |
| 2        | 48      | +     |       | $1.65 \times 10^6$                         | 329       | 318                                | 28     | 1.85 | 107               |
| 3        | 56      | +     |       | $4.23 \times 10^5$                         | 196       | 296                                | 17     | 1.37 | 85                |
| 4        | 53      |       | +     | $< 1 \times 10^3$                          | 58        | 36                                 | 13     | 0.92 | 43                |
| 5        | 43      | +     |       | $2.55 \times 10^4$                         | 261       | 173                                | 19     | 1.03 | 94                |
| 6        | 29      | +     |       | $1.64 \times 10^6$                         | 435       | 308                                | 26     | 2.21 | 78                |
| 7        | 38      |       | +     | $< 1 \times 10^3$                          | 63        | 42                                 | 15     | 1.05 | 65                |
| 8        | 57      |       | +     | $< 1 \times 10^3$                          | 29        | 28                                 | 20     | 1.11 | 82                |
| 9        | 48      |       | +     | $< 1 \times 10^3$                          | 57        | 61                                 | 16     | 0.95 | 77                |
| 10       | 61      | +     |       | $8.75 \times 10^8$                         | 196       | 457                                | 31     | 2.36 | 126               |
| 11       | 39      |       | +     | $< 1 \times 10^3$                          | 46        | 35                                 | 17     | 1.07 | 61                |
| 12       | 45      | +     |       | $7.38 \times 10^3$                         | 214       | 637                                | 27     | 1.96 | 117               |
| 13       | 36      |       | +     | $< 1 \times 10^3$                          | 53        | 38                                 | 15     | 0.85 | 75                |
| 14       | 38      |       | +     | $1.33 \times 10^3$                         | 169       | 169                                | 22     | 1.53 | 90                |
| 15       | 42      | +     |       | $6.13 \times 10^6$                         | 301       | 297                                | 25     | 1.42 | 103               |
| 16       | 31      |       | +     | $1.78 \times 10^3$                         | 282       | 363                                | 23     | 1.98 | 112               |
| 17       | 55      | +     |       | $3.59 \times 10^5$                         | 239       | 385                                | 27     | 2.01 | 125               |
| 18       | 35      | +     |       | $2.08 \times 10^6$                         | 197       | 403                                | 19     | 1.76 | 94                |
| 19       | 44      |       | +     | $< 1 \times 10^3$                          | 34        | 29                                 | 13     | 1.03 | 68                |
| 20       | 51      |       | +     | $< 1 \times 10^3$                          | 39        | 47                                 | 17     | 1.08 | 59                |
| 21       | 36      | +     |       | $1.65 \times 10^3$                         | 163       | 578                                | 23     | 2.16 | 119               |
| 22       | 53      | +     |       | $4.43 \times 10^7$                         | 417       | 196                                | 27     | 1.31 | 202               |
| 23       | 49      | +     |       | $3.86 \times 10^4$                         | 247       | 205                                | 24     | 1.53 | 89                |

**Abbreviations:** ALT, alanine aminotransferase; Cr, creatinine; HBeAb, antibody to hepatitis B extracellular core antigen; HBeAg, hepatitis B extracellular core antigen; INR, international normalized ratio; PT, prothrombin time.

\*All 23 liver transplant recipients were men who were positive for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb).

**Figure 1.** Kaplan-Meier Plots for Liver Graft and Patient Survival After Orthotopic Liver Transplant With Donor Livers Positive for Hepatitis B Surface Antigen

(A) Cumulative graft survival plot, (B) Cumulative patient survival plot

ratio of HBsAg-positive liver donors to the whole liver donor pool is much higher in China than it is other countries or regions.

