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ORIGINAL ARTICLE

Donor–recipient human leukocyte antigen A mismatching is associated with hepatic artery thrombosis, sepsis, graft loss, and reduced survival after liver transplant

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Abstract

Human leukocyte antigen (HLA) matching is not routinely performed for liver transplantation as there is no consistent evidence of benefit; however, the impact of HLA mismatching remains uncertain. We explored the effect of class I and II HLA mismatching on graft failure and mortality. A total of 1042 liver transplants performed at a single center between 1999 and 2016 with available HLA typing data were included. The median follow-up period was 9.38 years (interquartile range 4.9–14) and 350/1042 (33.6%) transplants resulted in graft loss and 280/1042 (26.9%) in death. Graft loss and mortality were not associated with the overall number of mismatches at HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ loci. However, graft failure and mortality were both increased in HLA mismatching on graft failure and mortality the presence of one ($p = 0.004$ and $p = 0.01$, respectively) and two ($p = 0.01$ and $p = 0.04$, respectively) HLA-A mismatches. Elevated hazard ratios for graft failure and death were observed with HLA-A mismatches in univariate and multivariate Cox proportional hazard models. Excess graft loss with HLA-A mismatch (138/940 [14.7%] mismatched compared with 6/102 [5.9%] matched transplants) occurred within the first year following transplantation (odds ratio 2.75; $p = 0.02$). Strikingly, transplants performed at a single all grafts lost due to hepatic artery thrombosis were in HLA-A–mismatched transplants (31/940 vs. 0/102), as were those lost due to sepsis (35/940 vs. 0/102). In conclusion, HLA-A mismatching was associated with increased graft loss and mortality. The poorer outcome for the HLA-mismatched group was due to hepatic artery thrombosis and sepsis,

Abbreviations: AMR, antibody-mediated rejection; ArLD, alcohol-related liver disease; CI, confidence interval; CREG, cross-reactive group; DBD, donation after brainstem death; DCD, donation after circulatory death; GI, gastrointestinal; HAT, hepatic arterial thrombosis; HCC, hepatocellular carcinoma; HLA, human leukocyte antigen; HR, hazard ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; MM, mismatch; OR, odds ratio.

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and these complications occurred exclusively with HLA-A–mismatched transplants. These data suggest that HLA-A mismatching is important for outcomes following liver transplant. Therefore, knowledge of HLA-A matching status may potentially allow for enhanced surveillance, clinical interventions in high-risk transplants or stratified HLA-A matching in high-risk recipients.

INTRODUCTION

Mismatches in donor and recipient human leukocyte antigens (HLAs) are associated with adverse outcomes for most solid organ transplants, including kidney,[1–4] heart and lung,[5–8] and pancreas[9] transplants, which can be mitigated by donor–recipient HLA matching, desensitization strategies, and personalized immunosuppression regimens. However, the evidence that mismatches at class I (HLA-A, HLA-B, HLA-C) or class II (HLA-DR, HLA-DQ) HLA loci influence outcomes for liver transplantation remains inconsistent.[10,11] The liver is considered to have a low immunological barrier to transplantation; unmatched liver transplants are well tolerated,[11] and typically lower levels of immunosuppression are required compared to other transplanted organs. Additionally, immunosuppression-free tolerance is achievable in selected patients,[12] suggesting that the liver has distinct immunological characteristics compared with other solid organ transplants.

One previous study of 799 liver transplant recipients reported reduced survival following transplants mismatched at HLA-A and separately, increased rates of immune-mediated disease recurrence in those with HLA-DR mismatches.[10] Conversely, an earlier, very large cohort of nearly 30,000 liver transplants between 1987 and 2002, recorded in the Organ Procurement and Transplantation Network database, did not show consistent associations with HLA mismatches and clinical outcomes, although in univariate analysis an increased graft loss at 5 years with two HLA-A mismatches was observed.[11]

As there is no clear evidence for benefit, liver transplants are not routinely HLA matched; however, our understanding of the immunological outcomes of liver transplant has changed over recent years. Historically, transplanted livers were thought to be resistant to antibody-mediated rejection (AMR), which causes significant problems in other solid organ transplants. Now AMR is an increasingly recognized cause of liver graft dysfunction and loss, which can in some cases be modifiable via augmented immunosuppressive therapy.[13–15] In addition, immunosuppression regimens have changed over the years, influencing the rates of rejection,[16–18] and protocolized withdrawal of immunosuppression is gaining traction.[12] Changes in immunosuppressive regimens over the years have influenced outcomes, and therefore, it is important to reassess the significance of HLA matching to transplant outcomes including modern era practice.

We undertook a retrospective assessment of transplant outcomes following liver-only transplantation by exploring the importance of HLA matching at class I and class II HLA loci in our institution. Historically, both liver donor and recipient underwent HLA typing at the time of liver transplantation, although no matching nor tailoring of immunosuppression regimen was undertaken based on the results. Here we compare the outcome of liver transplants with HLA-matched and HLA-mismatched grafts, assessing graft and patient survival in a large cohort study with prospective HLA evaluation.

PATIENTS AND METHODS

Study population

All liver transplants performed at the Royal Free Hospital, London between October 20, 1999, and December 15, 2016, were analyzed. During this period routine HLA typing of both donors and recipients was performed. Patients were identified from the hospital's liver transplant database. Clinical, demographic, and transplant outcomes data were extracted on August 1, 2018. The database is prospectively completed following listing of each patient for transplantat and is maintained as a statutory requirement for data returns to the UK National Transplant Database. The data fields collected are >96% complete.

Each transplant was linked to the donor and recipient HLA typing data. A total of 1165 liver transplants were identified over this period, of which 123 were excluded due to missing HLA typing data for either donor or recipient, leaving a cohort of 1042 transplants. Patient numbers included in the cohort are shown in Figure 1.

Underlying liver disease was taken as that recorded on entry to the liver transplant waiting list. Where hepatocellular carcinoma (HCC) was present, patients were reported for both background cause of liver disease and HCC. Clinical outcomes and cause of graft loss were those as recorded in the transplant database, grouped into clinically relevant categories.

Ethical considerations

All patient data were collected routinely in the course of clinical care, anonymized, and analyzed retrospectively.

