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Prophylaxis against *de novo* hepatitis B for liver transplantation utilizing hep B core (+) donors: does hepatitis B immunoglobulin provide a survival advantage?

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None of the authors have any conflict of interests to declare.

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Summary

Donor liver allografts with positive serology for hepatitis B core antibody [HBc (+)] have been increasingly used for liver transplantation. However, the optimal prophylactic regimen to prevent development of *de novo* hepatitis B has not been determined. To evaluate this, we screened United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) registry data for adult recipients of HBc (+) organs who were HBsAg (−), and evaluated the effects of using prophylactic anti-viral therapies (HBIG and lamivudine) on patient and graft survival. Out of a total cohort of 958 patients transplanted since 2004, 61 received HBIG alone, 116 received lamivudine alone, 66 both, 509 neither and 206 were missing this information. Based on several multivariable Cox regression models, patients receiving HBIG therapy-only were observed to have a statistically significant (approximately 70%) reduction in risk of mortality compared with patients receiving lamivudine-only therapy [HR = 0.29, 95% CI (0.10, 0.86), $P = 0.026$], and a nonstatistically significant reduction in risk of graft failure. However, no graft failures were attributed to *de novo* hepatitis B, suggesting that any improved graft/patient survival possibly associated with HBIG therapy occurs independently of *de novo* hepatitis B virus (HBV) reduction. While this study cannot prove that HBIG therapy is protective for graft and patient survival after liver transplantation, these findings do highlight the need to further examine and study prophylactic use in recipients of HBc (+) donors.

Introduction

The continuing imbalance between the number of patients on the liver transplant waiting list and the availability of donor organs has led to increasing utilization of extended criteria donors (ECD). These ECD organs may carry an increased risk of poor outcomes based on potential higher rates of delayed graft or primary nonfunction, risk of transmission of malignancy and/or infectious disease, and other potentially life-threatening complications. With the advent of relatively new anti-viral agents, the utilization of donors exposed to hepatitis B {hepatitis B core antibody (+) [HBc (+)]}, but who are hepatitis B surface antigen (−) [HBsAg (−)], and without signs of active disease, has increased.

While there has been an increase in the use of HBc (+) donors in general, there is a wide variation in practice patterns between liver transplant centers with regard to the utilization of HBc (+) grafts and their prophylactic strategies against the development of *de novo* hepatitis B (HBV). It has been well documented that transplantation of HBc (+) donor liver allografts into non-HBV-infected recipients, in the absence of effective prophylaxis, can lead to a high incidence of *de novo* HBV [1–9]. In the past, this risk precluded the use of these potentially lifesaving grafts. However, with the proven effectiveness of

anti-HBV agents in preventing recurrent HBV after transplantation, the use of HBc (+) grafts has increased in the HBV-naive recipient population.

Hepatitis B immunoglobulin (HBIG) has been demonstrated to reduce the incidence of *de novo* HBV in HBV-naïve transplant recipients of HBc (+) grafts either alone or in combination with lamivudine [3,10–16]. Recent reports have demonstrated that monotherapy with the anti-nucleoside lamivudine can also prevent *de novo* HBV after liver transplantation with these grafts [1,13,17]. A recent systematic review of the literature by Avelino-Silva revealed a diverse array of protocols to prevent *de novo* HBV after liver transplantation, which include HBIG alone, lamivudine alone and various combinations and dosing regimens of both, without any clearly superior result and with little specific detail [18]. Importantly, HBIG administration can cost as much as $100 000 in the first year after transplantation for active HBV and up to $50 000 each year thereafter [19].

Given the variability in utilization of lamivudine and HBIG alone or in combination for the prevention of *de novo* HBV after transplantation with HBc (+) organs and the high cost of its use, we evaluated the UNOS database to determine if any differences in the incidence of *de novo* hepatitis, as well as any differences in patient and graft survival, existed between the treatment regimens.

Materials and methods

Data and study design

Data were obtained on all recipients receiving a liver transplant before May 5th, 2008 from the UNOS STAR registry data. Recipients under the age of 18 years were excluded, and analysis was further restricted to recipients who received a transplant during or after 2004 (the year lamivudine usage was first documented in the dataset). Recipient HBc status and donor HBsAg status were also checked. Hepatitis B surface antibody (HBsAb) status for donors is available from 5/3/2006 onward. But, of note, HBsAb status for recipients is currently not recorded in UNOS.

We performed analysis of two separate cohorts of patients. Our primary analysis was focused on HBsAg (−) patients who received HBc (+) organs. For these patients, we presumed the primary indication for receipt of HBIG/lamivudine was to serve as a prophylaxis for prevention of HBV after transplantation with an HBc (+) organ. In a follow-up study, we performed a secondary data analysis of hepatitis C virus positive [HCV (+)] patients, to evaluate whether differences in outcomes (patient and graft survival) between the prophylaxis therapy groups existed for these patients, independent of patient HBV status or donor HBc status.

Outcomes and covariates

The primary outcomes investigated were overall recipient and graft survival. Donor covariates examined included gender, ethnicity, age, history of hypertension, history of diabetes, hepatitis C antibody (HCV) status (positive, negative, unknown), organ share type (local, regional, national), and donor risk index (DRI). Recipient covariates included gender, ethnicity, age, known malignancies since listing, diabetes, functional status at transplant, HBc status (positive, negative, unknown), HCV serostatus, model for end stage liver disease (MELD) score, and post-transplant levels of international normalized ratio (INR), total bilirubin (TB), and creatinine (Cr). DRI and MELD scores were calculated using standard formulas [20,21].[1] Patients were classified on the basis of whether they received HBIG alone, lamivudine alone, both, neither, or were missing this information.

Statistical methods

Differences in recipient and donor covariates between the different anti-viral treatment methods were assessed using ANOVA (continuous covariates) or the chi-square test (categorical covariates). Covariates were evaluated for their influence on recipient and graft survival by fitting Cox proportional hazards (PH) regression models and calculating hazard ratios (HRs) along with 95% confidence intervals [22]. Continuous covariates were dichotomized by picking the cut point with the largest log-rank statistic [23]. Graft failures were treated both separately from patient mortality by censoring at time of death (if not concurrent with a graft failure), and also by creating a combined outcome consisting of either graft failure or patient mortality. Kaplan–Meier and cumulative incidence curves were used to visualize differences in patient and graft survival between the prophylactic therapy groups [24]. To assess the confounding effects of covariates on the association between anti-viral treatment method and recipient and graft survival, multivariable Cox PH models were fitted using a variant of the ''purposeful selection algorithm'' [25]. Briefly, the algorithm first selects covariates with univariate P-values <0.25, and fits a model based on backwards elimination [the Akaike information criterion (AIC) was used to select the model]. Next, covariates eliminated by backwards elimination were assessed for potential confound-

[1]DRI is composed of donor age, race (white, African American or other), cause of death (trauma, stroke, anoxia, other), donation after cardiac death, split/partial liver graft, height, share type, and cold time. MELD score (laboratory based) is composed of a patient's INR, TB, and Cr levels.

ing with the remaining covariates, and any covariate resulting in a 15% or greater change in the remaining parameter estimates was re-inserted into the model. Lastly, covariates initially excluded based on the univariate *P*-value cutoff were also assessed for confounding with the included covariates, and added in a likewise fashion. HRs and 95% CIs were reported for comparisons between anti-viral treatment methods, and proportional hazards assumptions were checked using scaled Schoenberg residuals. Statistical analysis was conducted using SAS version 9.1 and R version 2.10.1 [26].

