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ORIGINAL ARTICLE

HLA matching between donors and recipients improves clinical liver transplant graft survival

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Abstract

Background and Aims: The importance of human leukocyte antigen (HLA) matching between liver transplant donors and recipients on graft survival remains unclear and is not a clinical consideration in liver transplantation. This study aimed to determine the relationship between HLA matching and liver graft survival using a large-scale multi-centre database (UNOS/OPTN) and multivariate logistic analysis. The secondary aim was to determine whether this relationship was influenced by transplant indication and donor status.

Methods: This retrospective observational analysis was performed using 22 702 liver transplant recipients from the UNOS/OPTN database. Patients were divided into two groups based on number of HLA mismatches (0–3 mismatches vs. 4–6 mismatches) and then subcategorized by indication and donor status. Risk-adjusted outcomes were assessed by multivariate Cox analysis adjusting for donor and recipient characteristics and visualized using Kaplan–Meier survival curves.

Results: Allograft survival and risk of acute rejection were associated with degree of HLA mismatch. This association between HLA mismatch and graft survival persisted in individuals who underwent transplant for hepatitis, metabolic, drug toxicity, and congenital indications. Donor status also influenced the relationship between HLA mismatch and graft survival. Graft survival in DBD recipients was longer than in DCD in the 4–6 HLA mismatch group, whereas no significant difference was found in the 0–3 HLA mismatch group.

Conclusion: HLA mismatch significantly reduced graft survival and increased risk of acute rejection. This association was noted only in specific indications. These findings are of potential clinical relevance to organ allocation, allograft matching algorithms, immunosuppression protocols, and transplant surveillance.

Abbreviations: BMI, body mass index; DBD, donation after brain death; DCD, donation after circulatory death; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HR, hazard ratio; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; OPTN, Organ Procurement and Transplant Network; TIPSS, Transjugular Portosystemic Shunt; UNOS, United Network for Organ Sharing.

Sarah Nabulsi and Afolarin A. Otunla contributed equally.

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KEYWORDS
acute rejection, graft survival, hla matching, indications, liver

1 | INTRODUCTION

Despite the widespread adoption of liver transplantation over the last 40 years, the role of human leukocyte antigen (HLA) matching between donors and recipients remains unclear. Several studies have produced ambiguous results with previous authors identifying both a positive contribution[1–3] and a negative effect of HLA matching on liver graft survival.[4,5] A dualistic effect of HLA matching on liver graft survival has even been suggested: improved survival from an immunologic standpoint, but worse survival when analysing all causes of liver dysfunction.[6] A United Network for Organ Sharing (UNOS)/Organ Procurement and Transplant Network (OPTN) database analysis published in 2006 failed to identify an association between HLA matching and graft survival.[7] Currently, HLA typing is neither included in UNOS allocation algorithms nor performed prior to liver transplantation.

Using an updated UNOS/OPTN database and multivariate logistic analysis, we sought to investigate whether HLA matching had a role in graft survival in the largest cohort of patients analysed to date. The aim of the study was to determine the association between HLA matching and liver graft survival in univariate and multivariate analyses. The secondary aim was to determine whether a difference would be noted in patients being transplanted for different indications and in the context of different organ donor status'.

Key points

This study aimed to investigate whether HLA matching (how compatible two patients' immune systems are) affects the success of liver transplants. We used a large database of transplant cases to determine whether HLA matching influenced the long-term survival of transplanted livers. We found that the importance of HLA matching in liver survival varied by indication, which is a novel finding.

2 | METHODS

2.1 | Study design and patient selection

This retrospective observational analysis was performed using data for adult liver transplant recipients between 15 August 2001 and 8 May 2022 extracted from the UNOS/OPTN database. UNOS is a non-profit, private organization that manages the US organ transplant database; containing all organ transplant data for every transplant event that occurs in the country. The dataset is completely anonymized. We extracted baseline patient characteristics including recipient age, sex, body mass index (BMI), race, diabetes status, immunosuppressant regime, hepatitis C virus (HCV) and human immunodeficiency virus (HIV) status, creatinine levels, history of transjugular portosystemic shunt (TIPS) and portal vein thrombosis, model for end-stage liver disease (MELD) score, and donor age, sex, and race. Inclusion criteria included liver transplant recipients receiving a graft from a deceased donor. Patients who have had previous transplants, dual organ recipients, those receiving a living donor liver transplant, and patients with missing or implausible data points in variables of interest ($n = 156\,567$, 87.3%) were excluded from the study. This left a cohort of 22 702 patients. The primary explanatory variable of interest for this analysis was the number of HLA mismatches. The primary outcome of interest was graft survival at 5, 10, and 15 years. The secondary outcome of interest was the occurrence of acute rejection episodes, defined histologically.

2.2 | Statistical analysis

Patient characteristics were described using mean ± SD if continuous and normally distributed, median (inter-quartile range, IQR) if non-normally distributed, and count (%) if categorical. Baseline characteristics were compared between patients based on HLA mismatch status using the Student *t* test or Wilcoxon rank-sum test, as appropriate, for continuous variables and chi-square test for categorical or discrete variables. Furthermore, sample size calculations were conducted using the 'pwr' and 'effsize' R packages for both the primary and secondary analyses to determine the sample size needed in each HLA category to obtain a power of at least 0.8 with a significance level of $p < .05$ and assuming an effect size of 0.1.