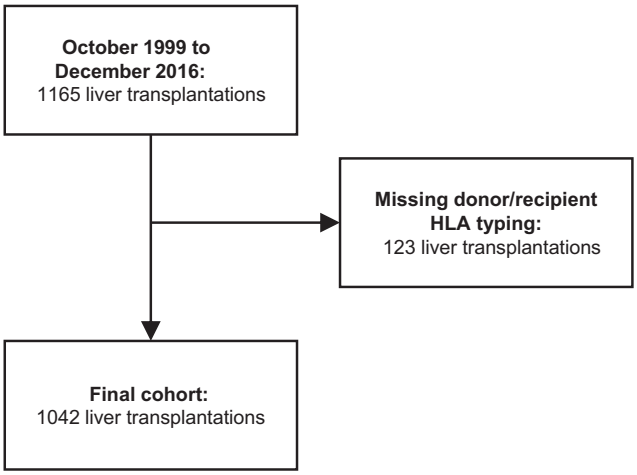


FIGURE 1 Flowchart of liver transplantations included in the study

HLA typing

Donor and recipient HLA class I and II typing was performed on samples obtained at the time of organ retrieval and admission for transplantation, respectively, by serological typing and polymerase chain reaction-sequence-specific amplification (Lamda Monoclonal Trays and generic Micro SSP, respectively; One Lambda Inc, West Hills, CA) between 1999 and 2004, polymerase chain reaction-sequence-specific oligonucleotide (LABType SSO; One Lambda Inc) between 2005 and 2015, and Pacific Biosciences' Single Molecule Real-time DNA sequencing technology in 2016. Broad serological HLA mismatches between donor and recipient were identified manually at the HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ loci and the number of mismatches was quantified at each locus (0, 1, or 2).

Clinical outcomes

Clinical outcomes were determined from the hospital transplant database as graft survival (an alive patient with a functioning graft) and patient survival. Causes of graft failure and death were similarly derived from the database and grouped into etiological categories; specifically, all infectious causes were grouped as sepsis and postoperative hemorrhage as early (<10 days following transplantation) or late (≥10 days following transplantation). Early graft loss and mortality were defined as these events occurring within 12 months of transplantation.

Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR) while categorical variables were expressed as frequencies and percentages. Differences between populations were analyzed with the Student *t*-test for continuous variables and chi-square or Fisher exact test for categorical variables. Graft or patient survival was estimated with Kaplan–Meier curves and association between HLA mismatch and graft and patient survival time by log-rank analysis. Hazards of graft failure and mortality were estimated by univariate and multivariate Cox proportional hazard models. Available donor and recipient risk factors, known to be associated with outcome following liver transplant, were included in the Cox proportional hazard models and are shown in Table 1. Factors with $p < 0.05$ at the univariate analysis were included in the multivariate analysis. A p value <0.05 was considered significant. Haldane–Anscombe corrections were applied when odds ratios (ORs) including 0 events were calculated. Analyses were performed with SPSS (version 25; IBM, New York, NY) and Prism (version 7; GraphPad Software, San Diego, CA).

RESULTS

A total of 1042 liver transplants were included with a median follow-up period of 9.38 years (IQR 4.9–14 years; Table 1). The median recipient age at transplantation was 52 years (IQR 43–58) and 692 recipients (66%) were male. Elective transplants accounted for 887 operations (88%), emergency procedures for the remaining 121 (12%) transplants, and 79 (8%) were repeat transplant procedures. The clinical and demographic characteristics of the cohort are summarized in Table 1.

Over the course of follow-up graft failure occurred following 350/1042 (33.6%) transplants and death after 280/1042 (26.9%) transplants. In those experiencing graft loss, the median period from transplant to graft loss was 20 months and in those dying in the follow-up period the median time from transplant to death was 33 months.

Broad HLA-A mismatches were associated with impaired graft and patient survival

We first tested whether the overall number of HLA mismatches was associated with differences in graft survival using time-to-event analyses (Figure 2). We observed that the total number of mismatches across combined HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ loci (Figure 2A); combined HLA-A, HLA-B, and HLA-DR (Figure 2B); or class I or class II loci alone (Figure 2C,D, respectively) were not associated with significant differences in graft survival over time.

Although the total number of HLA mismatches was not associated with differences in graft survival,

TABLE 1 Patient demographics and clinical characteristics of liver transplantation procedures included in the study

Demographics and characteristics	Values
Total	1042
Follow-up, years	9.38 (4.9–14)
Era of transplantation	
1999–2005	322 (31)
2006–2010	288 (28)
2011–2016	432 (41)
Male sex	692 (66)
Age, years	52 (43–58)
Ethnicity[a]	
White	764 (73)
Asian	196 (19)
Black	66 (6)
Other	15 (1)
Etiology of liver disease[b]	
Hepatitis C cirrhosis	224 (21)
ArLD	217 (21)
HCC	190 (18)
Primary sclerosing cholangitis	93 (9)
Primary biliary cholangitis	82 (8)
Retransplantation	79 (8)
Hepatitis B infection	69 (7)
Non-A–E acute liver failure	53 (5)
Cryptogenic cirrhosis	44 (4)
Nonalcoholic fatty liver disease	31 (3)
Autoimmune hepatitis	31 (3)
Other	119 (11)
Recipient BMI, kg/m^2 (median)[c]	25 (22–29)
MELD score (median)[d]	15 (11–21)
Failure grade	
Acute	121 (12)
Nonacute	887 (88)
Donor status	
Brainstem death (DBD)	944
Cardiac death (DCD)	92
Living	6
Male donor sex	529 (51)
Donor age, years	46 (33–56)
Cold ischemic time, minutes[e]	511 (406–650)

Note: Data are presented as *n* or *n* (%) or median (IQR).

Abbreviations: BMI, body mass index; DBD, donation after brainstem death; DCD, donation after circulatory death; HCC hepatocellular carcinoma; IQR, interquartile range; MELD, Model for End-Stage Liver Disease.

[a]*n* = 1041, as patients with HCC are also shown under the primary cause of liver disease.

[b]*n* > 1042, as patients with HCC are also shown under the primary cause of liver disease.

[c]*n* = 1010.

[d]*n* = 1038.

[e]*n* = 1008.

when we explored the effect of independent HLA mismatches we observed that one or two mismatches at the HLA-A locus were associated with a significant reduction in graft survival (p = 0.004 for one mismatch and p = 0.01 for two mismatches, respectively; Figure 3A) and patient survival (p = 0.01 and p = 0.04, respectively; Figure 3B) compared with transplants fully matched at HLA-A. Importantly, there were no significant differences in population demographics or clinical characteristics between those with and without HLA-A mismatches (Table 2). No significant differences in graft or patient survival were observed for mismatches at HLA-B, HLA-C, HLA-DR, or HLA-DQ (Figure 3C and Figure S1) except for reduced patient survival with transplants fully matched at HLA-C (p = 0.05 and 0.07 compared with 1 and 2 mismatches).