To account for missing values in HBIG/lamivudine usage and other covariates, we employed two different strategies. First, rather than eliminating patients with missing covariate information, we instead provided a separate ''missing'' category for each of the covariates. This allowed us to fit multivariable models without the need to eliminate patients who had missing covariate information. Second, we used multiple imputation [27] to create completed data sets with missing information filled-in. This is an established and broadly accepted method to enhance data sets with missing information. The method was primarily used as a sensitivity analysis, to assess the effect of those patients missing HBV prophylactic therapy information on the estimated relative risks between the different therapies. Specifically, if the recipients who are missing critical covariate information form a selective subsample of the entire sample, imputation analysis provides a safeguard against possibly biased results from the observed values alone [27]. Covariates were imputed following the procedures and guidelines outlined in [27] and [28]. In particular, all evaluated variables (including all covariates and response variables) were used to construct the imputed data sets, and 20 imputed data sets were generated by an iterative process (for details see [27]). Multivariable Cox models were fitted using the same covariates from the complete case models, and parameter estimates were obtained by averaging the estimates from the models fitted to each imputed data set. Standard errors were obtained using the imputation-corrected variance-covariance matrix. The R packages *Hmisc* version 2.3-0 and *Design* version 3.7-0 were used for implementation of the imputation procedures [29].

Confounding by indication of HBV prophylactic therapy was also assessed using propensity scores [30]. Propensity for type of prophylactic therapy was determined by fitting a multinomial logit model [31] with prophylactic therapy type as the outcome. Model selection was again performed using the purposeful selection algorithm, and predicted probabilities for each patient were obtained for use as the ''propensity'' to receive each therapy type. These scores were then included along with HBV prophylactic therapy type in multivariable Cox models for patient and graft survival.

Results

The UNOS data set included 28 161 liver transplants from 2004 onward. Of these donor organs, 1338 (4.75%) were HBc (+), while 26 352 (93.6%) were HBc (−) and 471 (1.7%) had unknown HBc status. Of these HBc (+) organs, 958 were transplanted into HBsAg (−) recipients ≥18 years old. Among these recipients, 61 were documented as receiving HBIG alone, 116 lamivudine alone, 66 both, 509 neither, and 206 were missing this information (Table 1). Summary demographics for donors and recipients are shown in Table 2. Nearly all (945) of the HBc (+) donors were HBsAg (−), indicating that the majority of these organs did not have active HBV infections. However, eleven were HBsAg (+) and two were unknown, but these were retained in the analysis to determine the survival of all HBc (+) organs transplanted into HBsAg (−) patients. UNOS began recording HBsAb donor status on 5/3/2006, and in our data set there were 201 HBsAb (+) donors, 99 HBsAb (−) donors, and the remaining 658 were either unknown or missing this information. Patients receiving HBIG had a significantly higher percentage of locally shared grafts, as well as a lower average DRI score. Percentage of patients that were HBc (+) and HCV (+) were not significantly different between HBIG and lamivudine recipients. Likewise, average MELD scores did not differ between the two groups. Patients receiving lamivudine had a slightly higher percentage of HCV (+) donor grafts, though the difference was not statistically significant.

Kaplan–Meier curves for patient survival and cumulative incidence curves for graft failure stratified by antiviral treatment method are shown in Fig. 1a and b, respectively. The chi-square test for differences in patient survival and graft failure between treatment methods were both significant ($P < 0.001$ and $P = 0.03$, respectively). Curves for the 206 patients with missing HBIG/lamivu-

Table 1. Distribution of prophylactic therapy among HBsAg (−) patients receiving HBc (+) organs.

Medication	Number of recipients	Percentage of total
HBIG alone	61	6.4
Lamivudine alone	116	12.1
Both	66	6.9
Neither	509	53.1
Missing	206	21.5
Total	958	100.0

HBIG, hepatitis B immunoglobulin.

Table 2. Summary demographics for covariates among HBsAg (–) recipients of HBc (+) donor grafts, subsetted by lamivudine/HBIG usage.

Covariate	Level	Lamivudine (*n* = 116)	HBIG (*n* = 61)	Lamivudine + HBIG (*n* = 66)	Neither (*n* = 509)	Missing (*n* = 206)	*P*-value*
Donor covariates							
Gender	Female	55 (47)	32 (52)	29 (44)	195 (38)	90 (44)	0.12
	Male	61 (53)	29 (48)	37 (56)	314 (62)	116 (56)	0.63
Age	<55	78 (67)	43 (70)	46 (70)	340 (67)	126 (61)	0.50
	≥55	38 (33)	18 (30)	20 (30)	169 (33)	80 (39)	0.89
Ethnicity	White	49 (42)	30 (49)	26 (39)	199 (39)	90 (44)	0.75
	Black	44 (38)	18 (30)	18 (27)	175 (34)	67 (33)	0.43
	Hispanic	11 (9)	6 (10)	11 (17)	62 (12)	26 (13)	
	Other	12 (10)	7 (11)	11 (17)	73 (14)	23 (11)	
History of hypertension	No	58 (50)	30 (49)	29 (44)	259 (51)	97 (47)	0.94
	Yes	54 (47)	30 (49)	35 (53)	237 (47)	105 (51)	0.88
	Unknown	4 (3)	1 (2)	2 (3)	13 (3)	4 (2)	
History of diabetes	No	103 (89)	50 (82)	56 (85)	436 (86)	177 (86)	0.78
	Yes	9 (8)	10 (16)	8 (12)	64 (13)	24 (12)	0.48
	Unknown	4 (3)	1 (2)	2 (3)	9 (2)	2 (5)	
Hepatitis C	Negative	89 (77)	53 (87)	58 (88)	420 (83)	188 (91)	0.03
	Positive	24 (21)	7 (11)	7 (11)	83 (16)	15 (7)	0.31
	Unknown	3 (3)	1 (2)	1 (1)	6 (1)	3 (1)	
Share type	Local	48 (42)	42 (69)	43 (65)	260 (51)	128 (62)	<0.001
	Regional	34 (29)	17 (28)	17 (26)	140 (28)	62 (30)	<0.001
	National	34 (29)	2 (3)	6 (9)	109 (21)	16 (8)	
DRI†	–	1.76 (0.50)	1.56 (0.38)	1.63 (0.36)	1.68 (0.43)	1.63 (0.43)	0.04
		N = 103	*N* = 50	*N* = 61	*N* = 442	*N* = 176	0.02
Patient covariates							
Gender	Female	33 (28)	15 (25)	20 (30)	145 (28)	69 (33)	0.63
	Male	83 (72)	46 (75)	46 (70)	364 (72)	137 (67)	0.76
Age	<55	52 (45)	37 (61)	34 (52)	268 (53)	112 (54)	0.32
	≥55	64 (55)	24 (39)	32 (48)	241 (47)	94 (46)	0.13
Ethnicity	White	79 (68)	39 (64)	48 (73)	351 (69)	149 (72)	0.56
	Black	11 (9)	6 (10)	2 (3)	56 (11)	24 (12)	0.74
	Hispanic	21 (18)	12 (20)	12 (18)	76 (15)	21 (10)	
	Other	5 (4)	4 (7)	4 (6)	26 (5)	12 (6)	
Known malignancies since listing	No	105 (91)	57 (93)	61 (92)	473 (93)	192 (93)	0.30
	Yes	9 (8)	4 (7)	4 (6)	17 (3)	9 (4)	0.86
	Unknown	2 (2)	0 (0)	1 (2)	19 (4)	5 (2)	
Diabetes at registration	No	88 (76)	54 (89)	49 (74)	391 (77)	157 (76)	0.29
	Yes	25 (22)	6 (10)	17 (26)	101 (20)	46 (22)	0.13
	Unknown	3 (3)	1 (2)	0 (0)	16 (3)	3 (1)	
Function status at transplant	Poor	20 (17)	6 (10)	10 (15)	48 (9)	35 (17)	0.008
	Ave	22 (19)	12 (20)	21 (32)	81 (16)	43 (21)	0.28
	Well	54 (47)	30 (49)	22 (33)	275 (54)	94 (46)	
	Unknown	20 (17)	13 (21)	13 (20)	105 (21)	34 (17)	
HepB core	Negative	60 (52)	32 (52)	28 (42)	272 (53)	131 (64)	0.04
	Positive	51 (44)	28 (46)	35 (53)	213 (42)	63 (31)	0.65
	Unknown	5 (4)	1 (2)	3 (5)	24 (5)	12 (6)	
HCV serostatus	Negative	33 (28)	27 (44)	20 (30)	159 (31)	76 (37)	<0.001
	Positive	79 (68)	32 (52)	45 (68)	319 (63)	100 (49)	0.23
	Unknown	4 (3)	2 (3)	1 (2)	31 (6)	30 (15)	
MELD‡	–	19.94 (8.88)	19.77 (9.99)	21.70 (8.37)	19.30 (8.88)	20.98 (9.6)	0.10
		N = 114	*N* = 57	*N* = 64	*N* = 500	*N* = 204	0.39

