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Low incidence of acute rejection in hepatitis B virus positive liver transplant recipients and the impact of hepatitis B immunoglobulin

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Abstract

Historically, hepatitis B virus (HBV) liver transplantation (LT) recipients have less acute cellular rejection (ACR) than those without HBV. We questioned whether this has persisted in an era of decreased Hepatitis B immunoglobulin use (HBIG) given its *in vitro* immunoregulatory effects.

We compared the incidence, risk factors and outcomes of ACR among 40,593 primary LT recipients with HBV, hepatitis C, steatohepatitis, and immune liver disease (OPTN 2000–2011). We also assessed the *in vitro* effect of HBIG on alloimmune lymphoproliferation and regulatory T cell generation using mixed lymphocyte reactions.

In multivariate analysis, HBV status remained a strong independent predictor of freedom from ACR (OR 0.58, 95% CI: 1.5–2.1). Patient (67.7% vs 72.3%) and graft (60.8% vs 69.1%) survival were significantly lower in patients with ACR versus no ACR for all causes except HBV. HBIG use had no statistical association with ACR. *In vitro*, HBIG at concentrations equivalent to clinical dosing did not inhibit lymphoproliferation or promote regulatory T cell development.

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The authors of this manuscript have no conflicts of interest to disclose.

In summary, the incidence and impact of ACR is lower now for HBV LT and does not appear to be secondary to HBIG by our *in vitro* and *in vivo* analyses. Rather, it may be due to the innate immunosuppressive properties of chronic HBV infection.

Keywords

Hepatitis B virus; Rejection; Liver transplantation; Hepatitis B immunoglobulin; Immunosuppression

1. Introduction

Hepatitis B virus (HBV) infects approximately 400 million persons worldwide causing over 1 million deaths per year [1]. Globally, 30% of cirrhosis and 53% of hepatocellular carcinoma cases are attributed to HBV, with liver transplantation (LT) as the main treatment option. From the mid-1990s until mid-2000s, the gold standard for prevention of HBV reinfection following LT has been hepatitis B immunoglobulin (HBIG) treatment with or without nucleos(t)ide antiviral analogues [2]. Over the past decade, more effective antiviral agents with low incidences of resistance (e.g. tenofovir, entecavir) have become available, allowing post-LT transition from long-term high-dose HBIG to short courses, lower doses or even no HBIG therapy [3]. Thus, the role of HBIG following LT to prevent HBV recurrence has become a major question, because of increased effectiveness of antiviral therapy [4–6]. Although given in much lower doses, HBIG may have immunological properties similar to intravenous immunoglobulin (IVIG), which among other mechanisms has inhibitory effects on dendritic cell presentation & T cell proliferation [7–9]. Prior to the year 2000, HBV+ LT recipients were reported to have lower acute cellular rejection (ACR) rates than those without HBV [10] perhaps attributable to the administration of HBIG. In the more recent era (2000-present), we hypothesized that rejection rates might have increased in HBV+ recipients given the paradigm shift away from HBIG therapy [7]. We also were interested in whether HBIG truly has *in vitro* immunoregulatory effects, which would support maintenance of HBIG for non-viral immunological reasons, rather than the trend to discontinue. Thus, our aim was to examine the relationship between HBV, HBIG use and rejection in the current era of LT.

2. Materials and methods

2.1. Clinical study design

A retrospective case-control study of primary LT was conducted for the following diagnoses: HBV, Hepatitis C virus (HCV), steatohepatitis (non-alcoholic steatohepatitis [NASH] and/or alcoholic cirrhosis) and immune-mediated liver disease (primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and/or autoimmune hepatitis). National data was obtained from the Organ Procurement and Transplantation Network (OPTN) Database. Local data was obtained using our center's electronic medical record to abstract more granular information on ACR (e.g. biopsy-proven ACR, treatment course) and HBIG use. All end stage liver disease (ESLD) patients 18 years of age who were listed for first liver or liver/kidney transplant from 1/1/2000 through 12/31/2011 were included to allow for at least

1 year of follow up data. Patients with a prior LT, status 1 listing, and with combined heart, lung, or pancreas transplants were excluded. The outcomes were to 1) determine the more recent prevalence of ACR and related patient/graft survival in HBV+LT recipients compared with the other groups listed above; 2) assess whether rejection rates in HBV were associated with use or non-use of HBIG; 3) identify other risk factors associated with ACR in relation to HBV.