For the primary analysis of graft survival, we first performed univariate Cox proportional regression tests, Kaplan–Meier methods, and log-rank tests where the explanatory variable of interest was the number of HLA mismatches. We next developed multivariable proportional hazard models to account for potential confounders. Variables that were significant ($p < .05$) on univariate analysis, or with a strong clinical or biological relationship with the outcome were included in multivariate analysis model. We considered the following variables for multivariate adjustment: recipient age, sex, BMI, race, diabetes, HCV and HIV status, creatinine levels, history of TIPS or portal vein thrombosis, MELD score, and donor age, sex, indication, and race.

When designing the Cox proportional regression models, we dichotomized age (65 years and over = 1, younger than 65 years = 0), BMI (30 kg/m^2 and over = 1, <30 kg/m^2 = 0), organ cold ischemic time (18 h or more = 1, <18 h = 0), MELD score (24 or more = 1, <24 = 0), and creatinine (1.5 mg/mL or more = 1, <1.5 mg/mL = 0).

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We processed race as a dummy variable, using White race as the reference and comparing it to Black race and other. We used variate p-values and Akaike information criteria (AIC) to optimize our model fit. Diagnostic tests were performed to confirm model fit.

All Statistical analyses were performed using R version 4.0.5 (R Core Team). Additional packages used were dplyr (version 1.0.7; https://cran.r-project.org/web/packages/dplyr/index.html).

3 | RESULTS

3.1 | Study population

Of the 22 702 patients eligible for analysis after application of inclusion and exclusion criteria, 3337 had 0–3 HLA mismatches and 19 365 had 4–6 HLA mismatches (Table 1). The sample size in each category exceeded the number of 1380 patients needed to achieve statistical power of 0.8.

The two groups were similar in recipient and donor sex, recipient BMI, use of immunosuppressants, history of diabetes, history of TIPS and history of portal vein thrombosis, and organ cold ischemic time.

3.2 | HLA mismatch is correlated with graft survival

Allograft survival was correlated with degree of mismatch. Allografts in patients with 0–3 HLA mismatches survived for 123 days longer than those in patients with 4–6 HLA mismatches (3131 days vs. 3008, $p < .001$).

Cox proportional hazard models were used to assess the effect of HLA mismatching on graft survival. In multivariate analysis adjusted for potential risk factors (Table 2), the association between HLA mismatch and graft survival was not observed at 5 years (HR: 1.05, 95% CI: 0.98–1.13, $p = .14$); however, it was noted at both 10 years (HR: 1.07, 95 CI: 1.02–1.12, $p < .01$) and 15 years (HR: 1.06, 95% CI: 1.02–1.10, $p < .01$).

TABLE 1 Donor and recipient characteristics for adult liver transplants.

	HLA matching		
	0–3 HLA mismatches ($n = 3337$)	4–6 HLA mismatches ($n = 19\,365$)	*p*-value
Recipient factors			
Age (years) (median)	57	56	<.05
BMI (kg/m^2) (median)	27.9	27.7	.33
Male (*n*) (%)	2246 (67.4)	12 697 (65.6)	.05
Female (*n*) (%)	1091 (32.6)	6668 (34.4)	.05
Race-White (*n*) (%)	2603 (78.0)	13 820 (71.4)	<.001
Race-Black (*n*) (%)	178 (5.3)	1842 (9.5)	<.001
Race-Other (*n*) (%)	556 (16.7)	3703 (19.1)	<.001
Diabetes (*n*) (%)	833 (25.0)	4897 (25.3)	.61
HCV status (negative) (*n*) (%)	2171 (65.1)	12 800 (66.1)	.24
HIV status (negative) (*n*) (%)	3326 (99.7)	19 273 (99.5)	.25
Creatinine (mg/mL) (median, IQR)	1.00 (0.75)	1.00 (0.73)	.31
History of TIPS (negative) (*n*) (%)	3083 (92.4)	17 929 (92.6)	.46
History of portal vein thrombosis (negative) (*n*) (%)	3142 (94.2)	18 230 (94.1)	.97
MELD score (≥24) (*n*) (%)	1127 (33.8)	6597 (34.1)	.07
Overall acute rejection (*n*) (%)	221 (6.6)	1746 (9.0)	<.001
Donor factors			
Age (years) (median, IQR)	41 (28)	41 (28)	<0.05
Male (*n*) (%)	1962 (58.8)	11 620 (60.0)	.19
Female (*n*) (%)	1375 (41.2)	7745 (40.0)	.19
Race-White (*n*) (%)	2554 (76.5)	12 314 (63.6)	<.001
Race-Black (*n*) (%)	290 (8.7)	3778 (19.5)	<.001
Race-Other (*n*) (%)	493 (14.8)	3273 (16.9)	<.001
Transplant factors			
Cold ischemic time (h) (median, IQR)	6 (2.5)	6.1 (2.6)	.28
Duration of graft survival (days) (median, IQR)	3131	3008	<.001

Abbreviations: BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; MELD score, model for end-stage liver disease score; TIPS, transjugular intrahepatic portosystemic shunt.

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TABLE 2 Univariate and multivariate (red) Cox proportional hazards analysis on graft survival at 5, 10, and 15 years.

