Epidemiological characteristics of de novo hepatitis B infection in liver transplant recipients—An experience from a tertiary care centre in Qatar

Arun P. Nair¹ | Sreethish Sasi² | Muna S. Al-Maslamani¹ | Prem Chandra³ | Samar A. Hashim¹ | Sulieman Abu Jarir¹ | Moutaz Derbala⁴

Abstract

Background: The emergence of hepatitis B surface antigen in a patient with previously negative hepatitis B virus (HBV) serology post-orthotrophic liver transplant (OTLX) is known as de novo hepatitis B (DNHB). As there are no data on patients with DNHB available from Qatar, we aim to do a pioneer study indexing their clinical profile and epidemiology of patients with DNHB in Qatar.

Materials and Methods: This descriptive epidemiological study was done by retrospectively reviewing records of 159 post-OTLX patients. HBV serology of these patients post-OTLX was reviewed, and 17 were identified as DNHB cases. Baseline epidemiological characteristics were defined and compared between DNHB cases and the rest. DNHB cases were analyzed statistically using the chi-square test and Kaplan-Meier curve.

Results: The majority of the subjects were men (65%) and Qataris (40%). Mean age was 57.4 ± 12.5 years. Bulk of them underwent OTLX in China (44%). The overall incidence of DNHB was 10.7%, with transplants in China having significantly higher incidence than transplants from all other countries. The mortality rate was 23.5% in DNHB cases compared to 2.8% in non-DNHB. 67% of patients survived at least 64 months after the diagnosis of DNHB. Five-year survival did not vary significantly between those with DNHB and those without.

Conclusion: Orthotrophic liver transplant in centers selecting donors liberally without screening for HBV poses the risk of DNHB. We recommend having protective levels of HBs antibodies before OTLX. Prophylactic antiviral treatment should be considered until peri-operative HBV transmission has been excluded by screening hepatic tissue for HBV DNA.

Keywords
antiviral agents, de novo B, hepatitis B, immunosuppression, liver transplantation
1 | INTRODUCTION

The appearance of hepatitis B surface antigen (HBsAg) in a patient with previously negative hepatitis B serology post-orthotopic liver transplantation (OTLX) is known as de novo hepatitis B (DNHB). The etiology of DNHB may be a transfusion of blood product, infection in donor liver or occult pre-transplant infection in the recipient. Internationally, there is an increasing demand and burden of shortage for donor livers, which is more pronounced in the middle eastern countries due to the high prevalence of hepatitis B and hepatitis C. Hence, liver from hepatitis B core antibody (HBCab)-positive donors is being increasingly used, which, however, has the risk of higher hepatitis B virus (HBV) reactivation post-OTLX due to immunosuppressive therapy. Many international studies have shown that HBcAb-positive grafts can be donated safely, and adequate antiviral prophylaxis decreases post-OTLX reactivation of HBV significantly. Risk of DNHB post-OTLX has been reported as highly variable, ranging from 16% to 88% in international studies and 5% to 7% in studies from the middle east region. However, there are no studies available indexing the clinical profile and epidemiology of patients with DNHB post-OTLX from the state of Qatar.

2 | PATIENTS AND METHODS

A retrospective analysis of a prospectively maintained medical record database was conducted in a cohort of 159 patients who were citizens or residents in Qatar, underwent transplantation in various parts of the world, and were followed up in Liver Transplantation Clinic at Hamad Medical Corporation. The period of transplantation was from 1986 to 2018, and the period of follow-up evaluated was from 2011 May to 2018 May. Liver transplantation program in Qatar was officially started in December 2011. Still, patients had to travel abroad for transplantation because of the limited capacity of local transplant facilities, lack of compatible donors, and long waiting lists. However, most of these patients had post-operative follow-up in Liver Transplantation Clinic at Hamad Medical Corporation, which was started in 2008. Patients fit for liver transplantation were evaluated by a multidisciplinary team involving experts from hepatobiliary surgery, gastroenterology, infectious diseases, and radiology. A pre-transplant workup was done every 6 months until the donor was available and repeated within 1 week before transplantation. A complete set of investigations including blood type, antibody screen, viral hepatitis profile, serum hepatitis C virus (HCV)-RNA titers, HCV genotype, HBV DNA, hepatitis B envelope antigen (HBcAg) and antibody, autoimmune markers, iron and copper studies, immune protein electrophoresis, tumor markers, complete blood count, complete metabolic panel, coagulation studies, fibrinogen levels, cytomegalovirus status, quantiferon testing, varicella titters, and cryptococcal antibodies was performed pre-operatively. Hepatitis A and hepatitis B, annual influenza, and pneumococcal vaccines were administered. A protective level of hepatitis B antibody titer was defined as ≥10 IU/L.