Data from the OPTN database included the following: patient and donor age, gender, race, and BMI, donor/recipient gender matching, ABO blood type and CMV status, patient and donor health history, cold-ischemia time, calculated model for end-stage liver disease (MELD) score, laboratory values, presence of hepatocellular carcinoma (HCC), and immunosuppression regimens. HBIG use was defined as any recorded documentation of HBIG therapy following LT. Information on HBIG use was only available in 155 (7.6%) HBV+ LT recipients as this is not a required OPTN input field. However, there was no statistically significant difference in omitted data when HBV+ recipients were stratified by rejection status, age or sex. To improve the sensitivity of our national analysis, we also examined HBIG use in relation to biopsy-proven ACR at our own center. At our center ACR is treated by a standard protocol that includes Solu-Medrol 500 mg intravenously for 3 days, followed by a standardized oral prednisone taper and an increase in calcineurin inhibitor trough levels and/or the addition of mycophenolate mofetil based on time from liver transplantation. In OPTN, ACR was reported by each institution and may not have been biopsy-proven. Graft survival was defined as time from LT to graft failure, censoring for death with a functioning graft. Patient survival was defined as time from LT to patient death. Our institutional review board approved the data analysis.

2.2. In vitro study design

In this approach, we studied the effects of HBIG on the generation of regulatory T cells (Tregs) using our validated assays (Treg-MLR) with laboratory volunteer peripheral blood mononuclear cells (PBMC) [11–13]. We tested whether HBIG (supplied by Cangene®, Winnipeg, Canada) at indicated concentrations would inhibit MLRs but simultaneously generate CD4⁺CD127[−]CD25⁺FOXP3⁺ total Tregs and CD4⁺CD127[−]CD25^{High}FOXP3⁺ natural Tregs (nTregs) in contrast to cultures without HBIG. The research was conducted on HLA-typed human subjects after obtaining written consent.

2.2.1. Culture conditions—Responder PBMC (A) were labeled with CFSE following the manufacturer's instructions (labeling efficiency of >99%). They were stimulated with x-irradiated (3,000 RADS) PBMC labeled with PKH26 from 2 HLA-DR matched (Bx) vs. mismatched (Ix) volunteer donors, in 15% normal human AB serum containing complete media. The cultures were incubated at 37°C in a 5% CO₂ humidified atmosphere for 5, 7 ± 9 days before processing [11–13].

2.2.2. Assessment of proliferation—This was measured using both CFSE labeling in flow cytometry (as below) for cell counts and by standard ³H-TdR incorporation assays [11]. Radioactive incorporation was measured using a Packard-Beta counter (Meriden, CT). The Stimulation Index (SI) was calculated using the formula:

$$\frac{\text{CPM in experimental combinations}}{\text{CPM in responder plus x- irradiated autologous stimulator}}$$

For measuring inhibitory effects, the percentage of medium control was calculated using the formula:

$$\frac{\text{SI in HBIG combinations}}{\text{SI in media controls}} \times 100$$

2.2.3. Assessment of Treg generation by flow cytometry—The extent of proliferation and the expression of CD25 and FOXP3 were analyzed in CD4⁺ cells of the non-proliferating (CFSE high) and proliferating (CFSE low) populations that were negative for both CD127-PE and PKH26 (thus gating out CD127⁺ responders and any residual stimulators). Data were calculated as percentage of CD4⁺ cells that were CD127⁻CD25⁺FOXP3⁺ (total Tregs) or CD127⁻CD25^{High}FOXP3⁺ (nTregs).