We next tested a range of factors, including numbers of HLA mismatches, for association with graft failure. Univariate Cox regression analysis revealed that factors associated with impaired outcome were HLA-A mismatch (hazard ratio [HR], 1.93 for 1 mismatch; p = 0.004 and HR, 1.77 for 2 mismatches; p = 0.01), indication for transplantation (compared with alcohol-related liver disease [ArLD]: HCC HR, 1.47, p = 0.04; primary sclerosing cholangitis HR, 1.59, p = 0.04; and retransplant HR, 1.62, p = 0.03), and increasing donor age (HR, 1.01; p < 0.001). Modern era transplantation was associated with improved outcomes (2011–2016 compared with 1999–2005 HR, 0.64; p = 0.003). All of these factors remained significantly associated with graft failure in multivariate analysis (Table 3). Mismatches at HLA-B, HLA-C, HLA-DR, and HLA-DQ were not associated with differences in the hazard of graft loss.

To test whether the era of transplantation was associated with differences in the impact of HLA-A mismatching on graft survival, we undertook Kaplan–Meier and univariate Cox regression analyses (Figure S2). These demonstrated a consistent trend in improved graft survival with transplants fully matched at the HLA-A locus compared with those with one or two mismatches across all three eras, suggesting that the impact of HLA-A mismatch was consistent throughout the study.

Analysis of factors associated with patient mortality revealed similar associations as for graft failure in the whole cohort; increased mortality was observed with mismatches at HLA-A (HR, 1.93 for one mismatch; p = 0.01 and HR, 1.70 for two mismatches; p = 0.04), increasing recipient age (HR, 1.02; p < 0.001), donor age (HR, 1.01; p < 0.001), and indication for transplantation (compared with ArLD: HCC HR, 1.64; p = 0.02; retransplantation HR, 1.87; p = 0.01) following univariate Cox regression analysis. Conversely, improved mortality outcomes were associated with modern era of transplantation (2011–2016 compared with 1999–2005 HR, 0.62; p = 0.005) and the presence of HLA-C mismatch

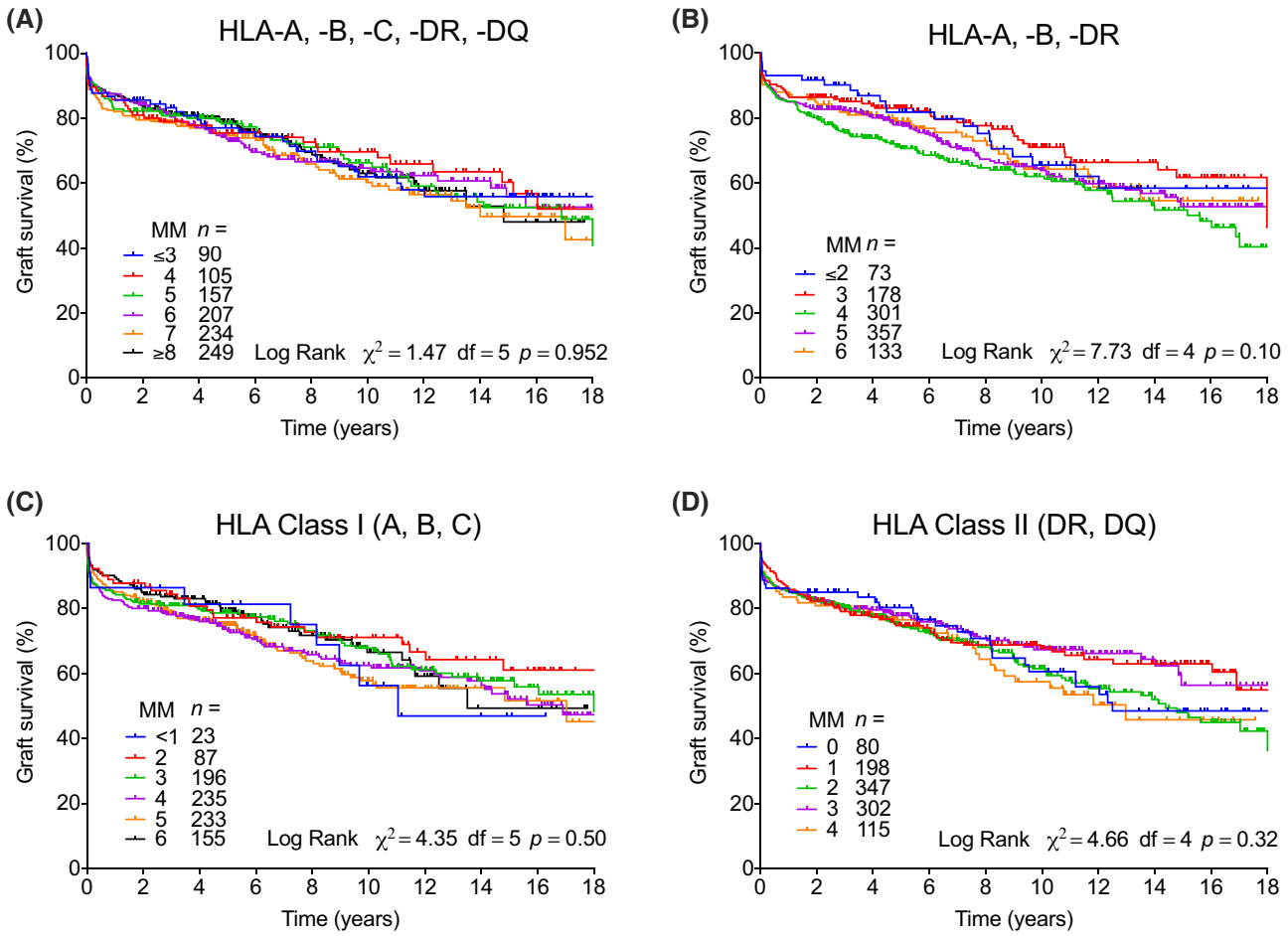


FIGURE 2 Effect of the overall number of HLA mismatches upon long-term graft survival. Kaplan–Meier plots of survival grouped by total number of HLA mismatches at (A) all HLA loci (A, B, C, DR, DQ); (B) HLA-A, HLA-B and HLA-DR; (C) HLA class I (HLA-A, HLA-B, HLA-C); and (D) HLA class II (HLA-DR, HLA-DQ). Survival curves compared by log-rank analyses. *$p < 0.05$; **$p < 0.01$