Post-operative visits were monthly during the first 6 months and then every 2 months. Hepatitis B serology, HBV DNA, and liver imaging were done every 6 months during the first year, then yearly, or earlier if there is a significant rise in transaminase levels. Biopsy of the transplanted liver was done annually or with changes in serum transaminase levels. The DNHB patients in this study were defined as those who were tested negative to HBsAg before transplantation but positive to the same at any time after the procedure, provided other possible modes were ruled out. DNHB patients were evaluated further with HBV DNA titer, elastography, and liver biopsy to assess the grade of hepatitis and stage of fibrosis. Our treatment protocol was entecavir 0.5 mg once daily. Hepatitis B immunoglobulin (HBIG) was not used in any of the cases. Prospectively maintained records in the Liver Transplant Clinic were reviewed retrospectively for demographic, transplant, treatment, and follow-up related information of DNHB cases.

2.1 | Statistical analysis

The normally distributed data and results were reported with mean and SD; the remaining results were reported with median and interquartile range. Categorical data were summarized using frequencies and percentages. Preliminary analyses were conducted to examine the distribution of the data variables using the Kolmogorov-Smirnov test. Associations between two or more qualitative variables were assessed using the Chi-square ($\chi^2$) test, Fisher exact, or Yates-corrected chi-square tests as appropriate. Quantitative data and outcome measures between the two independent groups were analyzed using unpaired “t” test (or Mann-Whitney U test for skewed data). Survival functions were estimated with the Kaplan-Meier survival curve method. Additionally, the mean duration of follow-up with 1- and 5-year survival proportions was also calculated, and for those who did not survive, the cause of mortality was recorded. This was further classified into liver-related and unrelated causes of mortality and included in statistical analysis. Pictorial presentations of the key results were made using appropriate statistical graphs. All $P$ values presented were two-tailed, and $P < .05$ were considered as statistically significant. All statistical analyses were done using statistical packages SPSS 22.0 (SPSS Inc) and Epi-info (Centers for Disease Control and Prevention) software.

3 | RESULTS

One hundred fifty-nine patients from Qatar underwent liver transplantation during 1986–2019. Among them, 65% were males, and mean age was 57.4 ± 12.5 years. The availability of donor information was limited as most patients (138 out of 159) underwent transplantation in centers abroad. Hence, the donor profile was excluded from the scope of this study. The most common indication for LT was HCV-related cirrhosis in 95 patients. According to the definition, 17 patients were deemed to be DNHB-positive. None of
TABLE 1  Epidemiology profile of DNHB cases