2.3. Statistical analyses

Patient characteristics were compared between four indications for LT: HBV, HCV, steatohepatitis, and immune-mediated. Frequency counts and percentages are shown for categorical variables and were compared using chi-square or Fisher's exact tests. Means and standard deviations are shown for continuous variables and analyzed using t-tests and analysis of variance with Tukey tests for post hoc comparisons. Medians and interquartile ranges are shown for continuous variables that deviated from normality and were compared using Wilcoxon tests. Unadjusted logistic regression models were utilized to find univariate predictors of acute cellular rejection in all patients as well as in the subset of patients with HBV. A multivariate logistic regression model to predict ACR was constructed using variables deemed important *a priori*: age, race, HBV status, and immunoprophylaxis use. Patient and graft survival were estimated using Kaplan-Meier methods and differences between groups were analyzed using log-rank tests. For the Treg-MLR, Student T-tests and Wilcoxon signed rank tests for parametric and non-parametric calculations respectively were used. The SAS statistical software version 9.3 (SAS Institute Inc, Cary, NC) was used for all data analyses.

3. Results

3.1. Recipient characteristics

Over the 10-year study period, 40,593 liver transplantations for HBV, HCV, steatohepatitis, and immune-mediated liver disease were identified in the OPTN [Table 1]. Of these, 2035 (5%) were HBV+. HBV+ recipients were 53.1 ± 9.5 years of age and were more likely to be male, Asian, and have HCC compared to those without HBV (p < .0001). The mean calculated MELD score in HBV+ recipients (18.7 ± 12.2) was significantly lower than recipients with steatohepatitis (21.4 ± 9.5, p < .0001), but similar to other causes. Of 1,077 LT performed at our center during the same study period, 64 (5.9%) were due to HBV. They were 52.8 ± 7.2 years of age, 83.6% male and 27.9% Asian.

3.2. Acute cellular rejection

From the OPTN data, 8425 (21%) had at least one ACR episode. Univariate predictors of ACR included HBV, young age, female sex, black race, HCC status, female gender, donor age, graft cold ischemia time, and donor-recipient gender matching (Table 2). In multivariable analysis adjusted for age, gender, and immunosuppression, HBV status remained a strong negative predictor of ACR (OR = 0.58, 95% CI: 0.51–0.67, $p < 0.001$, Fig. 1). Overall graft (60.8% vs. 69.1%) and patient (67.7% vs. 72.3%) survival were significantly lower in those with ACR compared to those without ACR, except in HBV+ recipients where there was a trend toward lower patient but not graft survival (Fig. 2A and B) (see Table 3).

Only 155 HBV+ recipients had available information on HBIG use in the OPTN data (100 HBIG, 55 no HBIG). There was no statistically significant association between HBIG (17% vs. no HBIG (7.2%) and rejection using OPTN data ($p = 0.09$, Table 4). In our own center-specific analyses, there was also no statistically significant association between HBIG use and biopsy-proven ACR (18.8% with HBIG vs. 12.5% without HBIG, $p = 0.56$, Table 4).

3.3. Direct effect of HBIG on lymphoproliferation in MLR

Increasing concentrations of HBIG (0 and 0.78–100 $\mu\text{g/mL}$) equivalent to clinical blood concentrations were tested in MLRs using PBMC of healthy volunteers ($n = 7$). The CPM (shown) was also converted to stimulation indices (Fig. 3A), with calculations to percentages of medium control to account for variability between individual volunteer responders (Fig. 3B). HBIG (i) did not have mitogenic effects (top), (ii) did not inhibit MLRs of normal laboratory volunteers to HLA-DR matched (middle) or completely mismatched (bottom) stimulators. This lack of effect was over a wide concentration range of HBIG covering sub-therapeutic ($<8 \mu\text{g/mL}$), therapeutic and even supra-therapeutic ($>42 \mu\text{g/mL}$) levels.