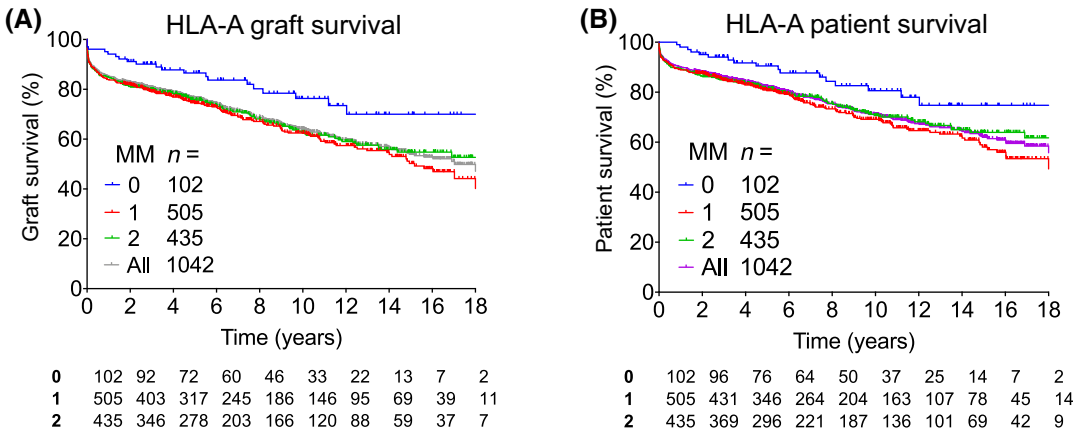
(HR, 0.75 for 1 mismatch; $p = 0.05$). Multivariate Cox regression analysis retained the associations between HLA-A mismatch, era, donor and recipient age, and indication for transplantation but HLA-C mismatch was no longer associated (Table S1).

Kaplan–Meier analysis of HLA-C, HLA-DR, and HLA-DQ mismatching did not reveal any consistent association between graft failure rates and study era (1999–2005, 2006–2010, and 2011–2016; Figure S3). When the HLA-B locus was tested, no significant differences in graft failure were seen between matched and unmatched transplants in the earlier two eras, but in 2011–2016 a significant increase in graft failure with one or two mismatches at HLA-B was observed (Figure S3). Graft failure rates in the modern era were 0/13 for those fully matched at HLA-B and 78/419 in those with one or two mismatches. The causes of graft loss in the HLA-B–mismatched transplants were predominantly infection and recurrent liver disease (Table S2).

Specific HLA-A mismatches and combinations of mismatches are associated with graft loss

To assess whether specific HLA-A mismatches were associated for impaired graft survival, we analyzed the five most prevalent HLA-A mismatches in the cohort. This demonstrated a consistent reduction in graft survival over time with mismatches at HLA-A2 ($p = 0.01$), HLA-A1 ($p = 0.003$), and HLA-A24 ($p = 0.01$), but a nonsignificant trend with HLA-A3 and HLA-A11 (Figure 4A,B). These associations were confirmed with univariate and multivariate Cox regression analyses (Figure 4C) using the same multivariate model as in Table 3.

Although we did not observe any differences in overall patient or graft survival with mismatches at loci other than HLA-A, we tested whether there was an additive effect of mismatches at other loci in addition to HLA-A1 mismatch, which was the mismatch most



(C)

	Graft survival				Patient survival			
	MM	χ^2 =	df=	*p*=	MM	χ^2 =	df=	*p*=
HLA-A	0 vs. 1	8.39	1	0.004**	0 vs. 1	6.80	1	0.009**
	0 vs. 2	6.33	1	0.01*	0 vs. 2	4.35	1	0.04*
	1 vs. 2	0.58	1	0.45	1 vs. 2	1.08	1	0.30
HLA-B	0 vs. 1	0.58	1	0.45	0 vs. 1	1.33	1	0.25
	0 vs. 2	0.73	1	0.39	0 vs. 2	1.14	1	0.29
	1 vs. 2	0.15	1	0.70	1 vs. 2	0.05	1	0.82
HLA-C	0 vs. 1	1.68	1	0.20	0 vs. 1	3.95	1	0.05*
	0 vs. 2	0.94	1	0.33	0 vs. 2	3.30	1	0.07
	1 vs. 2	0.18	1	0.67	1 vs. 2	0.11	1	0.74
HLA-DR	0 vs. 1	0.00	1	0.97	0 vs. 1	0.06	1	0.81
	0 vs. 2	0.11	1	0.74	0 vs. 2	0.11	1	0.74
	1 vs. 2	0.40	1	0.53	1 vs. 2	0.01	1	0.90
HLA-DQ	0 vs. 1	0.04	1	0.84	0 vs. 1	0.02	1	0.89
	0 vs. 2	1.75	1	0.19	0 vs. 2	0.89	1	0.35
	1 vs. 2	2.49	1	0.11	1 vs. 2	0.95	1	0.33

FIGURE 3 HLA-A mismatch and long-term graft and patient survival. Kaplan–Meier plots of (A) graft survival and (B) patient survival comparing 0, 1, and 2 mismatches at HLA-A. (C) Log-rank analysis of graft and patient survival by number of mismatches at each HLA locus. *$p < 0.05$; **$p < 0.01$

significantly associated with graft loss. We observed that for the four most prevalent additional mismatches in those with HLA-A1 mismatch, the presence of an additional mismatch at HLA-B8 ($p = 0.03$) or HLA-D17 ($p = 0.01$) was associated with an increased hazard of graft failure compared with no HLA-A1 mismatch (Figure 5). Whether these associations relate to the highly linked HLA haplotypes common in this population, linkage disequilibrium between the HLA loci and other closely positioned non-HLA loci on chromosome 6, or a true influence of specific class I and class II non-A HLA mismatches remains uncertain.

Overall, these observations suggested that donor–recipient HLA-A mismatching had a major influence on graft and patient survival, consistent across a range of specific HLA-A mismatches. The effect was increased even further when HLA-A was combined with specific additional class I and II HLA mismatches.