	5 years		10 years		15 years	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Recipient factors						
Age (≥65 years = 1, <65 years = 0)	1.28 (1.20–1.36)	<.001	1.27 (1.22–1.33)	<.001	1.22 (1.18–1.27)	<.001
BMI	1 (1–1.01)	<.001	1.01 (1.00–1.01)	<.001	1 (1–1.01)	<.001
Sex (male = 1, female = 0)	1.01 (0.98–1.04)	.47	1.00 (0.97–1.01)	.85	1.01 (0.98–1.04)	.50
White (reference)	1		1		1	
Black (Black = 1, other = 0)	1.33 (1.22–1.45)	<.001	1.17 (1.1–1.24)	<.001	1.12 (1.07–1.18)	<.001
Other (other = 1, Black or White = 0)	1.20 (1.13–1.28)	<.001	1.08 (1.04–1.13)	<.001	1.06 (1.02–1.10)	<.01
Diabetes (yes = 1, no = 0)	0.97 (0.91–1.03)	.29	1.04 (1.00–1.08)	.07	1.03 (1–1.07)	.06
HCV status (positive = 1, negative = 0)	0.69 (0.65–0.75)	<.001	0.75 (0.72–0.79)	<.001	0.83 (0.8–0.87)	<.001
HIV status (positive = 1, negative = 0)	1.27 (1.03–1.56)	<.05	1.41 (1.12–1.78)	<.01	1.27 (1.03–1.56)	<.05
Creatinine	0.91 (0.90–0.93)	<.001	0.91 (0.9–0.93)	<.01	0.91 (0.9–0.93)	<.001
TIPS (positive = 1, negative = 0)	1.07 (0.98–1.16)	.12	0.99 (0.94–1.05)	.70	0.96 (0.92–1.01)	.11
History of portal vein thrombosis (positive = 1, negative = 0)	1.24 (1.13–1.36)	<.001	1.35 (1.27–1.44)	<.001	1.29 (1.22–1.37)	<.001
MELD score (≥24 = 1, <24 = 0)	1.02 (0.94–1.10)	.66	1.18 (1.12–1.24)	<.001	1.22 (1.17–1.27)	<.001
Dialysis in week before transplant (yes = 1, no = 0)	1.36 (1.24–1.48)	.001	1.42 (1.34–1.51)	<.001	1.41 (1.33–1.48)	<.001
Donor factors						
Age (≥65 years = 1, <65 years = 0)	0.93 (0.86–1.02)	.13	0.92 (0.87–0.98)	<.01	0.92 (0.88–0.97)	<.01
Sex (male = 1, female = 0)	0.96 (0.91–1.01)	.09	0.98 (0.95–1.02)	.34	0.98 (0.95–1.01)	.21
White (reference)	1		1		1	
Black (Black = 1, other = 0)	1.06 (1.00–1.13)	.06	1.11 (1.06–1.16)	<.001	1.11 (1.07–1.15)	<.001
Other (other = 1, Black or White = 0)	1.14 (1.07–1.22)	<.001	1.05 (1.01—1.10)	<.001	1.02 (0.98–1.06)	<.45
Indication						
Drug	1.15 (0.88–1.52)	.3	1.07 (0.88–1.29)	.51	0.98 (0.84–1.15)	.83
Hepatitis	1.10 (0.99–1.23	.08	1.37 (1.28–1.48)	<.001	1.26 (1.19–1.34)	<.001
Cancer	1.32 (1.18–1.47)	<.001	1.55 (1.44–1.67)	<.001	1.52 (1.43–1.61)	<.001
Autoimmune	1.09 (0.97–1.22)	.15	1.21 (1.13–1.31)	<.001	1.15 (1.08–1.23)	<.001
NASH	1.77 (1.6–1.96)	<.001	1.96 (1.82–2.10)	<.001	1.83 (1.73–1.95)	<.001
Metabolic	1.01 (0.85–1.21)	.87	1.40 (1.26–1.55)	<.001	1.31 (1.2–1.44)	<.001
Alcohol	1.79 (1.63–1.96)	<.001	1.81 (1.70–1.92)	<.001	1.57 (1.49–1.66)	<.001
Congenital	1.22 (1.02–1.45)	<.05	1.39 (1.23–1.56)	<.001	1.30 (1.18–1.44)	<.001
Other (reference)	1		1		1	
Transplant factors						
Cold ischemic time	0.92 (0.91–0.93)	<.001	0.93 (0.93–0.94)	<.001	0.95 (0.94–0.96)	<.001
HLA mismatches (0–3 vs. 4–6)	1.05 (0.98–1.13)	.14	1.07 (1.02–1.12)	<.01	1.06 (1.02–1.10)	<.01

Abbreviations: BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HR, hazard ratio; MELD score, model for end-stage liver disease score; TIPS, transjugular intrahepatic portosystemic shunt.

This association between degree of HLA mismatch and graft survival was visualized using Kaplan–Meier survival curves (Figure 1). To appreciate the stepwise nature of this relationship, we then compared median graft survival between groups of patients at each level of mismatch, from no mismatch (0/6) to fully mismatched (6/6) (Figure 2). This analysis revealed a statistically significant difference ($p < .001$) in graft survival across the extent of mismatch.

3.3 | HLA mismatch is associated with acute rejection

Risk of acute rejection was correlated with degree of HLA mismatch. Allografts in patients with 0–3 HLA mismatches were 26% less likely to suffer from an acute rejection episode ($p < .0001$) than those in patients with 4–6 HLA.