3.4. Direct effect of HBIG on the generation of new Tregs in MLR

CFSE labeled responding PBMC were cultured with PKH26 labeled x-irradiated stimulator cells in the presence of 0 and 0.78–50 $\mu\text{g/mL}$ HBIG for 5, 7 and 9 days. Then flow cytometric analyses were performed (Methods) with the gating strategy shown in Fig. 4A. As previously reported with other agents [11–13], we tested the influence of HBIG on the development of newly generated Tregs in the proliferating fraction (Fig. 4B and C). The percentage of CD127⁺CD25⁺FOXP3⁺ total Tregs in the medium controls without HBIG comprised 10–40% of the CD4⁺ cells in the proliferating fraction depending on individual MLR combinations in each experiment, with the percentage of CD127⁺CD25^{High}FOXP3⁺ nTregs being slightly lower, also consistent with previous observations [11–13]. There was no significant effect of HBIG in any concentration on the generation of these Tregs in culture over that of media controls, in contrast to other immunoregulatory agents tested previously [12,13].

4. Discussion

Several key findings in this report provide insight on ACR and the potential impact of HBIG over the most recent decade of LT for HBV. Consistent with historical data, HBV+ LT

recipients in the current era have the lowest incidence of ACR of all LT recipients, and HBV is a strong independent predictor of lack of rejection on multivariate analysis. In addition, patient and graft survival does not appear to be affected by ACR compared to non-HBV+ recipients. This low ACR rate is likely independent of HBIG use, as there was no association from both national and local data. However, both data sets are limited by the small sample sizes recorded as being treated with/without HBIG. Finally, supporting no definitive association between HBIG and less rejection, HBIG at clinically applicable concentrations does not appear to inhibit immune responses or promote Treg development and expansion in MLR.

Our results confirm previous studies that have reported a low incidence of ACR following LT for HBV in the 1980s–90s, although mechanisms for this association have not been fully elucidated [8,10]. Chronic HBV infection is the result of an inadequate immune response towards the virus. Dendritic cells of patients with chronic HBV are impaired in their maturation and function, resulting in more tolerogenic rather than immunogenic responses and viral persistence [14]. Dendritic cells represent the most potent antigen-presenting cells and thus play an important role in the induction of specific T-cell rejection responses following organ transplantation. Thus, down-regulation of innate immunity may explain a mechanism whereby HBV+ recipients exhibit lower ACR rates [14]. This is in contrast to other viral hepatitis, such as HCV, in which the virus evades (rather than actively downregulates) host innate immune signaling through cleavage of immune signaling adaptor proteins, effectively inactivating viral RNA detection which contribute to persistence and chronicity [15,16].

Prior *in vitro* studies have also tested the impact of HBIG on alloimmune responses [10,17], in that similar to IVIG, it might inhibit the *in vitro* equivalent of acute rejection, the MLR, by suppressing lymphoproliferation, cytokine production and dendritic cell maturation [17–19]. Our *in vitro* studies, however, demonstrated the “inertness” of HBIG, i.e. there was no mitogenic or stimulatory capability, unlike other antibodies [20], and no inhibitory effect on normal MLRs. Most importantly, in contrast to prior reports on HBIG [17] and IVIG [18,19], HBIG at therapeutic concentrations did not show any enhancing (or inhibitory) role on the generation of regulatory T cells. With more centers using limited amounts of HBIG in favor of oral agents to prevent viral reactivation [5,6,20–22], this practice does not appear to have the consequence of higher rates of ACR.

There are important limitations to this study. First, data mainly came from a national database (OPTN) that has missing clinical variables. Information on HBIG use was only available in 7.6% of the HBV+ LT recipients, raising the possibility of type II error. Second, OPTN data are limited by the heterogeneity of program practices and lack of uniformity in follow-up. One seemingly counterintuitive finding was that ACR was associated with increased use of corticosteroids and calcineurin-inhibitors [Fig. 1]. However, it is likely that this association was seen because these agents are used to treat or prevent ACR. Third, the concentrations of HBIG utilized clinically in LT recipients (back-calculated to be ~42 mg/kg = trough level of ~5.3 mg/kg) or in our *in vitro* experiments (equivalent to be ~6.7 mg/kg) were much lower compared to IVIG for transplant recipient desensitization (2gm/kg) or in prior *in vitro* studies [23,24]. Thus, the question remains whether higher HBIG doses in

clinical practice and concentrations *in vitro* would result in tolerogenic or immunosuppressive effects, like IVIG.