| No. | Sex/age | Indication For OTLX* | Type of LT | Immunosuppression | Onset of DNHB (Mo.) | Rx | F/U (Mo.) after DNHB Dx | TB | AST | ALT | Liver biopsy | Hepatitis | Fibrosis | Elastography | Survival |
|-----|---------|----------------------|------------|-------------------|---------------------|----|------------------------|----|-----|-----|-------------|-----------|----------|--------------|---------|
| 1   | 48/M    | HCV                  | DDLT       | Tac + MMF         | 9.0                 | TDF| 10.9                   | 10 | 18  | 53  | III         | IV        | 4.51     | +            |         |
| 2   | 38/F    | CLD                  | DDLT       | Tac + MMF         | 13.7                | ETV| 16.9                   | 16 | 57  | 53  | I           | I         | 3.60     | +            |         |
| 3   | 50/M    | HCV                  | DDLT       | Tac + MMF         | 15.9                | 3TC| 61.1                   | 14 | 22  | 24  | NA          | NA        | NA       | +            |         |
| 4   | 56/F    | HCV                  | DDLT       | Tac + MMF         | 21.9                | ETV| 78                     | 16 | 36  | 35  | NA          | NA        | 7.78     | +            |         |
| 5   | 54/M    | HCV                  | DDLT       | Tac + MMF         | 23.4                | ETV| 82.8                   | 8  | 10  | 20  | II          | II        | 6.44     | +            |         |
| 6   | 57/M    | ALD + HCV            | DDLT       | Tac + MMF         | 25.9                | ETV| 63.9                   | 8  | 154 | 169 | III         | III       | NA       | −            |         |
| 7   | 57/M    | CC                   | DDLT       | Tac + MMF         | 26.8                | ETV| 61.2                   | 9  | 115 | 106 | I           | I         | 5.61     | +            |         |
| 8   | 60/F    | HCV                  | DDLT       | Tac + MMF         | 26.8                | ETV| 61.2                   | 9  | 115 | 106 | I           | I         | 5.61     | +            |         |
| 9   | 76/M    | HCV                  | DDLT       | Tac + MMF         | 38.1                | ETV| 38.9                   | 31 | 42  | 62  | NA          | NA        | NA       | −            |         |
| 10  | 54/M    | HCV                  | DDLT       | Tac + MMF         | 49.9                | ETV| 76.1                   | 6  | 20  | 17  | II          | II        | 6.91     | +            |         |
| 11  | 53/M    | HCV                  | DDLT       | Tac + MMF         | 50.1                | TDF| 85.9                   | 33 | 39  | 60  | II          | II        | 8.18     | +            |         |
| 12  | 61/M    | HCV                  | DDLT       | Tac + MMF         | 51.1                | ETV| 38                     | 13 | 77  | 89  | II          | II        | NA       | −            |         |
| 13  | 74/F    | CC                   | DDLT       | Tac + MMF         | 54.5                | TDF| 66.6                   | 21 | 29  | 24  | NA          | NA        | 7.42     | +            |         |
| 14  | 38/M    | CC                   | DDLT       | Tac                | 60.1                | ETV| 123.3                  | 11 | 94  | 140 | I           | I         | NA       | +            |         |
| 15  | 67/F    | HCV                  | DDLT       | Tac + MMF         | 79.9                | Nil| 1.1                    | 21 | 98  | 92  | NA          | NA        | 10.14    | +            |         |
| 16  | 44/M    | AI                   | DDLT       | Tac                | 83.4                | TDF| 57.7                   | 10 | 27  | 41  | NA          | NA        | NA       | +            |         |
| 17  | 65/M    | AI                   | DDLT       | Tac + MMF         | 92.4                | ETV| 47.7                   | 11 | 46  | 78  | NA          | NA        | 6.28     | +            |         |

Note: The table describes the complete epidemiological profile of all patients diagnosed with de novo hepatitis B post-liver transplant.

Abbreviations: 3TC, lamivudine; ALT, alanine aminotransferase in U/L; AST, aspartate aminotransferase in U/L; DDLT, dead donor liver transplant; DNHB, de novo hepatitis B; ETV, entecavir; MMF, mycophenolate mofetil; Tac, tacrolimus; TB, total bilirubin in µmol/L; TDF, tenofovir disoproxil fumarate.

*aReason for undergoing liver transplantation: AI, autoimmune liver cirrhosis; ALD, alcoholic liver disease; CC, cryptogenic liver cirrhosis; CLD, cholestatic liver disease; HCV, hepatitis C virus-related cirrhosis.

*bGrade of hepatitis and stage of fibrosis is determined based on the Scheuer scoring system.

*cMean elastography score of liver determined by ultrasound examination.