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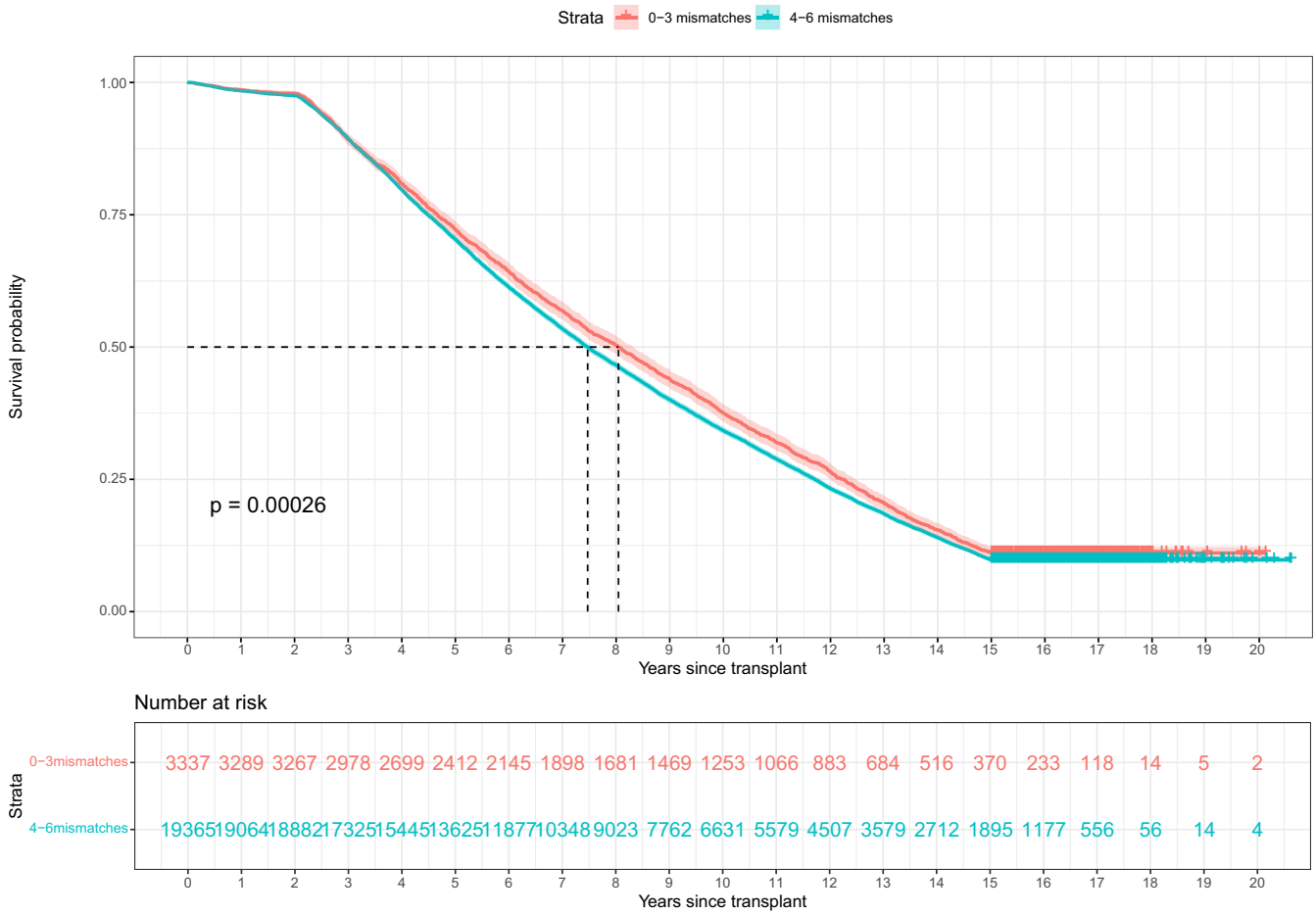


FIGURE 1 Kaplan–Meier survival curves of 0–3 HLA mismatches versus 4–6 HLA mismatches.

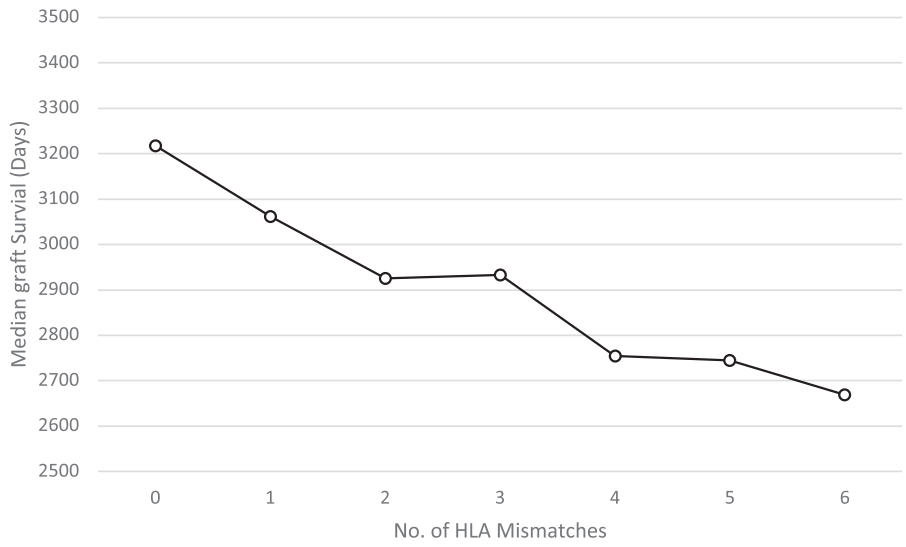


FIGURE 2 Graph displaying relationship between median graft survival (days) and number of HLA mismatches.