Cell entries are number (%) for categorical covariates and mean (SD) for continuous covariates.

HBIG, hepatitis B immunoglobulin.

*First *P*-value is for comparisons between all five groups; second *P*-value is for comparisons between ''lamivudine'', ''HBIG'', and ''lamivudine + HBIG'' groups only.

†126 (13%) of donors with missing donor risk index (DRI) score.

‡19 (2%) of recipients with missing model for end stage liver disease (MELD) score.

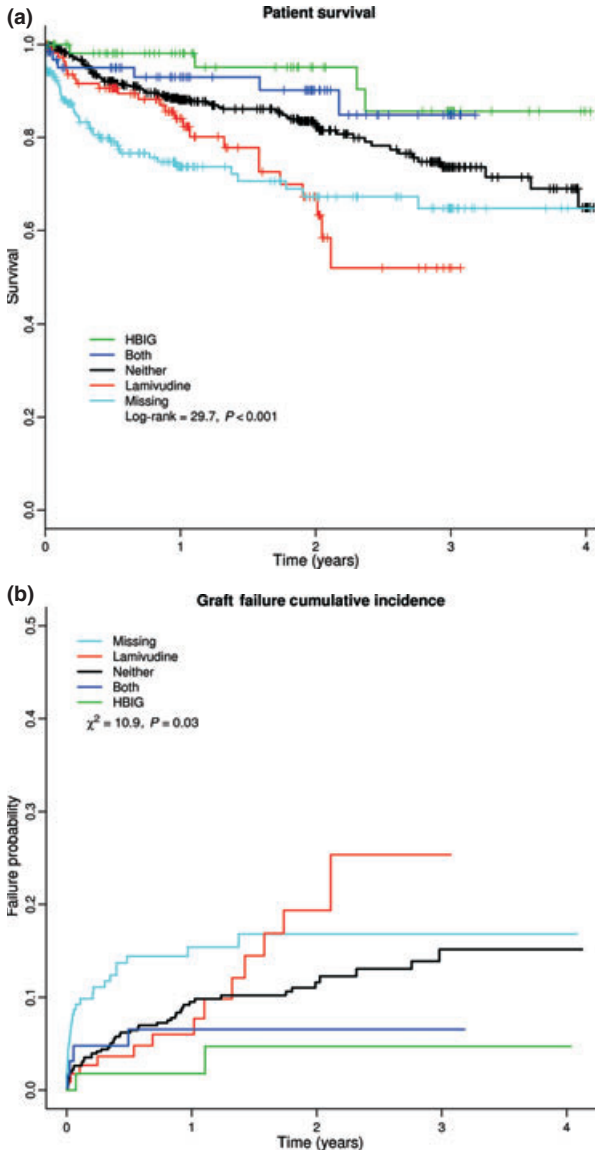

Figure 1 (a) Kaplan–Meier curves for patient survival, stratified by anti-viral prophylactic treatment in HBsAg (–) patients receiving HBc (+) donor allografts (year 2004 onwards). (b) Cumulative incidence curves for graft failure, stratified by anti-viral prophylactic treatment in HBsAg (–) patients receiving HBc (+) donor allografts (year 2004 onwards).

dine usage are also shown, and were found to significantly differ from the patients with known information ($P < 0.001$). Recipients of HBIG anti-viral therapy-only had a consistent approximately 75–80% reduction in risk of graft failure and mortality relative to recipients of lamivudine therapy-only ($P < 0.001$, see Tables 3 and 4). The HBIG-only group also had approximately 60–70% reduction in risk of patient mortality/graft failure relative to recipients of neither therapy, though this was only significant for the combined outcome (Table 4). Recipients of lamivudine alone had the worst patient and graft survival rates, with the exception of patients who were missing information on HBIG/lamivudine usage. However, the difference was not statistically significant for graft survival. Recipients of both HBIG and lamivudine had graft and patient survival rates that were intermediate between the HBIG alone and neither therapy groups, though closer to the former.

A check of the proportional hazards (PH) assumption for the hazard ratios between the different prophylaxis therapy groups revealed that the PH assumption was not violated, with the exception of the ''missing'' category group. Inspection of Fig. 1a and b reveal that the hazard ratio for these patients relative to the other therapy groups is initially higher during the 1st year, then subsequently subsides. However, as the violation of the PH assumption for the patients with missing prophylaxis therapy information will not affect the relative risks between the other therapy groups, we decided to retain these patients in the model to increase the sample size and better stabilize the parameter estimates in the model.

The influence of other clinically relevant recipient and donor characteristics on overall patient and graft survival are also given in Table 3. In addition to anti-viral treatment method, DRI, MELD, HBc status of the recipient, recipient age, and recipient functional status at transplant were all found to be significant. Multivariable Cox models were fit for patient and graft survival according to the procedures outlined in the Methods, and hazard ratios, 95% confidence intervals, and *P*-values for each included covariate are given in Supporting Information, Table S1. Many of the included covariates were not statistically significant, but were rather included on the basis of their confounding effects with other covariates in the model. In particular, recipient age, functional status, known malignancies since listing, HCV serostatus, and diabetes at registration, along with donor history of hypertension and diabetes, were all found to have a significant impact (>15% change) on the parameter estimate associated with lamivudine usage. Other statistically significant covariates included DRI and recipient gender, and inclusion of these covariates in the multivariable model resulted in a significant abatement of the risk of graft failure associated with lamivudine usage (Table 4, multivariable Model 1). After adjustment for these covariates, the difference in risk of graft failure between prophylactic therapy groups was no longer statistically significant. Similar covariates were included in the multivariable models for patient mortality and combined patient/graft failure (Supporting Information, Table S1). However, though the risk associated with lamivudine was again abated, the relative risks between lamivudine and HBIG, or combined HBIG/lamivudine

Table 3. Univariate hazard ratios for patient mortality and graft failure, among HBsAg (–) recipients of HBc (+) donor grafts.