HLA-A mismatches are associated with early graft loss due to hepatic arterial thrombosis and sepsis

The survival curves in Figure 3 demonstrated divergence in graft and patient survival of those mismatched at HLA-A in the period immediately following LT. We therefore explored the clinical events that occurred in the first 12 months following LT. Lower graft and patient survival with one or two HLA-A mismatches were driven by graft failure or death predominantly in the first 2 months following LT (Figure 6A,B). When long-term analysis was censored by survival at 12 months following LT, no significant difference in graft survival was observed for HLA-A–mismatched transplants, compared with fully HLA-A–matched transplants (Figure 6C,D), confirming that the main influence of HLA-A mismatch on adverse outcomes was in the early period after LT.

TABLE 2 Patient demographics and clinical characteristics of liver transplantation procedures by HLA-A mismatch status

	HLA-A 0 mismatch	HLA-A 1+2 mismatches	
Demographics and characteristics	**Values**	**Values**	***p* value**
Total	102	940	
Follow-up, years	8.87 (4.9–13)	9.39 (4.9–14)	0.22
Era of transplantation			0.46
1999–2005	26 (26)	296 (32)	
2006–2010	31 (30)	257 (27)	
2011–2016	45 (44)	387 (41)	
Male recipient sex	70 (69)	622 (66)	0.62
Age, years	52 (47–58)	51.5 (43–58)	0.15
Ethnicity			0.14
White	84 (82)	680 (72)	
Asian	12 (12)	184 (20)	
Black	4 (4)	62 (7)	
Other	2 (2)	14 (1)	
Etiology of liver disease			0.59
Hepatitis C infection	25 (25)	199 (21)	
ArLD	28 (27)	189 (20)	
HCC	22 (22)	168 (18)	
Primary sclerosing cholangitis	7 (7)	86 (9)	
Primary biliary cholangitis	5 (5)	77 (8)	
Retransplantation	7 (7)	72 (8)	
Hepatitis B virus infection	6 (6)	63 (7)	
Non-A–E acute liver failure	5 (5)	48 (5)	
Cryptogenic cirrhosis	3 (3)	41 (4)	
Nonalcoholic fatty liver disease	0 (0)	31 (3)	
Autoimmune hepatitis	4 (4)	27 (3)	
Other	12 (12)	107 (11)	
Recipient BMI, kg/m^2	25 (23–29)	25 (22–29)	0.40
MELD score	14 (10–21)	15 (11–21)	0.20
Failure grade			0.97
Acute	12 (12)	109 (12)	
Nonacute	87 (88)	800 (88)	
Donor status			0.14
Brainstem death (DBD)	90 (88)	854 (91)	
Cardiac death (DCD)	10 (10)	82 (8.7)	
Living	2 (2)	4 (0.4)	
Male donor sex	59 (58)	470 (50)	0.13
Donor age, years	44.5 (35–56)	46 (33–57)	0.99
Cold ischemic time, minutes	526 (439–681)	509 (404–645)	0.30

Note: Data are presented as *n* or *n* (%) or median (IQR).

Abbreviations: ArLD, alcohol-related liver disease; BMI, body mass index; DBD, donation after brainstem death; DCD, donation after circulatory death; HCC, hepatocellular carcinoma; HLA, human leukocyte antigen; IQR, interquartile range; MELD, Model for End-Stage Liver Disease.

Exploration of the reasons for graft loss following LT revealed that, as expected, immediate surgical complications (intraoperative complications, primary nonfunction, hemorrhage, and venous occlusion) occurred earliest, followed by arterial thromboses, nonoperative site hemorrhages, and sepsis. Later in the first year following liver transplantation, the main causes of graft loss were primary disease recurrence, comorbidities, rejection, and biliary disorders (Figure 6E and Table 4).

TABLE 3 Univariable and multivariable Cox regression analysis of clinical and demographic factors associated with graft failure

Demographics and characteristics	Univariate				Multivariate			
	HR	95% CI		*p* value	HR	95% CI		*p* value
		Lower	Upper			Lower	Upper	
Era of transplantation								
1999–2005	1							
2006–2010	0.89	0.70	1.15	0.38	0.85	0.66	1.10	0.21
2011–2016	0.64	0.48	0.86	0.003*	0.59	0.44	0.79	<0.001*
Recipient age	1.01	1.00	1.02	0.11				
Donor age	1.01	1.01	1.02	<0.001*	1.015	1.008	1.022	<0.001*
Female (vs. male)	1.02	0.82	1.28	0.84				
Ethnicity								
White	1							
Asian	1.02	0.66	1.60	0.92				
Black	1.07	0.65	1.76	0.80				
Recipient BMI	0.99	0.96	1.01	0.26				
MELD	1.00	0.99	1.01	0.82				
Diagnosis								
ArLD	1							
Hepatitis C infection	1.40	0.94	2.07	0.10	1.38	0.93	2.05	0.11
HCC	1.47	1.02	2.13	0.04*	1.58	1.09	2.28	0.02*
Primary sclerosing cholangitis	1.59	1.02	2.49	0.04*	1.73	1.11	2.70	0.02*
Primary biliary cholangitis	1.08	0.67	1.73	0.76	1.05	0.65	1.70	0.83
Retransplantation	1.62	1.04	2.52	0.03*	1.63	1.05	2.54	0.03*
Hepatitis B virus infection	1.19	0.62	2.28	0.61	1.16	0.60	2.23	0.66
Non-A–E acute liver failure	1.22	0.70	2.11	0.48	1.20	0.69	2.08	0.52
Cryptogenic cirrhosis	1.44	0.83	2.50	0.19	1.45	0.83	2.53	0.19
Nonalcoholic fatty liver disease	1.11	0.44	2.78	0.83	1.24	0.49	3.12	0.65
Autoimmune hepatitis	1.28	0.67	2.46	0.46	1.33	0.69	2.56	0.39
Other	1.10	0.71	1.71	0.67	1.12	0.72	1.74	0.61
Acute failure (vs. nonacute)	1.01	0.74	1.40	0.94				
DCD (vs. DBD)	1.13	0.75	1.70	0.56				
Cold ischemic time	1	1	1.00	0.73				
HLA-A								
0 mismatches	1							
1 mismatch	1.93	1.23	3.03	0.004*	1.91	1.22	3.01	0.005*
2 mismatches	1.77	1.12	2.80	0.01*	1.71	1.08	2.71	0.02*
HLA-B								
0 mismatches	1							
1 mismatch	1.27	0.66	2.41	0.48				
2 mismatches	1.32	0.70	2.49	0.39				
HLA-C								
0 mismatches	1							
1 mismatch	0.85	0.65	1.10	0.21				