In conclusion, HBV+ LT recipients in the current era are at low risk for ACR and its associated complications. *In vitro* and *in vivo*, HBIG at current clinical concentrations does not appear to prevent ACR, inhibit immune responses or promote Treg development and expansion. These findings all support the immunological safety of minimizing both maintenance immunosuppressive therapy and the use of HBIG in HBV+ recipients.

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Abbreviations

HBV	Hepatitis B virus
HCV	Hepatitis C virus
LT	liver transplantation
HBIG	Hepatitis B immunoglobulin
ACR	acute cellular rejection
HCC	hepatocellular carcinoma
IVIG	intravenous immunoglobulin
OPTN	Organ Procurement and Transplantation Network
PBC	primary biliary cirrhosis
PSC	primary sclerosing cholangitis
UNOS	United Network for Organ Sharing

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Fig. 1.

Odds ratios for predictors of acute cellular rejection (OPTN). In multivariable analysis adjusted for age, gender, and immunosuppression, HBV status remained a strong negative predictor of ACR (OR = 0.58, 95% CI: 0.51–0.67, $p < 0.001$). Strong positive predictors of ACR include black race, a race other than white, calcineurin inhibitors, and steroids.

Fig. 2.

Kaplan-Meier patient and graft survival curves in liver transplant recipients with and without acute cellular rejection stratified by HBV status (OPTN). Patient and graft survival are better in HBV+ LT recipients compared to non-HBV+ recipients. In non-HBV+ recipients, ACR results in lower patient ((A), $p < .001$) and graft ((B), $p < .01$) survival. However, in HBV+ recipients, ACR had a trend toward impacting patient survival ((A), $p = .06$), but not graft ((B), $p = .15$) survival.

Fig. 3. Effect of HBIG on lymphoproliferation in MLR. 1×10^5 responding PBMC (A) were cultured with 1×10^5 irradiated stimulator cells from an HLA-DR matched (Bx) or HLA mismatched (Ix) volunteer, in presence of indicated concentrations of HBIG ($n = 7$). Standard ^3H -TdR assays were performed on indicated days and the data calculated as stimulation index (A) or as percentage of medium control (i.e. 100%) (B). Note that HBIG at 0.78–100 $\mu\text{g/ml}$ (4.875–625 IU/L) failed to inhibit MLRs at any dose. Equivalent results were seen with both HLA DR-matched and HLA mismatched stimulators.

Fig. 4.

Effect of HBIG on the generation of FOXP3⁺ Tregs in the Treg-MLR. Lymphocytes were gated on CFSE bright/dim cells negative for CD127-PE and PKH26, followed by gating for CD4⁺CFSE^{dim} (proliferating) or CD4⁺CFSE^{high} (non-proliferating) responders. The expression of CD25 and FOXP3 was then analyzed as percentage of CD4⁺ cells that were CD127⁻CD25⁺FOXP3⁺ (total Tregs) or CD127⁻CD25^{High}FOXP3⁺ (nTregs) in the proliferating and non-proliferating CD4⁺ responders (A). The percentage of developing total Tregs and nTregs in responder cells stimulated with HLA-DR matched (B) and HLA mismatched (C) are shown (n = 7). HBIG at 0.78–100 µg/ml did not have any effect on generation of Treg subsets in the proliferating fraction.

Table 1

Patient characteristics by indication for liver transplant in OPTN.