					Patient mortality			Graft failure			Combined		
Variables	Levels	*N*	Deaths (%)	Graft failures (%)	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Donor variables													
Gender	Female	400	65	47	1	–	–	1	–	–	1	–	–
	Male	555	91	50	1.01	(0.73, 1.39)	0.96	0.76	(0.51, 1.14)	0.18	0.93	(0.71, 1.21)	0.58
Age	<55	631	94	57	1	–	–	1	–	–	1	–	–
	≥55	324	62	40	1.35	(0.98, 1.86)	0.07	1.42	(0.95, 2.12)	0.09	1.41	(1.07, 1.85)	0.01
Ethnicity	White	393	66	38	1	–	–	1	–	–	1	–	–
	Black	320	39	27	0.71	(0.48, 1.06)	0.09	0.85	(0.52, 1.40)	0.53	0.77	(0.55, 1.07)	0.12
	Hispanic	116	26	18	1.23	(0.78, 1.93)	0.38	1.52	(0.87, 2.67)	0.14	1.27	(0.86, 1.88)	0.22
	Other	126	25	14	1.22	(0.77, 1.94)	0.39	1.18	(0.64, 2.18)	0.6	1.19	(0.80, 1.78)	0.39
History of hypertension	No	472	75	40	1	–	–	1	–	–	–	–	0.23
	Yes	459	77	53	1.07	(0.78, 1.47)	0.67	1.39	(0.92, 2.09)	0.12	1.18	(0.90, 1.55)	0.42
	Unknown	24	4	4	1.26	(0.46, 3.44)	0.66	2.19	(0.78, 6.11)	0.14	1.41	(0.62, 3.21)	
History of diabetes	No	820	137	82	1	–	–	1	–	–	1	–	–
	Yes	114	16	11	0.86	(0.51, 1.44)	0.56	0.98	(0.52, 1.83)	0.94	1.08	(0.72, 1.61)	0.72
	Unknown	21	3	4	1.23	(0.39, 3.88)	0.72	0.85	(0.85, 6.39)	0.1	1.44	(0.59, 3.50)	0.43
Hepatitis C	Negative	805	124	79	1	–	–	1	–	–	1	–	–
	Positive	136	28	13	1.37	(0.91, 2.07)	0.13	0.99	(0.55, 1.78)	0.97	1.31	(0.92, 1.86)	0.14
Share type	Local	519	82	51	1	–	–	1	–	–	1	–	–
	Regional	269	44	28	1.09	(0.76, 1.58)	0.63	1.11	(0.70, 1.76)	0.67	1.12	(0.81, 1.53)	0.5
	National	167	30	18	1.16	(0.76, 1.76)	0.48	1.1	(0.64, 1.89)	0.72	1.33	(0.94, 1.88)	0.1
DRI	<1.3	185	26	11	1	–	–	1	–	–	1	–	–
	≥1.3	645	117	76	1.42	(0.93 2.17)	0.11	2.13	(1.13, 4.01)	0.02	1.7	(1.15, 2.50)	0.008
Patient variables													
Gender	Female	282	49	35	1	–	–	1	–	–	1	–	–
	Male	673	107	62	0.8	(0.57, 1.12)	0.18	0.67	(0.44, 1.01)	0.06	0.78	(0.58, 1.04)	0.09
Age	<55	503	72	58	1	–	–	1	–	–	1	–	–
	≥55	452	84	39	1.45	(1.06, 1.98)	0.02	0.82	(0.54, 1.23)	0.33	1.13	(0.86, 1.48)	0.37
Ethnicity	White	663	107	69	1	–	–	1	–	–	1	–	–
	Black	99	23	10	1.48	(0.95, 2.33)	0.09	0.99	(0.51, 1.92)	0.98	1.34	(0.90, 2.00)	0.15
	Hispanic	142	20	11	0.84	(0.52, 1.36)	0.48	0.73	(0.39, 1.39)	0.34	0.83	(0.55, 1.24)	0.35
	Other	51	6	7	0.77	(0.34, 1.74)	0.52	1.36	(0.63, 2.97)	0.43	0.91	(0.48, 1.72)	0.77
Known malignancies since listing	No	885	146	94	1	–	–	1	–	–	1	–	–
	Yes	43	7	2	0.82	(0.38, 1.73)	0.59	0.38	(0.09, 1.56)	0.18	0.68	(0.34, 1.39)	0.29
	Unknown	27	3	1	0.65	(0..21, 2.04)	0.46	0.35	(0.05, 2.48)	0.29	0.63	(0.24, 1.70)	0.37
Diabetes at registration	No	737	115	78	1	–	–	1	–	–	1	–	–
	Yes	194	39	18	1.31	(0.91, 1.89)	0.14	0.9	(0.54, 1.50)	0.68	1.18	(0.86, 1.63)	0.31
	Unknown	23	2	1	0.44	(0.11, 1.78)	0.25	0.35	(0.05, 2.53)	0.3	0.81	(0.33, 2.00)	0.65
Functional status at transplant	Poor	119	31	15	1	–	–	1	–	–	1	–	–
	Ave	179	35	15	0.57	(0.35, 0.92)	0.02	0.56	(0.27, 1.14)	0.11	0.5	(0.32, 0.77)	0.001
	Well	475	55	45	0.33	(0.21, 0.52)	<0.001	0.63	(0.35, 1.12)	0.12	0.41	(0.29, 0.60)	<0.001
	Unknown	182	35	22	0.49	(0.30, 0.80)	0.004	0.73	(0.38, 1.42)	0.35	0.48	(0.31, 0.74)	<0.001
HepB core	Negative	521	83	48	1	–	–	1	–	–	1	–	–
	Positive	389	60	41	0.93	(0.66, 1.29)	0.66	1.1	(0.73, 1.67)	0.65	0.96	(0.72, 1.27)	0.78
	Unknown	44	13	8	2.03	(1.13, 3.64)	0.02	2.1	(0.99, 4.44)	0.05	1.8	(1.06, 3.03)	0.03
MELD	<25	680	88	66	1	–	–	1	–	–	1	–	–
	≥25	256	66	31	2.3	(1.67, 3.17)	<0.001	1.39	(0.91, 2.14)	0.13	1.9	(1.44, 2.51)	<0.001
HCV serostatus	Negative	314	49	22	1	–	–	1	–	–	1	–	–
	Positive	573	94	69	1.02	(0.72, 1.44)	0.91	1.69	(1.05, 2.74)	0.03	1.11	(0.82, 1.50)	0.48
	Unknown	67	12	6	1.09	(0.59, 2.00)	0.79	1.18	(0.48, 2.90)	0.73	1.18	(0.70, 1.99)	0.54
HBIG/lamivudine	Neither	507	75	50	1	–	–	1	–	–	1	–	–
	Lamivudine	116	25	13	1.75	(1.11, 2.75)	0.02	1.24	(0.67, 2.29)	0.48	1.41	(0.99, 2.13)	0.1
	HBIG	61	4	2	0.38	(0.14, 1.05)	0.06	0.3	(0.07, 1.24)	0.1	0.34	(0.13, 0.84)	0.02
	Lamivudine–HBIG	66	6	4	0.6	(0.26, 1.37)	0.22	0.59	(0.21, 1.64)	0.31	0.63	(0.32, 1.24)	0.18
	Missing	205	46	28	2.1	(1.45, 3.03)	<0.001	1.82	(1.14, 2.89)	0.01	2	(1.46, 2.72)	<0.001

DRI, donor risk index; HBIG, hepatitis B immunoglobulin; MELD, model for end stage liver disease.