*dPatients who survived till end of the study are represented by + and those who died during the period of follow-up are represented by −. Dx, diagnosis.
| Pt.no | Serological markers | Before OTLX | Date of OTLX | Date of DNHB | At seroconversion | Duration of follow-up after OTLX (mo) |
|-------|---------------------|------------|--------------|--------------|------------------|--------------------------------------|
| 1     | HbsAg/Ab -/-        | 02-09-2016 | 04-06-2017   | 9 +/-        | 19.8             |
|       | HbcAb -             |            |              |              |                  |
|       | HbeAg/Ab -/-        |            |              | +/-          |                  |
|       | HBV DNA Undetectable|            |              | +/-          |                  |
| 2     | HbsAg/Ab -/-        | 01-12-2006 | 23-01-2008   | 13.7 +/-     | 137              |
|       | HbcAb -             |            |              | +           |                  |
|       | HbeAg/Ab -/-        |            |              | +/-          |                  |
|       | HBV DNA >110 000 000|            |              | <20          |                  |
| 3     | HbsAg/Ab -/-        | 01-12-2011 | 31-03-2013   | 19.9 +/-     | Lost follow-up after 66.4 mo |
|       | HbcAb +             |            |              | +           |                  |
|       | HbeAg/Ab -/-        |            |              | +/-          |                  |
|       | HBV DNA Undetectable|            |              | Undetectable|                  |
| 4     | HbsAg/Ab -/+        | 05-01-2010 | 01-11-2011   | 21.9 +/-     | 100              |
|       | HbcAb -             |            |              | +           |                  |
|       | HbeAg/Ab -/-        |            |              | +/-          | +/-              |
|       | HBV DNA Undetectable|            |              | 110 000 000  | Undetectable     |
| 5     | HbsAg/Ab -/-        | 01-07-2009 | 12-06-2011   | 23.4 +/-     | 106              |
|       | HbcAb -             |            |              | +           |                  |
|       | HbeAg/Ab -/-        |            |              | +/-          | +/-              |
|       | HBV DNA Undetectable|            |              | 87 451 944   | Undetectable     |
| 6     | HbsAg/Ab -/-        | 01-05-2010 | 27-06-2012   | 25.9 +/-     | 89.7             |
|       | HbcAb -             |            |              | +           |                  |
|       | HbeAg/Ab -/-        |            |              | +/-          | +/-              |
|       | HBV DNA Undetectable|            |              | 49 658 203   | Undetectable     |
| 7     | HbsAg/Ab -/-        | 01-01-2011 | 27-03-2013   | 26.8 +/-     | 87.9             |
|       | HbcAb -             |            |              | +           |                  |
|       | HbeAg/Ab -/-        |            |              | +/-          | +/-              |
|       | HBV DNA Undetectable|            |              | >110 000 000 | 21               |
| 8     | HbsAg/Ab -/+        | 10-09-2008 | 05-12-2010   | 26.8 +/-     | 48               |
|       | HbcAb -             |            |              | +           |                  |
|       | HbeAg/Ab -/-        |            |              | +/-          | +/-              |
|       | HBV DNA Undetectable|            |              | Undetectable| Undetectable     |
| Pt. no | Serological markers Before OTLX | Date of OTLX | Date of DNHB | At seroconversion | Most recent | Duration of follow-up after OTLX (mo) |
|--------|---------------------------------|--------------|--------------|-------------------|-------------|--------------------------------------|
| 9      | HbsAg/Ab −/−                     | 02-01-2007   | 07-03-2010   | 38.1              | +/-         | 77                                   |
|        | HBcAb –                          |              |              |                   | +           |                                      |
|        | HBeAg/Ab −/−                     |              |              |                   | −/−         |                                      |
|        | HBV DNA Undetectable             |              |              |                   | <60         |                                      |
| 10     | HbsAg/Ab −/−                     | 01-11-2007   | 29-12-2011   | 49.9              | +/-         | 126                                  |
|        | HBcAb –                          |              |              |                   | +           |                                      |
|        | HBeAg/Ab −/−                     |              |              |                   | +/−         |                                      |
|        | HBV DNA Undetectable             |              |              |                   | 57 818      |                                      |
| 11     | HbsAg/Ab −/−                     | 01-01-2007   | 06-03-2011   | 50.1              | +/-         | 136                                  |
|        | HBcAb +                          |              |              |                   | +           |                                      |
|        | HBeAg/Ab −/−                     |              |              |                   | +/−         |                                      |
|        | HBV DNA Undetectable             |              |              |                   | 25 031 310  |                                      |
| 12     | HbsAg/Ab −/−                     | 01-12-2006   | 03-03-2011   | 51.1              | +/-         | 38.2                                 |
|        | HBcAb –                          |              |              |                   | +           |                                      |
|        | HBeAg/Ab −/−                     |              |              |                   | +/−         |                                      |
|        | HBV DNA Undetectable             |              |              |                   | >110 000 000 |                                      |
| 13     | HbsAg/Ab −/+                     | 01-04-2008   | 14-10-2012   | 54.5              | +/-         | 121                                  |
|        | HBcAb –                          |              |              |                   | +           |                                      |
|        | HBeAg/Ab −/−                     |              |              |                   | +/−         |                                      |
|        | HBV DNA Undetectable             |              |              |                   | 1 204 431   |                                      |
| 14     | HbsAg/Ab −/+                     | 01-10-2005   | 03-10-2010   | 60.1              | +/-         | 151                                  |
|        | HBcAb –                          |              |              |                   | +           |                                      |
|        | HBeAg/Ab −/−                     |              |              |                   | +/−         |                                      |
|        | HBV DNA Undetectable             |              |              |                   | >110 000 000 |                                      |
| 15     | HbsAg/Ab −/−                     | 01-08-2011   | 29-03-2018   | 79.9              | +/-         | 81                                   |
|        | HBcAb –                          |              |              |                   | +           |                                      |
|        | HBeAg/Ab −/−                     |              |              |                   | +/−         |                                      |
|        | HBV DNA Undetectable             |              |              |                   | Undetectable |                                    |