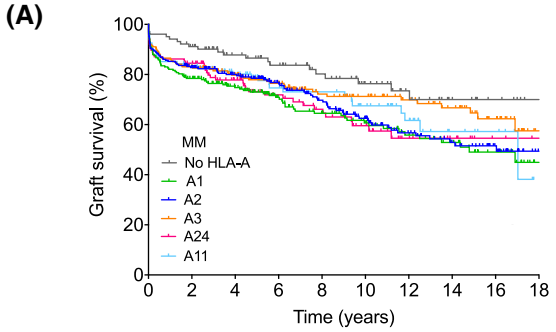
(Continues)

TABLE 3 (Continued)

Demographics and characteristics	Univariate				Multivariate			
	HR	95% CI Lower	95% CI Upper	*p* value	HR	95% CI Lower	95% CI Upper	*p* value
2 mismatches	0.89	0.69	1.15	0.37				
HLA-DR								
0 mismatches	1							
1 mismatch	1.01	0.70	1.44	0.97				
2 mismatches	0.94	0.65	1.34	0.72				
HLA-DQ								
0 mismatches	1							
1 mismatch	0.98	0.78	1.23	0.84				
2 mismatches	1.26	0.91	1.73	0.16				

Abbreviations: ArLD, alcohol-related liver disease; BMI, body mass index; CI, confidence interval; DBD, donation after brainstem death; DCD, donation after circulatory death; HCC, hepatocellular carcinoma; HLA, human leukocyte antigen; HR, hazard ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease.

*$p < 0.05$.



No HLA-A	102	92	72	60	46	33	22	13	7	2
A1	218	166	131	94	76	61	43	32	21	3
A2	244	196	164	128	104	75	52	39	25	6
A3	201	163	137	100	77	66	50	39	23	4
A24	116	98	74	53	44	31	16	10	4	2
A11	108	89	72	52	43	33	22	10	7	1

(B)

MM	*n*	%	Log Rank χ^2	df	*p*=
A1	218	21	8.78	1	0.003**
A2	244	23	6.00	1	0.01*
A3	201	19	1.93	1	0.16
A24	116	11	6.02	1	0.01*
A11	108	10	3.03	1	0.08

(C)

MM	Univariate HR	95% CI Lower	95% CI Upper	*p*=	Multivariate HR	95% CI Lower	95% CI Upper	*p*=
A1	2.03	1.25	3.28	0.004**	2.04	1.25	3.32	0.004**
A2	1.79	1.12	2.87	0.02*	1.77	1.10	2.85	0.02*
A3	1.44	0.88	2.37	0.15				
A24	1.94	1.15	3.28	0.01*	2.17	1.25	3.78	0.006*
A11	1.64	0.95	2.83	0.07				

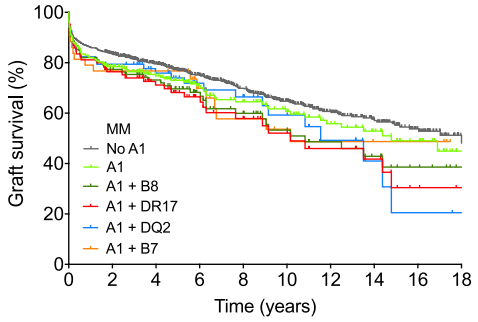
vs. no HLA-A mismatch

FIGURE 4 Prevalent HLA-A mismatches and long-term graft failure. (A) Kaplan–Meier survival curves with (B) log-rank analysis and (C) Cox regression analysis of the five most prevalent HLA-A mismatches compared with the population with no mismatches at HLA-A. *$p < 0.05$; **$p < 0.01$

Of the HLA-A–matched transplants, 6/102 (5.9%) failed in the first year compared with 138/940 (14.7%) of those with one or two HLA-A mismatches (OR 2.75, 95% CI 1.18–6.4; $p = 0.02$). Notably, all 31 grafts that were lost to hepatic arterial thrombosis (HAT) in the first year following liver transplantation were in patients with an HLA-A–mismatched graft (31/940 [3.3%] compared with 0/102 [0%] HLA-A–matched transplants; OR 7.1, 95% CI 0.4–116.8; $p = 0.17$), as were those lost due to sepsis (35/940 [3.7%] vs. 0/102 [0%]) (OR 8.04, 95% CI 0.49–132; $p = 0.14$; Table 4). When all occurrences of HAT were analyzed, including those that did not result in graft failure or death, 41/940 (4.4%) of HLA-A–mismatched transplants experienced HAT compared with 0/102 (0%) HLA-A–matched transplants (OR 9.5, 95% CI 0.58–154.91; $p = 0.12$).

When we tested for the presence of classical risk factors, as expected we observed that those who experienced hepatic artery thrombosis had significantly higher recipient age, poorer ABO matching, and multiple hepatic artery anastomoses compared with those who did not experience hepatic artery thrombosis (Table 5, see the column "Occurrence of hepatic artery thrombosis"). However, when this analysis was performed by grouping patients into those matched and mismatched at the HLA-A locus, no significant differences in the frequency of classical risk factors for hepatic artery thrombosis were observed between the HLA-A–matched and HLA-A–mismatched transplants (Table 5, see the column "HLA-A mismatch status"). This suggested that the increased rate of hepatic artery thrombosis in mismatched transplants was not driven

(A)



No A1	824	674	538	412	321	239	162	108	61	17
A1	218	166	131	94	76	61	43	32	21	3
A1 + B8	106	80	65	44	33	25	19	13	7	2
A1 + D17	85	63	50	33	25	19	14	10	4	2
A1 + DQ2	68	54	43	28	24	17	10	5	3	2
A1 + B7	43	33	27	20	15	12	10	9	7	1

(B)

MM	*n*	%	Log Rank χ^2=	df	*p*=	
A1	218	21	1.90	1	0.17	
A1 + B8	106	10	4.89	1	0.03	*
A1 + DR17	85	8	6.46	1	0.01	*
A1 + DQ2	68	7	2.11	1	0.15	
A1 + B7	43	4	0.87	1	0.35	

(C)

MM	Univariate HR	95% CI Lower	Upper	*p*=		Multivariate HR	95% CI Lower	Upper	*p*=	
A1	1.19	0.93	1.52	0.17						
A1 + B8	1.42	1.04	1.95	0.03	*	1.52	1.10	2.10	0.01	*
A1 + DR17	1.55	1.10	2.18	0.01	*	1.65	1.17	2.33	0.005	*
A1 + DQ2	1.34	0.90	1.99	0.15						
A1 + B7	1.25	0.76	2.08	0.38						

vs. no HLA A1 mismatch

FIGURE 5 Association of additional HLA loci mismatches in addition to HLA-A1 mismatch with graft failure. (A) Kaplan–Meier survival curves with (B) log-rank analysis and (C) Cox regression analysis comparing the four most prevalent additional non-HLA-A mismatches in the presence of at least 1 HLA-A mismatch to transplantations fully matched at HLA-A

by an over-representation of classical risk factors for hepatic artery thrombosis.