Indication	HBV N (%)	HCV N (%)	Steatohepatitis N (%)	Immune-mediated N (%)
Number of Patients	2035 (5.0)	21242 (52.3)	10644 (26.2)	6672 (16.4)
Age (Years)	53.1 ± 9.5	53.2 ± 7.2	55.0 ± 8.6	50.3 ± 12.8
Female Gender	372 (18.3)	5482 (25.8)	2832 (26.6)	3874 (58.1)
Race & ethnicity				
White	907 (44.6)	15167 (71.4)	8659 (81.4)	5095 (76.4)
Black	202 (9.9)	2135 (10.1)	341 (3.2)	768 (11.5)
Hispanic	138 (6.8)	3174 (14.9)	1412 (13.3)	620 (9.3)
Asian	746 (36.7)	554 (2.6)	113 (1.1)	112 (1.7)
Other	42 (2.1)	212 (1.0)	119 (1.1)	77 (1.2)
Calculated MELD score	18.7 ± 12.2	18.9 ± 10.2	21.4 ± 9.5	18.6 ± 10.1
Hepatocellular Carcinoma	643 (31.6)	5180 (24.4)	1136 (10.7)	327 (4.9)
Living Donor	72 (3.5)	866 (4.1)	330 (3.1)	743 (11.1)
Recipient BMI (kg/m ²)	26.7 ± 5.2	28.7 ± 5.3	29.3 ± 5.9	26.5 ± 5.4
Cold Ischemia Time (Hr)—Median (Q1, Q3)	7.0 (5.0, 9.0)	6.9 (5.0, 8.8)	6.9 (5.0, 8.7)	6.5 (4.9, 8.7)
ABO Match Compatibility				
Identical	1849 (90.9)	19997 (94.1)	9989 (93.9)	6237 (93.5)
Compatible	176 (8.7)	1122 (5.3)	591 (5.6)	395 (5.9)
Incompatible	10 (0.5)	123 (0.6)	64 (0.6)	39 (0.6)
Immunoprophylaxis				
Calcineurin inhibitor	1935 (95.1)	20266 (95.4)	10082 (94.7)	6397 (95.9)
Steroids	1702 (83.6)	17093 (80.5)	8629 (81.1)	5787 (86.7)

Table 2

Univariate comparison of liver transplant recipients with and without acute cellular rejection in OPTN.

Characteristic	Rejection N (%)	No rejection N (%)	Odds ratio (95% CI)
Number of Patients	8425 (21.0)	31644 (79.0)	
Age (Years)	51.4 ± 9.7	53.7 ± 8.7	0.973 (0.970, 0.975)
Female Gender	2929 (34.8)	9454 (29.9)	1.251 (1.189, 1.316)
Race & Ethnicity			
White	6049 (71.8)	23395 (73.9)	Reference
Black	943 (11.2)	2465 (7.8)	1.480 (1.366, 1.064)
Hispanic	1093 (13.0)	4180 (13.2)	1.011 (0.941, 1.087)
Asian	243 (2.9)	1261 (4.0)	0.746 (0.648, 0.858)
Other	97 (1.2)	343 (1.1)	1.094 (0.871, 1.373)
Cause of Liver Disease			
Hepatitis B	279 (3.3)	1719 (5.4)	0.428 (0.373, 0.491)
Hepatitis C	4366 (51.8)	16597 (52.5)	0.694 (0.651, 0.739)
Steatohepatitis	1969 (23.4)	4776 (15.1)	0.607 (0.564, 0.653)
Immune-mediated	1811 (21.5)	8552 (27.0)	Reference
Calculated MELD score	19.2 ± 9.9	19.6 ± 10.2	0.996 (0.994, 0.999)
Hepatocellular Carcinoma	1286 (15.3)	5966 (18.9)	0.775 (0.726, 0.828)
Recipient BMI (kg/m ²)	28.2 ± 5.5	28.5 ± 5.6	0.990 (0.986, 0.995)
Donor Factors			
Age (Years)	40.3 ± 16.6	41.0 ± 16.9	0.998 (0.996, 0.999)
Female Gender	3333 (39.6)	12808 (40.5)	0.963 (0.917, 1.011)
Donor Risk Index	1.35 ± 0.36	1.35 ± 0.36	1.011 (0.944, 1.084)
Donor BMI (kg/m ²)	26.6 ± 5.8	26.7 ± 5.8	0.998 (0.994, 1.002)
Living Donor	439 (5.2)	1540 (4.9)	1.075 (0.964, 1.198)
Donor-Recipient Compatibility			
Sex (donor female, recipient male)	1938 (23.0)	8074 (25.5)	0.872 (0.824, 0.923)
Sex (donor male, recipient female)	1533 (18.2)	4720 (14.9)	1.269 (1.191, 1.352)
Cold Ischemia Time (Hr)—median (Q1, Q3)	7.0 (5.2, 9.0)	6.7 (5.0, 8.6)	1.017 (1.011, 1.024)
Immunosuppression			
Calcineurin inhibitor	8228 (97.7)	30114 (95.2)	2.122 (1.826, 2.466)
Steroids	7333 (87.0)	25554 (80.8)	1.600 (1.493, 1.715)
Follow up time (Years)—Median (Q1, Q3)	3.9 (1.4, 6.7)	3.1 (1.0, 6.1)	1.030 (1.023, 1.038)