(Continues)
them had history of blood transfusion, surgery, contact with hepatitis B positive individuals, dental procedures, tattooing, or hijama. The overall incidence of DNHB was 10.7%. Sixteen out of these 17 patients underwent OTLX in China and one in Qatar. OTLX in China had a higher incidence of DNHB compared to all other countries (22.6% vs 1.12%, relative risk [RR] = 20.34; CI 2.7, 149.7). The mean age of DNHB cases was 56 years, and male:female ratio was 2:3. Most of them were Qatars (10/17), followed by Egyptians (6/17) and Yemeni (1/17). The most common indication for OTLX in DNHB cases was hepatitis C in 10 patients, followed by autoimmune hepatitis in 2, cholestatic hepatitis in 1, and cryptogenic liver cirrhosis in 3. One patient had both HCV and alcoholic liver disease. The mean duration of follow-up was 100 months, and the mean onset of infection was 46 months after OTLX. Average HBsAb before the transplant was 24 IU/L, with five of them having HBsAb > 10 IU/L. HBsAb titer > 10 IU/L and > 100 IU/L were present in 29.4% and 11.7% of DNHB cases, respectively. None of them had HBsAb titer > 1000 IU/L before transplantation. Only one patient had HBsAb levels more than 1000 IU/L, whereas all other patients had levels <10 IU/L post-transplantation. Two of them were HBCAb-positive before transplant. Four out of nine patients with liver biopsy had hepatitis grade II and fibrosis stage II according to the Scheuer score, with a mean elastography score of 6.7 ± 1.9.

The complete epidemiological profile of infected cases is given in Table 1, and a complete serological profile before and after transplant is given in Table 2. A flowchart describing the outcome in these patients is shown in Figure 1.

Most of the patients were treated with entecavir or tenofovir. As they were under regular follow-up with monitoring of transaminase levels and hepatitis B serological status, no prophylactic treatment was given, even for the two patients with positive HBCAb before transplantation. Few of the patients who were treated in centers outside the country received lamivudine or tenofovir (as mentioned in Table 1). These patients were continued on the same drugs as long as they were stable. DNHB cases had a mortality rate of 23.5% compared to 2.8% for non-DNHB cases (RR 8.4, 95% CI 2.3-30.4, \( P = .0002 \)). However, 67% of patients survived at least 64 months after the diagnosis of DNHB (Figure 2). 93.8% of those with DNHB survived 5 years after OTLX compared to 96.4% of those without (\( P = .605 \)). Eight out of the total of 159 patients passed away during the period of follow-up, and six were due to liver-related causes. Attributable mortality to liver-related causes was 75% of all-cause mortality in both infected and non-infected groups. Various factors that might affect the mortality rate among DNHB cases were statistically analyzed and presented in Table 3.