Table 4. Hazard ratios for hepatitis B immunoglobulin (HBIG) versus lamivudine prophylactic treatment from univariable (unadjusted) and multivariable Cox regression models for patient mortality and graft failure, among HBsAg (–) recipients of HBc (+) donor grafts†.

	Univariate (unadjusted)	Multivariable (Model 1, complete case)‡	Multivariable (Model 2, missing values imputed)	Multivariable (Model 3, propensity score adjusted)
Patient mortality				
Lamivudine versus neither	1.85 (1.17, 2.93)	1.50 (0.92, 2.42)	1.49 (0.93, 2.38)	1.60 (1.00, 2.54)*
HBIG versus neither	0.37 (0.13, 1.01)	0.43 (0.16, 1.21)	0.50 (0.20, 1.26)	0.38 (0.14, 1.05)
Combination§ versus neither	0.59 (0.26, 1.37)	0.42 (0.17, 1.05)	0.58 (0.26, 1.30)	0.47 (0.20, 1.11)
HBIG versus lamivudine	0.22 (0.13, 0.38)***	0.29 (0.10, 0.86)*	0.34 (0.12, 0.92)*	0.23 (0.08, 0.70)**
Combination versus lamivudine	0.34 (0.20, 0.60)***	0.28 (0.10, 0.75)**	0.39 (0.16, 0.92)*	0.30 (0.12, 0.74)**
Graft failure				
Lamivudine versus neither	1.28 (0.70, 2.37)	1.01 (0.51, 1.98)	1.11 (0.60, 2.05)	1.14 (0.61, 2.12)
HBIG versus neither	0.30 (0.07, 1.20)	0.34 (0.08, 1.42)	0.40 (0.11, 1.45)	0.32 (0.08, 1.34)
Combination versus neither	0.59 (0.21, 1.64)	0.54 (0.19, 1.52)	0.64 (0.23, 1.75)	0.56 (0.20, 1.60)
HBIG versus lamivudine	0.24 (0.11, 0.52)***	0.34 (0.07, 1.56)	0.36 (0.09, 1.48)	0.28 (0.06, 1.28)
Combination versus lamivudine	0.48 (0.22, 1.03)	0.54 (0.17, 1.71)	0.58 (0.19, 1.76)	0.50 (0.16, 1.56)
Patient mortality/graft failure combined				
Lamivudine versus neither	1.48 (0.99, 2.33)	1.20 (0.78, 1.84)	1.21 (0.82, 1.78)	1.29 (0.85, 1.95)
HBIG versus neither	0.33 (0.13, 0.81)*	0.40 (0.16, 1.00)	0.41 (0.18, 0.94)*	0.37 (0.15, 0.91)*
Combination§ versus neither	0.63 (0.32, 1.24)	0.54 (0.26, 1.11)	0.60 (0.31, 1.17)	0.57 (0.29, 1.15)
HBIG versus lamivudine	0.24 (0.15, 0.40)***	0.33 (0.12, 0.88)*	0.34 (0.14, 0.82)*	0.28 (0.11, 0.75)**
Combination versus lamivudine	0.45 (0.27, 0.74)**	0.45 (0.20, 1.00)*	0.50 (0.24, 1.04)	0.44 (0.21, 0.95)*

HBIG, hepatitis B immunoglobulin.

†Entries in cells are hazard ratios with 95% confidence intervals.

‡The complete case models are based on 927 patients for graft failure (92 events) and 911 patients for patient survival combined patient/graft failure (150 patient deaths and 206 who either died or experience a graft failure).

§Combination therapy patients received HBIG and lamivudine.

*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$.

therapy groups remained statistically significant (Table 4). To assess whether patients with missing information on HBIG/lamivudine usage (205 patients, 21.5%) impacted the estimated relative risks between the different therapies, we used multiple imputation as a sensitivity analysis to fill-in this missing information (see Methods). The resulting estimated hazard ratios and associated confidence intervals were largely unchanged from the complete case models (Table 4, multivariable Model 2), suggesting that the patients with missing prophylaxis therapy information were not systematically biased toward any particular therapy group. Lastly, we fitted multivariable models adjusted for the propensity to receive each type of prophylaxis therapy (see Methods for details). The resulting hazard ratios and associated confidence intervals for each covariate are given in Supporting Information, Table S2. The propensity to receive HBIG was significantly associated with both improved graft and patient survival, whereas propensity to receive lamivudine was associated with reduced survival. Neither result was statistically significant, however, because of the large variability in estimating the hazard ratios. The propensity to receive combined HBIG/lamivudine therapy was associated with diminished patient/graft survival, suggesting that these patients had values of other covariates associated with reduced survival. The propensity to be missing prophylaxis therapy information was not significantly associated with patient and/or graft survival, in accordance with the lack of impact imputing the therapy information for these patients had on the hazard ratios for the different therapy groups. Hazard ratios for comparing different prophylaxis therapy groups on patient/graft survival after adjusting for these propensity scores are given in Table 4 (multivariable Model 3). While the relative risk associated with lamivudine usage is again abated in all cases, the relative risk for patient and combined patient/graft survival is still statistically significant between the lamivudine-only and the HBIG and combined HBIG/lamivudine therapy groups.

The distribution for causes of patient mortality and graft failure are given in Table 5. Patients who received ''neither therapy'' or lamivudine monotherapy had slightly higher percentages of infection-related mortality compared with HBIG or combination therapy patients, though the result was not statistically significant ($P = 0.23$, log-rank test). No graft failures were attributed to *de novo* HBV. Seven patients (6.0%) had graft failures in the lamivudine group were attributed to recurrent

Table 5. Causes for patient death and graft failure among HBsAg (−) recipients of HBc (+) donor grafts, stratified by anti-viral prophylactic treatment (*N*, percentage of total patients). Graft failures may be attributable to multiple causes, and cause of patient death is based on the primary cause given.

	Neither (*n* = 509)	Lamivudine (*n* = 116)	HBIG (*n* = 61)	Combination§ (*n* = 66)
Patient death				
Hepatitis	6 (1.2)	1 (0.9)	0 (0)	0 (0)
Infection	30 (5.9)	6 (5.2)	1 (1.6)	1 (1.5)
Graft related – nonhepatitis	3 (0.6)	6 (5.2)	1 (1.6)	1 (1.5)
Cardiac–Respiratory–Renal–Metabolic	12 (2.4)	5 (4.3)	1 (1.6)	1 (1.5)
Malignancy	8 (1.6)	1 (0.9)	0 (0)	0 (0)
Other	16 (3.1)	6 (5.2)	1 (1.6)	3 (4.5)
Total number of deaths	75 (14.7)	25 (21.6)	4 (6.6)	6 (9.1)
Graft failure				
De novo hepatitis	0 (0)	0 (0)	0 (0)	0 (0)
Recurrent hepatitis	21 (4.1)	7 (6.0)	0 (0)	0 (0)
Infection	10 (2.0)	2 (1.7)	0 (0)	1 (1.5)
Recurrent disease – nonhepatitis	6 (1.2)	4 (3.4)	1 (1.6)	0 (0)
Vascular thrombosis	8 (1.6)	3 (2.6)	1 (1.6)	2 (3.0)
Biliary tract complication	7 (1.4)	2 (1.7)	0 (0)	0 (0)
Total	50 (9.8)	13 (11.2)	2 (3.3)	4 (6.1)