Table 3

Univariate comparison of HBV+ recipients with and without acute cellular rejection in OPTN.

Characteristic	HBV with ACR	HBV without ACR	Odds ratios (95% CI)
Number of Patients (%)	279 (14.0)	1719 (86.0)	
Age (Years)	50.8 ± 9.6	53.5 ± 9.4	0.972 (0.959, 0.984)
Female Gender	61 (21.9)	306 (17.8)	1.292 (0.948, 1.761)
Race & ethnicity			
White	108 (38.7)	780 (45.4)	Reference
Black	44 (15.8)	154 (9.0)	2.064 (1.396, 3.050)
Hispanic	19 (6.8)	117 (6.8)	1.173 (0.694, 1.982)
Asian	100 (35.8)	637 (37.1)	1.134 (0.847, 1.517)
Other	8 (2.9)	31 (1.8)	1.864 (0.835, 4.160)
Calculated MELD score	19.5 ± 11.7	18.5 ± 12.2	1.007 (0.996, 1.018)
Hepatocellular Carcinoma	61 (21.9)	579 (33.7)	0.551 (0.408, 0.744)
Simultaneous liver-kidney transplant	10 (3.6)	108 (6.3)	0.555 (0.286, 1.074)
Living Donor	5 (1.8)	63 (3.7)	0.479 (0.191, 1.202)
Immunosuppression			
Calcineurin inhibitor	275 (98.6)	1641 (95.5)	3.268 (1.187, 8.998)
Steroids	246 (88.2)	1438 (83.7)	1.456 (0.991, 2.140)
Donor Factors			
Age (years)	41.2 ± 16.5	41.7 ± 17.3	0.998 (0.991, 1.006)
Female gender	103 (36.9)	720 (41.9)	0.812 (0.625, 1.055)
Donor BMI (kg/m ²)	26.3 ± 5.5	26.1 ± 5.4	1.008 (0.985, 1.031)
Spilt/partial graft	8 (2.9)	98 (5.7)	0.488 (0.235, 1.014)
Donation after cardiac death	7 (2.5)	52 (3.0)	0.824 (0.370, 1.833)
Donor Risk Index	1.36 ± 0.35	1.39 ± 0.37	0.803 (0.554, 1.162)
Follow up time (Years)—Median (Q1, Q3)	4.97 (1.73, 7.96)	4.01 (1.37, 7.58)	1.043 (1.006, 1.081)

Table 4

HBIG use in hepatitis b virus positive liver transplant recipients by rejection status.

OPTN data (Patient n = 155)			
	No HBIG	Yes HBIG	P-value
No Rejection	51	83	0.090
Yes Rejection	4	17	
Total	55 (35.5%)	100 (64.5%)	
Single center data (Patient n = 64)			
	No HBIG	Yes HBIG	P-value
No Rejection	14	39	0.566
Yes Rejection	2	9	
Total	16 (25%)	48 (75%)	

Note: Acute cellular rejection (ACR) was biopsy-proven in the single center data. ACR within OPTN is center-reported and not verified by biopsy.