We next tested whether transplants that were complicated by hepatic artery thrombosis or lost with sepsis were more likely to have adverse donor risk profiles. Donor risk index[19] characteristics that recorded in our data set were compared between those experiencing HAT and those not, and those resulting in graft loss with sepsis and those not (Table S3A,B). We observed no significant differences in the presence of adverse donor features in those experiencing HAT nor septic graft loss, although there was a nonsignificant trend of increased donor age in those experiencing septic graft loss (Table 3).

DISCUSSION

In this study we sought to explore the influence of HLA mismatching on clinical outcomes following liver transplantation. Our data demonstrate increased graft loss and patient death in those with HLA-A locus donor–recipient mismatch in this predominantly northern European, white population. We have demonstrated an association with both reduced patient survival and graft survival and mismatching at the HLA-A locus, which is maintained in adjusted multivariate Cox-proportional hazard models. Graft loss associated with HLA-A mismatches predominantly occurred in the first 12 months following liver transplantation and was predominantly driven by the presence of HAT and sepsis. Notably all grafts lost with HAT and sepsis occurred in HLA-A–mismatched transplants and none in those matched at HLA-A, suggesting that immune factors are important in early graft loss following liver transplant, despite the dogma that liver transplantation is relatively immune tolerant. Intriguingly, mismatches at HLA-B were also significantly associated with increased graft failure in the modern era only, although the numbers are too small to draw conclusions about the importance of this observation.

Our observation of an association between HLA-A mismatch and impaired patient survival and graft survival has been reported in other[10,20] but not all[11,21–31] liver transplant cohorts. Wider evidence for HLA-A mismatching impacting negatively on patient outcomes includes increased early acute rejection episodes[32] and failure of operational tolerance[33] in pediatric living donor liver transplant recipients. Similarly, higher rates of acute cellular rejection are associated with more class I[34] and specifically HLA-A mismatches[35] following deceased donor liver transplantation, although this has not been observed consistently in all studies.[36] Taken together, the evidence suggests an important role for HLA-A mismatching in liver transplant outcomes and alloimmune responses.

We observed no association between the total number of HLA mismatches at HLA-B, HLA-C, HLA-DR, or HLA-DQ loci in isolation on graft or patient survival, consistent with a range of other reports,[10,11,20,22,27,28,37–40] although again the literature is inconsistent with both positive and negative associations between matching at these loci and graft outcomes being reported.[21,24,26,31,41,42] Indeed, dualistic effects of HLA matching have been reported depending on the underlying cause of liver disease, with improved outcomes with poorly HLA-matched grafts in the presence of immune-mediated liver diseases and the opposite for nonimmune-mediated liver diseases.[24] Recent evidence suggests that class II HLA mismatching may also be associated with increased development of donor-specific antibodies.[34,43]