The association between HLA mismatch and graft survival is dependent on transplant indication. Indications for liver transplant were categorized into hepatitis-related, alcohol-related, cancer-related, autoimmune, non-alcoholic steatohepatitis (NASH), congenital, metabolic, and other. A sample size calculation revealed that all stratified groups satisfy the minimum requirement of 100 patients in each category to reach a power of 0.8, except the congenital and drug-induced groups. The baseline recipient and donor characteristics stratified by indication and HLA mismatch are described in Table 3. Graft survival by recipient disease aetiology was depicted using Kaplan–Meier survival curves (Figure 3).

A statistically significant reduction in graft survival in the 4–6 HLA mismatches group compared to the 0–3 HLA mismatches group

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was seen in hepatitis (198.5 days survival reduction, $p < .01$), other (559 days survival reduction, $p < .01$), congenital (805 days survival reduction, $p < .05$), and metabolic (318.5 days survival reduction, $p < .05$) indications (Table 3).

Multivariate analyses at 5, 10, and 15 years demonstrated that the influence HLA mismatch exerted on graft survival fluctuated over time in an indication-specific fashion (Table 4). For example, within the first 5 years of liver transplantation, HLA mismatch was associated with graft survival in patients with hepatitis (HR: 1.2, 95 CI: 1–1.4, $p < 0.05$) and drug-related (HR: 0.47, 95 CI: 0.23–0.96, $p < 0.05$) indications. However, at 10 and 15 years after liver transplant, HLA mismatch was no longer associated with graft survival in patients with hepatitis or

TABLE 3 Graft survival and acute rejection per indication between HLA-matched and HLA-mismatched patients.

	Overall acute rejection *n* (%)			Duration of graft survival (days) (median, IQR)		
Indication (*n*)	0–3 HLA mismatches	4–6 HLA mismatches	*p*-value	0–3 HLA mismatches	4–6 HLA mismatches	*p*-value
Hepatitis ($n = 5724$)	45 (5.4)	366 (7.5	<.05	3393.5 (2517.5)	3195 (2615.5)	<.01
Cancer ($n = 2723$)	17 (4.2)	205 (8.8)	<.01	2937.5 (2627.75)	2734 (2471)	.36
Autoimmune ($n = 2083$)	30 (10.0)	30 (10.0)	.13	2910 (2961)	2968 (2668)	.53
NASH ($n = 2547$)	18 (4.8)	18 (4.8)	.21	2125.5 (2098.5)	2060 (1896)	.13
Alcohol ($n = 5589$)	48 (5.7)	353 (7.4)	.07	2392 (2547)	2269 (2429.75)	.37
Congenital ($n = 606$)	11 (16.9)	109 (20.1)	.54	3612 (2807)	2807 (2585)	<.05
Drug ($n = 203$)	2 (13.3)	19 (16.2)	.77	4039 (2530)	3354 (3224)	.69
Metabolic ($n = 675$)	16 (15.0)	78 (13.7)	.74	3037 (2859.5)	2718.5 (2126.5)	<.05
Other ($n = 2552$)	34 (8.8)	231 (10.7)	.27	3810 (3014.5)	3251 (2953.5)	<.01

Abbreviations: HLA, human leukocyte antigen; NASH, non-alcoholic steatohepatitis.