HBIG, hepatitis B immunoglobulin.
§Combination therapy patients received HBIG and lamivudine.

hepatitis. Though the UNOS data does not specify whether these recurrences were HBV or HCV, it is presumed to be recurrent HCV since all seven patients had positive HCV serostatus. In the neither group, 21 patients (4.1%) had graft failures attributed to recurrent hepatitis (18 of these had positive HCV serostatus), while no patients in the HBIG-only or lamivudine/HBIG combination therapy group had graft failures attributed to recurrent hepatitis ($P = 0.026$ for differences between the four groups, log-rank test). Two patients (1.7%) in the lamivudine group and 10 patients (2.0%) receiving neither therapy had graft failures that were attributed to infection. Nobody receiving either HBIG alone or in combination with lamivudine had graft failures attributed to infection ($P = 0.72$ for differences between the four groups, log-rank test).

We also performed a secondary data analysis of HCV (+) patients, to evaluate whether differences in graft/patient survival between the prophylactic therapy groups persisted irrespective of recipient HBV status. Our database contained 9396 HCV (+) recipients aged ≥18 years who received liver transplants between 01/01/2004 and 05/05/2008 [10 938 were HCV (−), and 4376 were missing this information]. Among these HCV (+) patients, 248 were also HBsAg (+), while 8774 were HBsAg (−) and 374 were missing this information. Six hundred and twenty-two patients were recipients of HBc (+) donor grafts, while 8709 received HBc (−) donor grafts and 65 were missing HBc donor status information. A total of 80 HCV (+) patients received HBIG monotherapy, while 141 received lamivudine monotherapy, 86 received HBIG–lamivudine combination therapy, 6784 received neither therapy, and 2305 were missing this information (a complete cross-tabulation of how many patients received each prophylaxis therapy, stratified by recipient HBsAg and donor HBc status, is given in Supporting Information, Table S3).

Univariable (unadjusted) and multivariable hazard ratios for risk of patient mortality and graft failure between the different prophylactic therapy groups for this cohort of HCV (+) recipients are given in Table 6. Multivariable Cox models were fit for the three outcomes using the purposeful selection algorithm. Patients receiving HBIG monotherapy had approximately 45–50% reduced risk of patient mortality ($P = 0.006$) and graft failure ($P = 0.027$) relative to lamivudine monotherapy patients, based on unadjusted hazard ratios. Similar results held for the combination therapy group relative to lamivudine monotherapy. Adjusted hazard ratios between HBIG monotherapy/combination therapy and lamivudine monotherapy were similar in magnitude but slightly abated, and no longer statistically significant (Table 6). Other covariates included in the multivariable models included DRI, donor age, recipient age, gender, ethnicity, and functional status at transplant, and HBc status of the donor (complete results for the multivariable models are given in Supporting Information, Table S4). Causes of graft failure and patient death for this cohort of patients is detailed in Supporting Information, Table S5. Distributions for causes of patient mortality were very similar between the prophylaxis therapy groups. Only one patient in the lamivudine and HBIG monotherapy groups had hepatitis associated mortality, and no patients had graft failures associated with *de novo* hepatitis. Lamivudine monotherapy patients did have a slightly higher percent of patients with recurrent hepatitis associated graft failure

Table 6. Hazard ratios for hepatitis B immunoglobulin (HBIG) versus lamivudine prophylactic treatment from univariable (unadjusted) and multivariable Cox regression models for patient mortality and graft failure, among hepatitis C virus positive [HCV (+)] patients†.

	N	Failures (*n*)	Univariable	Multivariable
Patient mortality				
Neither	6775	1086	1.00	1.00
Lamivudine (versus neither)	141	26	1.30 (0.88, 1.92)	1.17 (0.79, 1.72)
HBIG (versus neither)	80	9	0.61 (0.32, 1.18)	0.61 (0.32, 1.18)
Combination (versus neither)	86	8	0.58 (0.29, 1.16)	0.55 (0.27, 1.10)
Missing (versus neither)	2281	469	1.58 (1.42, 1.76) ***	1.57 (1.41, 1.75)
Other contrasts				
HBIG versus lamivudine	–	–	0.47 (0.27, 0.81)**	0.52 (0.24, 1.12)
Combination versus lamivudine	–	–	0.45 (0.26, 0.77)**	0.47 (0.21, 1.04)
Graft failure				
Neither	6775	633	1.00	1.00
Lamivudine (versus neither)	141	16	1.33 (0.80, 2.17)	1.07 (0.64, 1.79)
HBIG (versus neither)	80	5	0.60 (0.25, 1.46)	0.53 (0.22, 1.30)
Combination (versus neither)	86	6	0.75 (0.34, 1.67)	0.61 (0.27, 1.40)
Missing (versus neither)	2281	275	1.55 (1.35, 1.79)***	1.53 (1.33, 1.77)
Other contrasts				
HBIG versus lamivudine	–	–	0.46 (0.23, 0.91)*	0.50 (0.18, 1.37)
Combination versus lamivudine	–	–	0.56 (0.28, 1.13)	0.58 (0.22, 1.47)
Patient mortality/graft failure combined				
Neither	6775	1432	1.00	1.00
Lamivudine (versus neither)	141	37	1.39 (1.00, 2.33)*	1.18 (0.84, 1.66)
HBIG (versus neither)	80	12	0.63 (0.35, 1.10)	0.62 (0.35, 1.10)
Combination (versus neither)	86	13	0.72 (0.41, 1.24)	0.67 (0.38, 1.17)
Missing (versus neither)	2281	599	1.51 (1.37, 1.66)***	1.51 (1.38, 1.67)
Other contrasts				
HBIG versus lamivudine	–	–	0.45 (0.29, 0.71)***	0.53 (0.27, 1.01)*
Combination versus lamivudine	–	–	0.52 (0.33, 0.82)**	0.57 (0.30, 1.08)

†Entries in cells are hazard ratios with 95% confidence intervals. There were a total of 9396 HCV (+) patients aged 18+ years who were transplanted between 01/01/2004 and 05/05/2008 (multivariable and univariable models were each based on the same number of recipients).
*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$;

(6.4% vs. 3.4%, 2.5%, and 0% for neither therapy, HBIG monotherapy, and combination therapy, respectively, $P = 0.02$, log-rank test).

Discussion

While the treatment options for preventing recurrent HBV after liver transplantation have been, for the most part, standardized, there is no consensus regarding the optimal prevention of *de novo* hepatitis in HBV-naive liver transplant recipients of HBc (+) grafts. Early studies on the use of HBc (+) grafts without prophylactic treatment revealed a high incidence of the development of *de novo* HBV (33–100%) in HBV-naïve recipients [1–9] and from 0% to 13% in patients with prior HBV exposure [4–7,9,16,32,33]. Several other studies included patients that either received HBIG alone or in combination with lamivudine [3,10–16]. The utilization of HBIG/lamivudine essentially eliminated the incidence of *de novo* HBV. However, HBIG monotherapy prophylaxis was associated with a low but present incidence of *de novo* HBV [3,15].