Comparative statistical findings indicate that both the mean/median AST and ALT were significantly higher in patients who died compared to those who survived (\( P < .05 \)) (Figure 3). Similarly, mortality was found to be considerably higher in patients with a severe degree of fibrosis compared to mild-to-moderate degrees of fibrosis (\( P < .05 \)). Other characteristics such as age, gender, nationality, blood group, time from OTLX to the detection of DNHB, and antiviral treatment did not show any significant association.
with mortality. Moreover, younger age and female gender were positively associated with higher proportions of survival; however, these differences were not statistically significant (P > .05), as shown in Table 3. A scatter diagram describing the linear relationship of total bilirubin, AST, and ALT with the time of onset of infection is shown in Figure 4, and a ROC curve to determine optimal cutoff values for bilirubin, AST, and ALT in predicting mortality is shown in Figure 5.

4 | DISCUSSION

Chronic hepatitis B caused by the HBV affects 350 million people worldwide, causing mortality in 20% of them every year due to complications such as cirrhosis and liver cancer. In patients with end-stage liver disease, whether acute or chronic, liver transplantation is the treatment of choice. With the introduction of liver transplantation, the survival of patients with fulminant hepatic failure has improved from 50% to 85% at 1 year. The most frequent source of liver is donation after brain death, followed by living donor liver transplantation. However, there is a growing shortage of donor liver worldwide, leading to a prolonged waiting time. 15% of these patients on the waiting list die every year. Efforts to overcome the shortage have resulted in expanding the donor pool by using grafts from elderly donors, steatotic donors, donors with malignancies, donors with viral hepatitis, donation after circulatory death, use of split liver grafts, and donors with infections or metabolic derangements. The long waiting list forced 86.8% of the patients in our study to choose transplantation centers outside Qatar. 44% of these patients went to China for LT. It is estimated that 20%-30% of the population of the People's Republic of China is infected with the HBV. There is limited regulation or oversight of organ donation, and there was no national organ registry or network till 2005. The incidence of DNHB post-liver transplantation in our study (10.7%) is much higher compared to international data (1.7%-3.5%). This can be attributed to the fact that many patients chose to undergo LT in centers outside Qatar with liberal donor selection criteria such as China.
### TABLE 3  Association of demographic and various other parameters with mortality