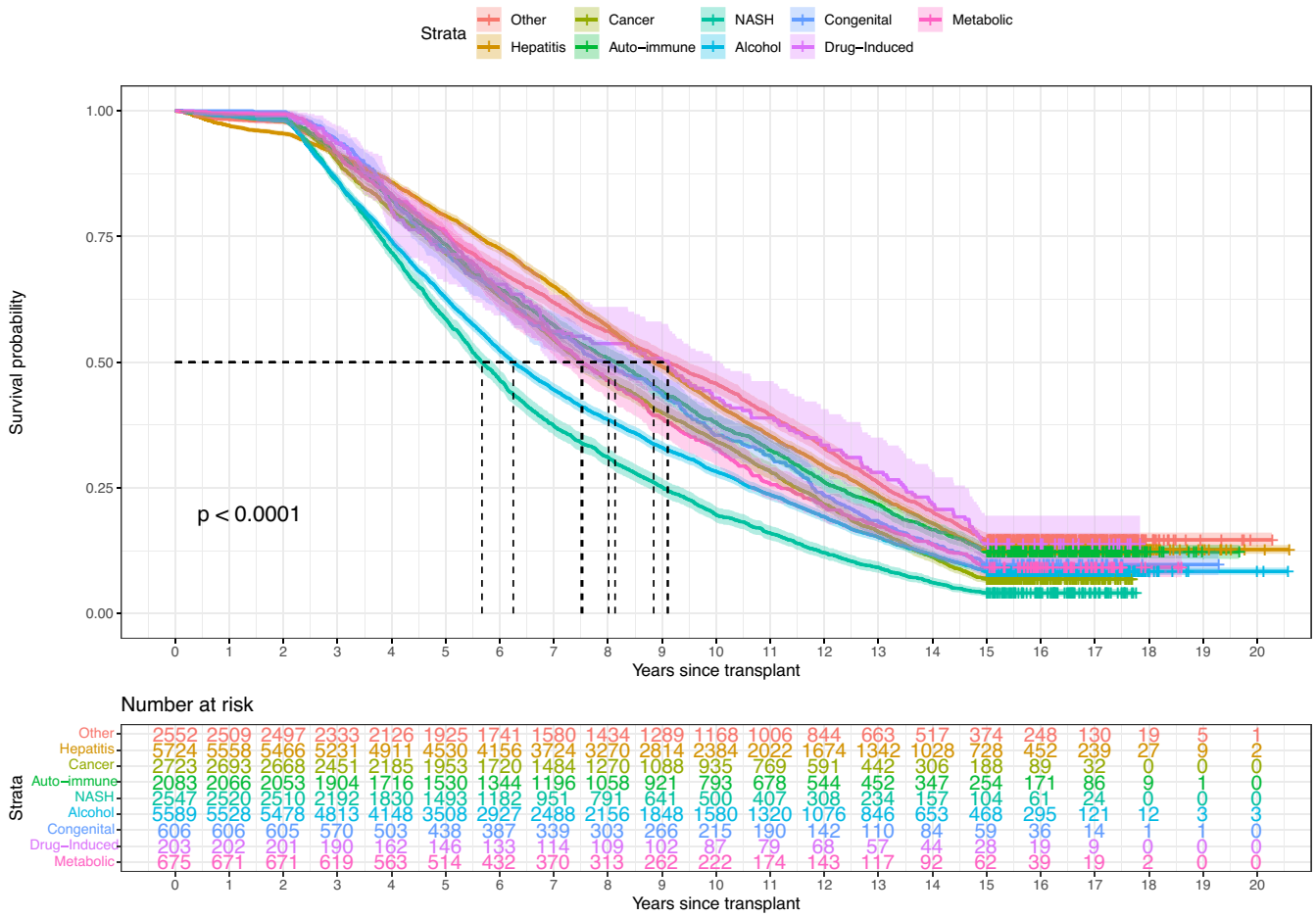


FIGURE 3 Kaplan–Meier survival curves displaying the relationship between graft survival and indication for liver transplant.

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TABLE 4 Univariate and multivariate (red) Cox proportional hazards model on graft survival 5, 10, and 15 years after liver transplantation per indication.

	5 years		10 years		15 years	
Indication	**HR (95%, CI)**	***p*-value**	**HR (95%, CI)**	***p*-value**	**HR (95%, CI)**	***p*-value**
Recipient factors						
Hepatitis	1.3 (1.1–1.5)	<.01	1.1 (1–1.2)	<.05	1.1 (0.99–1.2)	.07
	1.20 (1.01–1.43)	<.05	1.08 (0.98–1.20)	.11	1.1 (0.98–1.15)	·13
Cancer	1 (0.84–1.3)	.77	1.1 (0.93–1.2)	.42	1 (0.93–1.2)	.45
	1.02 (0.83–1.25)	.85	1.03 (0.90–1.18)	.62	1 (0.91–1.14)	.77
Autoimmune	0.85 (0.68–1.1)	.18	0.99 (0.85–1.2)	.95	1 (0.88–1.1)	.99
	0.80 (0.63–1.01)	.06	0.97 (0.82–1.14)	.70	1 (0.87–1.14)	.90
NASH	1.1 (0.96–1.4)	.13	1.1 (0.98–1.3)	.094	1.1 (0.96–1.2)	.23
	1.1 (0.92–1.31)	.31	1.06 (0.94–1.20)	.35	1 (0.91–1.14)	.72
Alcohol	1 (0.88–1.1)	.96	1 (0.96–1.1)	.29	1 (0.96–1.1)	.34
	0.96 (0.85–1.09)	.53	1.02 (0.94–1.12)	.64	1 (0.94–1.10)	.71
Congenital	1.1 (0.68–1.9)	.61	1.5 (1–2.1)	<.05	1.5 (1.1–2)	<.01
	1.1 (0.66–1.91)	.66	1.48 (1.03–2.13)	<.05	1.49 (1.11–2)	<.01
Drug	0.55 (0.28–1.1)	.07	0.79 (0.46–1.3)	.38	0.69 (0.45–1.1)	.09
	0.47 (0.23–0.97)	<.05	0.67 (0.38–1.18)	.17	0.64 (0.40–1)	.06
Metabolic	1.2 (0.78–1.9)	.37	1.3 (0.97–1.7)	.08	1.2 (0.99–1.5)	.061
	1.44 (0.90–2.29)	.13	1.32 (1.00–1.73)	<.05	1.28 (1.02–1.6)	<.05
Other	1.3 (1–1.7)	.02	1.3 (1.1–1.5)	<.01	1.2 (1.1–1.4)	<.01
	1.27 (1–1.62)	.05	1.20 (1.03–1.41)	<.05	1.16 (1.03–1.3)	<.05

Abbreviations: CI, confidence interval; HR, hazard ratio; NASH, non-alcoholic steatohepatitis.

drug-related indications, but instead strongly associated with congenital, metabolic, and other indications (Table 4).

3.4 | The association between HLA mismatch and graft survival is also influenced by donor status

Within our cohort, graft survival was significantly lower in donation after circulatory death (DCD) compared to donation after brain death (DBD) patients (Table 1). When stratified by HLA mismatch, univariate analysis revealed that this difference was more significant in the 4–6 HLA mismatches group (DBD mean graft survival 315 days longer than DCD, $p < .001$), than in the 0–3 HLA mismatches group (DBD mean graft survival 241 days longer than DCD, $p = .13$). This difference in significance was visualized using Kaplan–Meier survival curves (Figure 4A,B).

4 | DISCUSSION

The present study is the largest retrospective cohort study to demonstrate that HLA mismatch is associated with both reduced graft survival and increased acute rejection episodes in liver transplant recipients. We demonstrated a 123 day increase in survival and a lower incidence of acute rejection episodes (6.6% vs. 9.0%) in patients with 0–3 HLA mismatches vs patients with 4–6 mismatches. We have also demonstrated a differential effect of HLA matching on acute rejection incidence and graft survival, depending on indication for transplantation. Our findings provide clarity on the role of HLA matching on liver transplantation outcomes.