Yu *et al.* reported the first study which utilized lamivudine monotherapy for prophylaxis against *de novo* HBV [13]. In this study, nine patients who were HBV naïve received lamivudine alone and none developed *de novo* HBV. More recently, Prokaso *et al.* reported 13 HBsAg (−) recipients of HBc (+) donors who were treated with only lamivudine – 100 mg daily [1]. After a follow-up of 23 months, no *de novo* HBV occurred. One patient did, however, seroconvert from HBc (−) to (+).

Many programs continue to use combination HBIG/nucleoside therapy while others have transitioned to lamivudine or other nucleoside agents alone. The conclusion that can be drawn from this variability in practice is that there is no strong evidence in favor of one protocol over another and that programs are using their own experience or judgment to develop their protocols. No rigorous, well performed studies have been conducted.

Given the high cost of HBIG relative to other preventive therapies, it would seem logical to minimize the utilization of this expensive drug. It is important to note the underlying bias of the authors prior to initiating this

study, which was that HBIG would not be found to be necessary for the prevention of *de novo* HBV in patients receiving HBc (+) liver allografts, and that given the expense, it should not be administered. The data, however, indicate otherwise, but not for the reasons anticipated at the initiation of this study. While the initial focus of our investigation was to determine the differences in *de novo* HBV between prophylactic therapy groups, the finding of survival differences independently of *de novo* HBV led to more detailed analyzes.

While the authors fully acknowledge the deficiencies of the data set (discussed in detail below), the results gleaned from those 243 patients who were documented as receiving HBIG or lamivudine prophylactic therapy are informative. Based on our multivariable analysis, we observed that recipients of HBIG-only therapy had improved patient survival relative to lamivudine-only recipients (HR = 0.29, 95% CI 0.10–0.86, $P = 0.026$). Similarly, improved graft survival was observed for HBIG versus lamivudine-only recipients (HR = 0.34, 95% CI 0.07–1.56), though the result was not statistically significant. The combination therapy group (HBIG and lamivudine) was also observed to have longer patient survival relative to lamivudine-only therapy. Inclusion of important covariates did abate the elevated risk associated with lamivudine-only usage to an extent, in particular for graft failure. Further, a propensity score adjustment revealed that propensity to receive HBIG versus lamivudine therapy may be an important factor, though differences in patient survival between the two therapy groups were still significant after this adjustment. It should be noted, however, that adjustment of the hazard ratios was limited to the information available in the UNOS data base. Other covariates, such as size of the transplant center and socio-economic status of the patients, may have played a role in the observed survival differences.

To account for the missing HBIG/lamivudine therapy status, we used an imputation procedure as a sensitivity assessment of the results based on complete case data. The findings for the imputation analyzes were consistent with the results based on complete case data, suggesting that our findings are not a mere artifact of the missing HBV prophylactic usage in the UNOS database. Interestingly, Saab *et al.* in 2003 reported the UCLA experience with HBc and HCV (+) grafts, and noted that the recipients who received both HBIG and lamivudine had improved survival compared with those receiving either therapy alone or neither therapy [34]. In addition, the improvement in graft and patient survival was similar to what we observed in our study (HR approximately = 0.4 and 0.3, respectively), suggesting that our results may be valid despite the deficits in the data set.

Possible mechanisms behind the observed differences in survival may be the known anti-inflammatory effects of HBIG. HBIG has been demonstrated to inhibit the function of dendritic cells, macrophages, and T-cells and reduce the production of cytokines [35,36]. In addition, several studies have suggested a relationship between the administration of HBIG and lower rates of acute and chronic rejection in liver transplant recipients [36,37]. Moreover, a study performed by Bucuvalas demonstrated not only a reduced rate of acute rejection in pediatric liver transplant recipients but an improved survival as well [38].

We evaluated a second cohort of HCV (+) patients to evaluate whether differences in patient and graft survival between the prophylaxis therapy groups persisted irrespective of patient HBV status. While HBIG and HBIG–lamivudine combination therapy patients had reduced risks of mortality relative to lamivudine monotherapy patients, this difference was no longer statistically significant after adjusting for significant covariates (approximately 40% reduction, P = NS). No significant differences in causes of patient death were noted, though patients receiving HBIG monotherapy and combination therapy had a slightly lower risk of recurrent hepatitis-associated graft failure.

There are several significant limitations to this study. While the UNOS database contains a wealth of data, the conclusions that may be gleaned from the data are only as good as the information that is entered into the database. Though complete information was available for hepatitis as a contributory cause of graft failure, for patients without graft failure follow-up documentation of *de novo* and recurrent HBV was limited at best and thus, no definite conclusions regarding differences in the incidence of *de novo* HBV among the treatment groups can be made. In addition, nearly 75% of the transplant recipients who received an HBc (+) graft in this dataset were not documented as having received either HBIG or lamivudine (53%), or had missing data (21%). The lack of prophylactic therapy for *de novo* HBV in >50% of patients seams inconsistent with what would be considered standard of care. It is possible that these data were simply not entered into the UNOS database and it is conceivable that patients in this group may have received some unknown prophylaxis. This is also possible for those 20% of patients where the data were missing. Finally, the dosing schedule and administration route (i.e. intravenous or intramuscular) of HBIG, as well as the compliance with lamivudine usage, cannot be gleaned from these data as this information is not currently recorded by UNOS. As such, a possible explanation for the observed superiority of HBIG over lamivudine is that lamivudine therapy was interrupted because of side effects or compliance issues, while HBIG therapy was correctly administered. Further, no recommendation can be made regarding how to

proceed with implementing any form of prophylaxis utilizing HBIG based on this study. Better tracking of HBV occurrence and prophylactic usage in the UNOS data base would improve future studies of these outcomes.

We would like to strongly concede that these data do not necessarily *prove* that either HBIG is protective or that lamivudine is detrimental to graft and patient survival after liver transplantation. However, there is clearly significant variation in survival among the different prophylactic treatment groups, and these findings highlight the need to further examine and study prophylactic use in recipients of HBc (+) donors. Of course, the utilization of large databases for research is always limited by the quality of the data entered into the data set, but these resources are capable of detecting differences in treatment outcomes that may not be evident in smaller studies. Future studies need to (i) ascertain whether the observed relationship between prophylactic therapy usage and patient survival is causal, and (ii) explicate the mechanism causing the survival discrepancies between the prophylactic therapies. To achieve this, a prospective, randomized trial should be performed to definitively determine the nature of the relationship between these prophylactic agents and the results of liver transplantation utilizing HBc (+) donors.

Authorship

GNB: participated in the research design, data analysis, presentation of results, and drafting of the manuscript. FM and NF: participated in data analysis and presentation of results. CJC and ME: assessed the results and gave critical feedback. JFB: supervised the research. MRM: formulated the initial hypothesis, participated in the research design and drafting of the manuscript, and supervised the research. All authors read and approved the final draft of the manuscript.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Multivariable hazard ratios for patient mortality and graft failure, for HBsAg (−) recipients of HBc (+) donor grafts. Cells labeled ''Not included'' were evaluated but ultimately excluded from the final multivariable model.

Table S2. Multivariable hazard ratios for patient mortality and graft failure, adjusted by propensity scores, for HBsAg (−) recipients of HBc (+) donor grafts.

Table S3. Cross-tabulation of HBIG/lamivudine prophylaxis therapy groups by recipient HBsAg and donor HBc status, for the 9396 HCV (+) patients.