| No. of patients | Survivala | Mortalityb | Chi-Square/t valuec | P-valuec | Mean/risk difference (95% CI) |
|-----------------|-----------|------------|---------------------|----------|-----------------------------|
| Age (in y)      | 13        | 4          | 1.47                | .160     | −8.82 (−21.56, 3.91)        |
| Gender          |           |            |                     |          |                             |
| Male            | 7 (63.6%) | 4 (36.4%)  | 2.85                | .277     | Reference                   |
| Female          | 6 (100%)  | 0 (0%)     |                     |          | −36.4 (−64.8, −7.9)         |
| Nationality     |           |            |                     |          |                             |
| Qatari          | 7 (70%)   | 3 (30%)    | 0.70                | .706     | Reference                   |
| Egyptian        | 5 (83.3%) | 1 (16.7%)  |                     |          | −13.3 (−54.5, 27.9)         |
| Yemeni          | 1 (100%)  | 0 (0%)     | −36.4 (−64.8, −7.9) |          |                             |
| Blood group     |           |            |                     |          |                             |
| A (+)ve         | 4 (66.7%) | 2 (33.3%)  | 2.18                | .536     | Reference                   |
| B (+)ve         | 4 (100%)  | 0 (0%)     |                     |          | −33.3 (−71.1, 4.4)          |
| O (+)ve         | 4 (66.7%) | 2 (33.3%)  |                     |          | −33.3 (−71.1, 4.4)          |
| B (−)ve         | 1 (100%)  | 0 (0%)     | −33.3 (−71.1, 4.4)  |          |                             |
| Country of transplant | |            |                     |          |                             |
| China           | 12 (75%)  | 4 (25%)    | 0.33                | .998     | Reference                   |
| Qatar           | 1 (100%)  | 0 (0%)     | −25 (−46.2, −3.8)   |          |                             |
| Indication for transplant | |            |                     |          |                             |
| HCV cirrhosis   | 8 (72.7%) | 3 (27.3%)  | 1.17                | .760     | Reference                   |
| Cryptogenic liver cirrhosis | 2 (66.7%) | 1 (33.3%)  |                     |          | 6.1 (−53.4, 65.4)          |
| Autoimmune hepatitis | 2 (100%)  | 0 (0%)     | −27.3 (−53.6, −0.96)|          |                             |
| Cholestatic liver disease | 1 (100%)  | 0 (0%)     | −27.3 (−53.6, −0.96)|          |                             |
| Number of patients with HbsAb titer > 10 IU/L before OTLX | 5 (38.4%) | 0 (0%)     | 2.18                | .416     | −33.3 (−60, −6.7)          |
| Elapse time from OTLX to DNHB | 44.7 ± 28.5 | 35.5 ± 11.8 | 0.62                | .546     | 9.2 (−22.5, 40.9)          |
| LFT at detection of DNHB | |            |                     |          |                             |
| Total bilirubin | 14.3 ± 7.3 (median 11, range 6-33) | 41.5 ± 49.3 (median 22, range 8-114) | 1.1 | .394 | −27.2 (−55.2, 0.85) |
| AST             | 47.0 ± 34.2 (median 36, range 10-115) | 181.5 ± 186.9 (median 115, range 42-453) | 1.4 | .042 | −134.5 (−243, −26.1) |
| ALT             | 58.8 ± 37.8 (median 53, range 17-140) | 135.5 ± 73.4 (median 129, range 62-222) | 2.0 | .041 | −76.7 (−134.1, −19.3) |
| Degree of fibrosis | |            |                     |          |                             |
| Normal-mild     | 4 (100%)  | 0 (0%)     | 6.63                | .036     | Reference                   |
| Mild-moderate   | 9 (90%)   | 1 (10%)    |                     |          | 10 (−8.6, 28.6)            |
| Severe          | 0 (0%)    | 3 (100%)   | −                   |          | −                             |
| Antiviral treatment | |            |                     |          |                             |
| Lamivudine      | 1 (100%)  | 0 (0%)     | 1.32                | .517     | Reference                   |
| Entecavir       | 7 (63.6%) | 4 (36.4%)  |                     |          | 36.4 (7.9, 64.8)           |
| Tenofovir       | 5 (100%)  | 0 (0%)     | −                   |          | NA                          |

Note: The table compares various demographic, clinical, serological, and radiological features between patients with DNHB who survived and who died. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DNHB, de novo hepatitis B; NA, not applicable; OTLX, orthotopic liver transplant.

*aThis group represents the patients with DNHB who survived till the end of follow-up.

*bThis group represents the patient with DNHB who died during the period of follow-up.

*cChi-square Fisher exact test was used for 2 × 2 tables and for tables more than 2 × 2, Yates-corrected chi-square test was applied in case of small cell frequencies (50% or more cells have expected frequencies < 5), whereas quantitative outcome measures were compared by using t test or Mann-Whitney U test (for skewed data) as appropriate to compute respective statistical P-value.
It is crucial to expand the donor pool. DNHB infections usually develop after LT using HBCAb-positive grafts, especially in patients with no prior exposure to HBV. The risk of transmission of hepatitis B to a liver transplant recipient is between 60% and 80% when the donor is HBCAb-positive. Hence, HBCAb-positive donors have not been preferred. However, recent reports suggest that the use of HBCAb-positive grafts may not be independently associated with poor outcomes. The majority of DNHB cases in our study are expected to have received HBCAb-positive donor livers, but donor information was not available. The outcome of patients with DNHB was not inferior compared to those without DNHB.