The existing literature surrounding HLA matching and liver transplant outcomes has demonstrated varying results. Several studies have shown similar findings in terms of reduced acute rejection incidence with HLA-matched patients. However, the literature largely reports no effect of HLA matching on graft survival.[3,8-11] This difference in our findings can be partially explained by the significantly larger sample size (22 702 patients) of our study compared to those preceding it (varying from 20 to 1500 patients). The studies which do report a similar relationship between HLA matching and graft survival are exclusively univariate[2,12] and therefore not able to control for confounding variables to the same precision as our multivariate Cox proportional regression models. This is essential when investigating graft survival, due to its multifactorial nature.

Interestingly, we found that graft survival at 10 and 15 years, but not at 5 years, is influenced by the degree of mismatch. This is likely a reflection of the nature of HLA-mediated injury, producing a slower, more prolonged pattern of injury to the allograft through circulating DSA's, combined with the relative resistance of liver allografts to acute antibody-mediated rejection due to the livers' inherent 'tolerogenic' properties. This is reflected in the literature, where circulating

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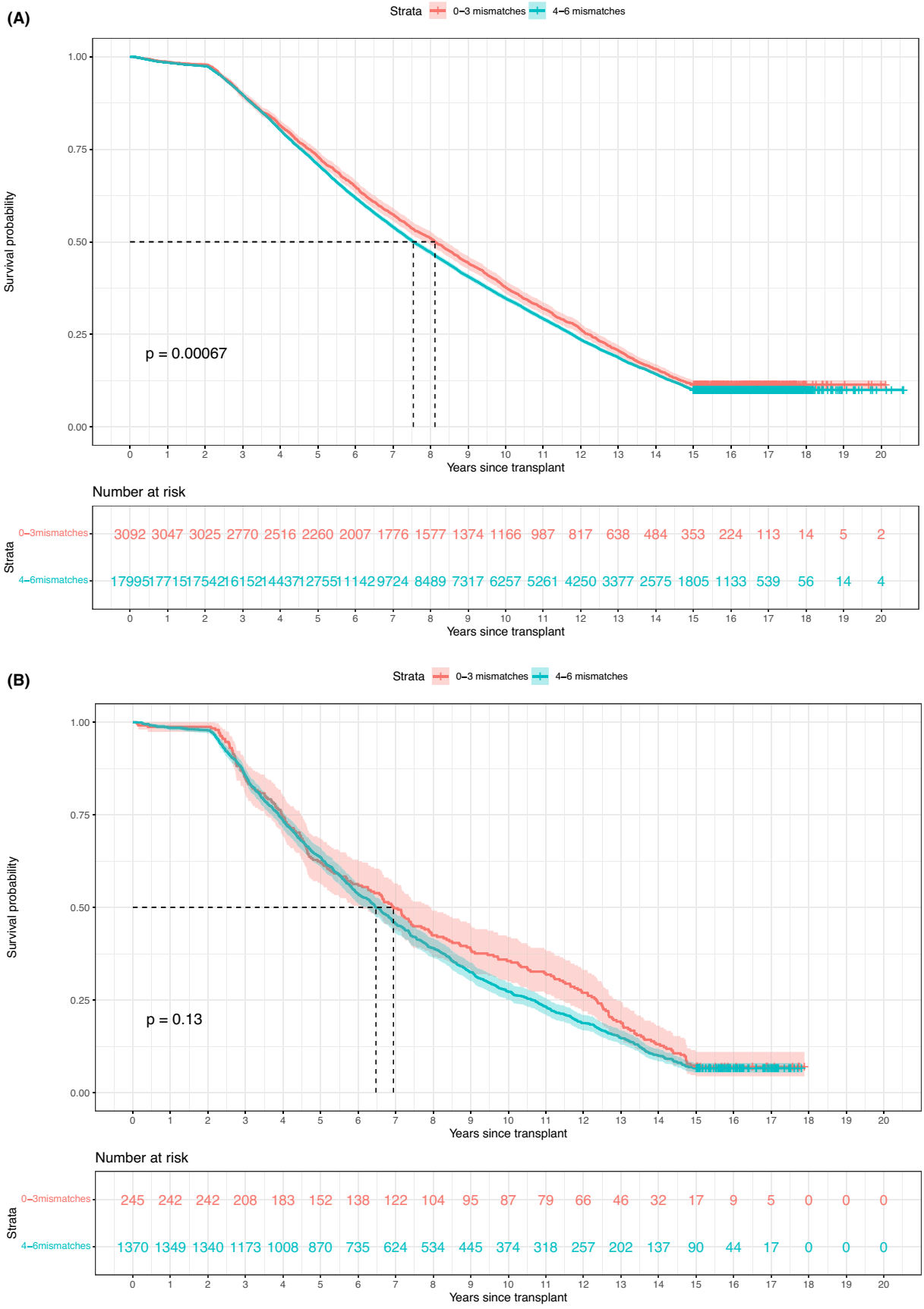


FIGURE 4 (A) Kaplan–Meier survival curves demonstrating the 0–3 HLA mismatch group versus the 4–6 HLA mismatch group in DBD patients. (B) Kaplan–Meier survival curves demonstrating the 0–3 HLA mismatch group versus the 4–6 mismatches group in DCD patients.