Table S4. Multivariable hazard ratios for patient mortality and graft failure for the HCV (+) patients. Cells labeled ''Not included'' were evaluated but ultimately excluded from the final multivariable model.

Table S5. Causes for patient death and graft failure among HCV (+) patients, stratified by anti-viral prophylactic treatment (*N*, percentage of total patients). Graft failures may be attributable to multiple causes, and cause of patient death is based on the primary cause given.

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References

1. Prokaso E, Strasser SI, Koorey DJ, Verran D, McCaughan GW. Long-term lamivudine monotherapy prevents development of hepatitis B virus infection in hepatitis B surface-antigen negative liver trasnplant recipients from hepatitis B core-postitive donors. *Clin Transplant* 2006; **20**: 369.
2. Douglas D, Rakela J, Wright T, Krom R, Wiesner R. The clinical course of transplantation-associated *de novo* hepatitis B infection in the liver transplant recipient. *Liver Transplant Surg* 1997; **3**: 105.
3. Dodson SF, Bonham CA, Geller DA, Cacciarelli TV, Rakela J, Fung JJ. Prevention of *de novo* hepatitis B infection in recipients of hepatic allografts from anti-HBc positive donors. *Transplantation* 1999; **68**: 1058.
4. Dodson SF, Issa S, Araya V, *et al.* Infectivity of hepatic allografts with antibodies to hepatitis B virus. *Transplantation* 1997; **64**: 1582.
5. Prieto M, Gomez MD, Berenguer M, *et al. De novo* hepatitis B after liver transplantation from hepatitis B core antibody-positive donors in an area with high prevalence of anti-HBc positivity in the donor population. *Liver Transplant* 2001; **7**: 51.
6. Manzarbeitia C, Reich D, Ortiz J, Rothstein K, Araya V, Munoz S. Safe use of liver donors with positive hepatitis B core antibody. *Liver Transplant* 2002; **8**: 556.
7. Dickson RC, Everhart JE, Lake JR, *et al.* Transmission of hepatitis B by transplantation of livers from donors

positive for antibody to hepatitis B core antigen. *Gastroenterology* 1997; **113**: 1168.
8. Wachs ME, Amend WJ, Ascher NL, *et al.* The risk of transmission of hepatitis B from HBsAg(−), HBcAb(+), HBIgM(−) organ donors. *Transplantation* 1995; **59**: 230.
9. Munoz SJ. Use of hepatitis B core antibody-positive donors for liver transplantation. *Liver Transplant* 2002; **8S1**: S82.
10. Uemoto S, Sugiyama K, Marusawa H, *et al.* Transmission of hepatitis B virus from hepatitis B core antibody positive donors in living related liver transplants. *Transplantation* 1998; **65**: 494.
11. Loss GE, Mason AL, Blazek J, *et al.* Transplantation of livers from HBcAb positive donors into HBcAb negative recipients: a strategy and preliminary results. *Clin Transplant* 2001; **15**(Suppl. 6): 55.
12. Holt D, Thomas R, Van Thiel D, Brems J. Use of hepatitis B core antibody-positive donors in orthotopic liver transplantation. *Arch Surg* 2002; **137**: 572.
13. Yu AS, Vierling JM, Colquhoun SD, *et al.* Transmission of hepatitis B infection from hepatitis core antibody-positive liver allografts is prevented by lamivudine therapy. *Liver Transplant* 2001; **7**: 513.
14. De Vera ME, Eghtesad D, Tom K Liver transplantations of HBcAb+ and HCV+ allografts. Abstract, 1138. ATC 2005: 6th Annual Joint Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation, May 2005.
15. Roque-Alfonso AM, Feray C, Samuel D, *et al.* Antibodies to hepatitis B surface antigen prevent viral reactivation in recipients of liver grafts from anti-HBc positive donors. *Gut* 2002; **50**: 95.
16. Dodson SF. Prevention of *de novo* hepatitis B infection after liver transplantation with allografts from hepatitis B core antibody positive donors. *Clin Transplant* 2000; **14S2**: 20.
17. Vizzini G, Gruttadauria S, Volpes R, *et al.* Lamivudine monoprophylaxis for *de novo* HBV infection in HBsAg-negative recipients with HBcAb-positive liver grafts. *Clin Transplant* 2011; **25**: E77.
18. Avelino-Silva VI, D'Albuquerque LA, Bonazzi PR, *et al.* Liver transplant from anti-HBc-positive, HBsAg-negative donor into HBsAg-negative recipient: is it safe? A systematic review of the literature. *Clin Transplant* 2010; **24**: 735.
19. Lok AS. Prevention of recurrent hepatitis B post-liver transplantation. *Liver Transpl* 2002; **8**: S67.
20. Feng S, Goodrich NP, Bragg-Gresham JL, *et al.* Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; **6**: 783.
21. Wiesner RH, Edwards E, Freeman R, *et al.* Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91.
22. Cox DR Regression models and life tables (with discussion). *J Roy Stat Soc* 1972; **34**:187.
23. Contal C, O'Quigley J. An application of change point methods in studying the effect of age on survival in breast cancer. *Computational Statistics Data Analysis* 1999; **30**: 253.
24. Klein JP, Moeschberger ML. *Survival Analysis, Techniques for Censored and Truncated Data*, 2nd edn. New York: Springer-Verlag, Inc, 2003: pp 92–99.
25. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code for Biology and Medicine* 2008; **3**: 17.
26. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing, 2007.
27. Clark TG, Altman DG. Developing a prognostic model in the presence of missing data: an ovarian cancer case study. *J Clin Epidemiol* 2003; **56**: 28.
28. Van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med* 1999; **18**: 681.
29. Harrell FE. *Regression Modeling Strategies*. New York: Springer-Verlag, 2001: pp 41–51.
30. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; **70**: 41.
31. Agresti A. *Categorical Data Analysis*, 2nd edn. New Jersey: John Wiley & Sons, Hoboken, 2002: pp 267–274.
32. Chen YS, Wang CC, de Villa V, *et al.* Prevention of *de novo* hepatitis B virus infection in living donor liver transplantation using hepatitis B core antibody positive donors. *Clin Transplant* 2002; **16**: 405.
33. De Villa AH, Chen YS, Chen CL. Hepatitis B core antibody-positive grafts: recipient's risk. *Transplantation* 2003; **75**: S49.
34. Saab S, Chang AJ, Comulada S, *et al.* Outcomes of hepatitis C- and hepatitis B core anitbody-positive grafts in orthotopic liver transplantation. *Liver Transplant* 2003; **9**: 1053.
35. Kwekkeboom J, Tha-In T, Tra WM, *et al.* Hepatitis B immunoglobulins inhibit dendritic cells and T cells and protect against acute rejection after liver transplantation. *Am J Transplant* 2005; **5**: 2393.
36. Tha-In T, Metselaar HJ, Titanus HW, *et al.* Superior immunomodulatory effects of intravenous immunoglobulins on human T-cells and dendritic cells: comparison to calcineurin inhibitors. *Transplantation* 2006; **81**: 1725.
37. Farges O, Saliba F, Farhamant H, *et al.* Incidence of rejection and infection after liver transplantation as a function of the primary disease: possible influence of alcohol and polyclonal immunoglobulins. *Hepatology* 1996; **23**: 240.
38. Bucuvalas JC, Anand R. Treatment with immunoglobulin improves outcome for pediatric liver transplant recipients. *Liver Transpl* 2009; **15**: 1564.