International data recommend HBsAb titer more than 1000 IU/L before transplantation. In our cohort, none of the patients had this level. It is recommended to maintain HBsAb titer more than 100 IU/L post-transplantation. 94% of the patients in our study had loss of HBsAb post-transplantation, and their titer was less than 10 IU/L. None of our patients received HBIG or nucleoside analogues (NA) as prophylaxis post-transplantation since donor data were not available. Liver transplantation (LT) from HBCAb-positive donors is being increasingly used due to the shortage of organs. In these patients, the risk of HBV reactivation is high after LT due to immunosuppressive therapy. In a study by Cholongitas et al, HBV recurrence was found to be 11% in HBsAg-positive LT patients who received HBCAb-positive grafts compared to HBCAb-negative grafts, but overall survival was the same in both groups. They also noted that without prophylaxis, HBV reactivation was 48% in naïve patients. In the early days, prophylaxis for recurrent HBV infection was given to HBsAg-positive patients using monotherapy with...
Bilirubin or lamivudine (3TC). This caused significant improvement of graft survival after LT, but the re-infection rates continued to be 30%-40%. Also, 3TC monotherapy resulted in the development of HBV reverse transcriptase mutations that lead to antiviral drug resistance. Combination therapies of HBIG with NA were successful in controlling HBV infection by reducing the HBV recurrence rate to less than 5%. DNHB infection rates in HBSAg-negative patients were reduced to 19%, 2.6%, and 2.8% using HBIG, 3TC, and combination, respectively. HBSAg seroclearance was observed in 35.2% (6/17) of DNHB patients in our cohort. Two each received treatment with entecavir and tenofovir monotherapy, one with their combination and one with lamivudine monotherapy. A meta-analysis by Zheng et al showed that entecavir was the best prophylactic option for reducing the risk of HBV recurrence when compared against 5 other regimens (entecavir, tenofovir, adefovir, lamivudine, lamivudine plus tenofovir, and lamivudine plus adefovir). Fung et al concurred that long-term entecavir monotherapy resulted in a durable HBSAg seroclearance rate of 92%, undetectable HBV DNA rate of 100% at 8 years, and excellent long-term survival of 85% at 9 years.

4.1 | Limitations
The determination of potential sources of HBV infection is of the utmost importance. Three possible routes (blood transfusions, recipient sources, and environmental factors) have been analyzed in this study. However, the non-availability of donor data made the evaluation of potential sources incomplete. This was not a controlled prospective work. Being retrospective in nature, follow-up and treatment strategies varied among patients. Our small number of patients limits the statistical power afforded by our data. Large, prospective, multicenter studies with long-term follow-up are required to provide statistically significant conclusions.

5 | CONCLUSION
Orthotopic liver transplant in centers selecting donors liberally without screening for HBV poses risk of DNHB. However, the 5-year survival of those with DNHB is comparable to those without DNHB. As there is a considerable demand for donor livers worldwide, patients can still be referred to such centers. However, it is prudent that accurate donor information with a clinical and serological profile should be made available by these centers. Recipients should be vaccinated and have protective levels of HBSAb more than 1000 IU/L before OTLX and more than 100 IU/L after OTLX. It is safe for patients with positive HBCAb and HBSAb to receive HBCAb-positive liver. If either of them is negative antiviral prophylaxis with NA is recommended post-LT. HBV naïve patients (negative for both HBCAb and HBSAb) ideally should not receive a liver from HBCAb-positive donors, but in case they do, prophylaxis with HBIG and lifelong NA is recommended post-LT.

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CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS
Arun Prabhakaran Nair involved in study design and concept, data entry, data analysis, manuscript preparation, and literature review. Sreethish Sasi (Corresponding author, Study guarantor) involved in data entry, data analysis, manuscript preparation, and literature review. Muna S. Al-Maslamani, Sulieman Abu Jarir, and Samar A. Hashim prepared manuscript and reviewed and edited the manuscript. Prem Chandra designed the study, analyzed the data, and prepared statistical tools. Moutaz Derbala (Mentor) involved in study design and concept, manuscript preparation, and manuscript review and editing.
ETHICAL APPROVAL

Ethical approval was obtained from Medical Research Center at Hamad Medical Corporation (approval number: MRC-01-18-333).

ORCID

Arun P. Nair https://orcid.org/0000-0001-5098-0172
Sreethish Sasi https://orcid.org/0000-0002-4098-0459
Moutaz Derbala https://orcid.org/0000-0003-2887-8328

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