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DSA levels are not correlated with survival rates at up to 5 years.[13] A recent systematic review conducted by Beyzaei et al[14] provides further weight to the argument that HLA-mediated liver damage manifests across a prolonged time period, finding that the effect of DSAs on allograft loss and rejection was more consistently demonstrated, with a larger effect size, in studies with follow-up periods greater than 5 years. The mechanisms behind this delayed pathology are yet to be elucidated; however, antibody-mediated chronic rejection, increased risk of hepatic fibrosis, and microvascular damage have been suggested as potential aetiologies.[15,16]

The present study utilizes the largest and most comprehensive database study to investigate and compare the influence of HLA matching on graft survival in different indications for liver transplantation. Taking advantage of the large sample, we were able to show that the effect of HLA matching on liver graft survival is observed in specific indications for liver transplant. We observed that HLA matching improved graft survival for recipients with hepatitis and drug toxicity at 5 years (but not in the longer term) and improved long-term graft survival (10 and 15 years) for recipients with metabolic, congenital, and 'other' causes of liver failure. We did not observe an association between HLA matching and graft survival in cancer, NASH, and alcoholic cirrhosis. Prior studies have shown an association of HLA matching with worse overall survival in autoimmune hepatitis, with the rationale that HLA epitopes that are matched to those of the recipient may induce a recurrent autoimmune response. We did observe an increase in graft survival at 5 years in patients with a higher degree of mismatching in autoimmune patients; however, this difference failed to reach statistical significance ($p = .062$).

The idea that the influence of HLA matching on liver graft survival could be indication-specific was first suggested by Markus et al in 1988,[17] who argued that their inability to detect an association between HLA matching and liver graft survival reflected the opposing effects of HLA matching in different indications. They proposed that HLA compatibility exerted a dualistic effect, on one hand preventing transplant rejection but on the other hand enhancing other immune mechanisms which cause allograft dysfunction. This 'dualistic' theory has traditionally been explored in several papers within the context of autoimmune disease.[3,18,19] In autoimmune disease, the putative mechanisms behind HLA's ability to influence graft survival externally of rejection are intuitive, as grafts with greater HLA compatibility would be seen as closer to self and more prone to autoimmune attack. This is reflected in the literature, where there is evidence to suggest that HLA matching is correlated with increased risk of autoimmune disease recurrence in liver and in other solid organ transplants.[20-23]

The manner in which HLA matching can influence graft survival beyond rejection is less clear in other indications; however, the ubiquity of HLA in the immune response provides a number of potential mechanisms. For example, a range of HLA serotypes have been demonstrated to be independently associated with the development of NASH and alcoholic fatty liver disease.[24-26]

Our study identified a significant survival advantage (733 days) in patients with better HLA matching who underwent transplantation for congenital metabolic defects. It must be noted that a significant proportion of these patients were paediatric recipients (20%), whereas paediatric recipients make up only 5.6% of the overall cohort. Prior studies on the effect of HLA matching and liver graft survival in paediatric cohorts have shown no effect of HLA matching, possibly due to their smaller sample sizes.[5,27] Whether this beneficial effect is to be attributed to the biology of metabolic disease or the young age of the patients cannot be inferred from our dataset, as there are few adult patients transplanted for metabolic disorders that could be used address this question. One may hypothesize that lower dose immunosuppression, frequently used in paediatric recipients, may have 'unmasked' a biologic effect of HLA matching, which is less relevant in adult patients who are treated with heavier immunosuppressive regimens.

Our study is the first to investigate the relationship between HLA matching and graft survival in DCD vs DBD patients. Our findings were two-fold. Firstly, we identified that the difference in graft survival in DBD vs DCD patients was reduced in the 0–3 HLA mismatches group. Secondly, HLA matching only exerted a statistically significant influence on graft survival in the DBD group, although the DCD-matched group was likely underpowered, given the small sample size. Larger studies are required to confirm our results as the number of DCD organs continues to expand.

The limitations of this study are tied to the inherent limitations of the UNOS/OPTN database. The UNOS/OPTN database contains a significant amount of missing data and, although our included patient cohort is large, we had to exclude 97 802 patients from the analysis because of incomplete HLA serotyping data. While the patients were stratified per indication, HLA loci were not. A potential extension to this study would be to group HLA loci into HLA-A, -B, and, -DR as several studies have shown differential impacts of mismatching at these respective loci on liver transplant outcomes.[28,29] Additionally, there is evidence that not all mismatches are the same, as loci that have similar molecular configurations (eplets) may exert different immunogenic responses.[30]

We were unable to control for other factors which may influence graft outcomes, including specific immunosuppressive regimens. There were also some important differences in the characteristics of the two groups, most significantly the 4–6 HLA mismatch group had more Black patients (an independent risk factor for poor graft survival)[31] than the 0–3 mismatch group. However, the effects of this were mitigated through its inclusion in multivariate modelling. Furthermore, as no temporal data are provided by the UNOS database regarding when acute rejection occurs, we were unfortunately not able to perform a time-dependent analysis. Despite these limitations, we believe that the current study's large, multi-institutional registry database, and comprehensive multivariate analysis have produced robust conclusions.

In conclusion, the present study found that HLA mismatching significantly reduced graft survival time and increased risk of acute rejection in first-time liver transplant recipients. This association was noted only in specific indications for liver transplant (hepatitis, drug

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toxicity, metabolic, congenital, and other causes). Although further studies will be required to better clarify the clinical importance of HLA matching in these patients' categories, our data have a potential clinical relevance, as one may want to modulate immunosuppression and/or increase surveillance in potential 'high–risk' category patients.

AUTHOR CONTRIBUTIONS

All authors have made a substantial contribution to the concept or design of the article, or the acquisition, analysis, or interpretation of data for the article.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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