In recent years, with continued improvements in organ transplant, the effectiveness of liver transplant on improving morbidity and mortality has been confirmed.<sup>1</sup> A growing number of patients with end-stage liver disease are waiting for liver transplant. Most critically ill patients die while waiting for an available organ because of the shortage of liver donors, and only 20% patients in the world receive a transplant. Therefore, many transplant centers have attempted to use marginal liver donors, including individuals of older age (> 65 y), mild-to-moderate steatosis (5 to 25%), long intensive care unit stay with inotropic support (> 4 days), altered liver function tests, hypernatremia, hypotension requiring pressor drugs, moderately prolonged ischemia (cold ischemia time > 12 h), asystolic recovery, split liver, pediatric age, and hepatitis B virus.<sup>2-6</sup> According to an analysis of United Network for Organ Sharing, there was no significant increase in the risk of using HBcAb-positive donor livers.<sup>7</sup> In 4 HBsAb-positive and HBcAb-positive recipients who received living donor grafts from HBcAb-positive donors, 1 recipient with HBsAb titer < 10 IU/L developed hepatitis B at 4 years after transplant, and the other 3 patients with HBsAb titer > 10 IU/L did not develop measurable HBsAg.<sup>8</sup> The use of HBcAb-positive liver donors appears safe and feasible with the control of HBsAg relapse. However, the safety of using HBsAb-positive liver donors in liver transplant was unknown because of limited trials.

The safety of and prognosis after liver transplant surgery with HBsAg-positive liver donors is

controversial. Previous limited studies suggested that patients with HBsAg-positive liver donors may develop hepatitis B infection that is uncontrollable because of postoperative immunosuppression. Until now, there has been no prospective research or large comprehensive case series about this issue, and only several case reports had shown successful results with the use of HBsAg-positive liver donors.<sup>9-10</sup>

Recipients that are HBsAg-negative who receive a liver graft that is HBcAb-positive are more susceptible to developing fulminant hepatitis B virus infection after liver transplant than are HBsAg-positive recipients, even with immunoprophylactic HBIg therapy.<sup>11</sup> However, due to the latent hepatitis B virus infection in whole body of those HBsAg-positive recipients, it is not so accidental to have a hepatitis B virus sources in liver donor. Thus, it may decrease the risk of developing fulminant hepatitis B virus infection to HBsAg-positive recipients after receiving a liver graft that is HBsAg-positive. The recurrent infection frequency in HBsAg-positive recipients that received HBcAb-positive liver graft ranges from 0% to 70%.<sup>11-12</sup> The present results showed that 17 of 23 HBsAg-positive recipients (74%) received HBsAg-positive liver grafts, with survival ranging from 9 to 38 months without graft rejection and while maintaining the HBsAg-positive viral serology after liver transplant. Therapy with entecavir is efficient and safe when used in the prophylaxis and treatment of hepatitis B virus recurrence after liver transplant.<sup>13</sup> It is very important to maintain high serum levels of HBsAb titers early after liver transplant to prevent hepatitis B virus recurrence. Lifelong administration of intravenous HBIg is safe, and recurrence of hepatitis

B virus has occurred only in few patients during long-term follow-up.<sup>14</sup> Immunoprophylactic therapy with HBIG and entecavir, rather than HBIG and lamivudine, which have been used previously,<sup>15</sup> was safe and effective in patients with liver grafts that were HBsAg-positive.

Large doses of steroids and immunosuppressive drugs are closely associated with the postoperative recurrence of hepatitis B and hepatitis C after liver transplant.<sup>16-17</sup> Discontinuation of steroids early after liver transplant can significantly reduce the risk of hepatitis B recurrence.<sup>18-19</sup> The present study also confirmed that discontinuing steroids early after liver transplant is a safe and effective immunosuppression strategy without increasing the frequency of acute rejection.<sup>20-23</sup> In the present study, we used basiliximab induction and a steroid-sparing immunosuppressive regimen (mycophenolate mofetil and tacrolimus), which was associated with a low incidence of acute rejection; only 1 of 23 patients had acute rejection, similar to that previously reported, and this was reversed by large doses of steroid therapy.<sup>24</sup> In the present study, 2 patients died of perioperative pulmonary infection, and 3 patients died of tumor recurrence. There were no clinical recurrences of hepatitis B virus infection in all patients who had follow-up. Therefore, this steroid-sparing immunosuppressive regimen was effective for liver transplant.

In summary, the present study suggests that HBsAg-positive livers can be safely transplanted to patients with hepatitis B virus-related end-stage liver disease. Nucleoside analogues in combination with HBIG and steroid-sparing immunosuppressive regimens are effective in reducing the risk of recurrent hepatitis B virus infection. The use of HBsAg-positive liver donors does not affect the survival and efficacy of liver transplant. However, further study is required to determine the long-term prognosis of HBsAg-positive donors in liver transplant.

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