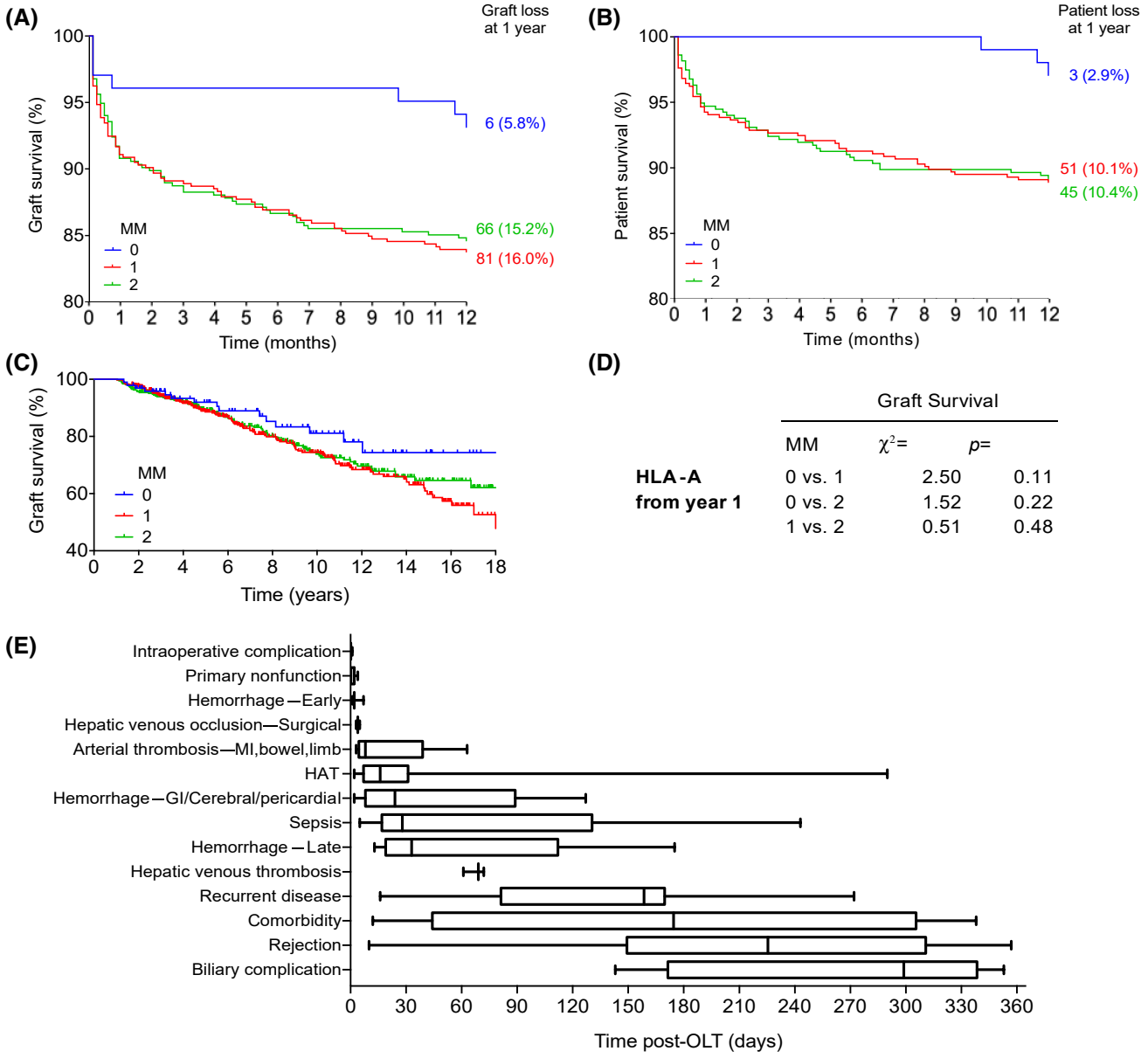


FIGURE 6 The influence of HLA-A mismatch on graft failure and mortality in the first year following liver transplantation. Kaplan–Meier plots for liver transplantations with 0, 1, and 2 HLA-A mismatches showing (A) 1-year graft survival and (B) 1-year patient survival. (C) Kaplan–Meier plot of long-term graft survival, censored by survival at 1 year following liver transplantation with (D) log-rank analysis. (E) Timing and causes of graft failure up to 1 year following liver transplantation. MI, myocardial infarction; OLT, orthotopic liver transplant

The differing reported effects of HLA matching may relate to variation in HLA typing methods, outcome measures, analytical approaches, patient cohorts, and immunosuppression regimens employed between studies. However, the degree of donor–recipient HLA matching overall does appear to influence individual liver transplant outcomes, consistent with our finding that HLA-A mismatching is an important predictor of adverse graft and patient outcomes.

Strikingly in our study, excess graft loss associated with HLA-A mismatch mainly occurred in the first year following liver transplantation and the majority of grafts lost with HLA-A mismatch were due to HAT and sepsis. It is novel and intriguing that HAT was observed exclusively in those who were HLA-A mismatched without an increase in the frequency of previously established risk factors for this in the mismatched group. HLA-A, along with other class I HLA antigens, is expressed on the vascular endothelium.[44] Classically, vascular thrombosis is typical of hyperacute rejection and acute AMR, which may be targeted against ABO or HLA antigens expressed on vascular endothelium.[14] Hence, our findings raise the question as to whether hepatic artery thrombosis may, in part, be an immunological phenomenon. Indeed, ABO-incompatible transplantation has been

TABLE 4 Causes of graft failure and presence of HLA-A mismatch in the first year following liver transplantation

	Time posttransplantation (days)		HLA-A mismatch and graft loss	
			HLA-A 0 mismatch	HLA-A 1 or 2 mismatches
Cause of graft loss	***n* (%)**	**Median (IQR)**	***n* (%)**	***n* (%)**
Sepsis—bacterial and viral	37 (24.2)	28 (17–129)	0 (0)	37 (100.0)
Hepatic artery thrombosis	31 (20.3)	16 (7–31)	0	31 (100.0)
Primary nonfunction	12 (7.8)	2 (0.5–2)	2 (16.7)	10 (83.3)
Rejection	10 (6.5)	226 (192–302)	1 (10.0)	9 (90.0)
Recurrent disease	8 (5.2)	159 (95–170)	0	8 (100.0)
Non-HAT	6 (3.9)	8 (5–31)	0	6 (100.0)
Hemorrhage—late	6 (3.9)	33 (21–91)	0	6 (100.0)
Intraoperative complication	6 (3.9)	0 (0–0)	1 (16.7)	5 (83.3)
Biliary complication	5 (3.3)	299 (200–324)	2 (40.0)	3 (60.0)
Comorbidity	4 (2.6)	175 (77–273)	0	4 (100.0)
Hemorrhage—early	3 (2.0)	2 (1–7)	0	3 (100.0)
Hemorrhage—GI	3 (2.0)	24 (2–51)	0	3 (100.0)
Hepatic venous occlusion—surgical	3 (2.0)	4 (3–5)	0	3 (100.0)
Hepatic venous thrombosis	3 (2.0)	69 (61–72)	0	3 (100.0)
Other	16 (10.5)	41 (12–125)	0	16 (100.0)

Abbreviations: GI, gastrointestinal; HAT, hepatic arterial thrombosis; HLA, human leukocyte antigen; IQR, interquartile range.

TABLE 5 Frequency of risk factors for hepatic artery thrombosis in the whole cohort of patients grouped by the occurrence of hepatic artery thrombosis and HLA-A mismatch status

	Occurrence of hepatic artery thrombosis			HLA-A mismatch status		
	No hepatic artery thrombosis	Hepatic artery thrombosis		HLA-A mismatch	No HLA mismatch	
	Value	**Value**	***p* value**	**Value**	**Value**	***p* value**
Total	1001	41		940	102	
Recipient age, years	52 (43–58)	49 (40.5–53)	0.04	52 (43–58)	52 (47–58)	0.1
Donor age, years	46 (33–56)	43 (32–55)	0.65	46 (33–57)	45 (35–56)	0.99
ABO status						
Match	936 (93.5)	37 (90.2)	0.03	878 (93.4)	95 (93.1)	
Compatible	64 (6.4)	3 (7.3)		60 (6.4)	7 (6.9)	0.88
Mismatch	1 (0.1)	1 (2.4)		2 (0.2)	0 (0)	
Presence of arterial conduit, arterial reconstruction, or hepatic vascular thrombosis	67 (6.7)	5 (12.2)	0.17	66 (7)	6 (5.9)	0.67
Hepatic arterial anastomosis						
Single	826 (83.5)[a]	26 (63.4)	<0.001	765 (82.4)[b]	87 (86.1)[c]	0.35
Multiple	163 (16.5)[a]	15 (36.6)		163 (17.6)[b]	14 (13.9)[c]	

Note: Data are presented as *n* or *n* (%) or median (IQR).

Abbreviations: HLA, human leukocyte antigen; IQR, interquartile range.

[a] *n* = 989.

[b] *n* = 928.

[c] *n* = 101.

shown to be a risk factor for hepatic artery thrombosis.[45–48] Although a recent meta-analysis of pediatric ABO-incompatible transplantation did not confirm this,[49] it may be influenced by small sample size and immunomodulatory strategies applied during emergency transplantation across ABO barriers. An

alternative hypothesis is that HLA-A mismatching may increase graft rejection, with resultant hepatic inflammation and infiltration contributing to elevated vascular resistance, vascular stasis, and elevated risk of thrombosis. This is supported by reports of prior episodes of acute cellular rejection in more than 50% of patients experiencing hepatic artery thrombosis and of chronic rejection occurring commonly following hepatic artery thrombosis.[50]

Few previous studies report a role for HLA matching in HAT. However, an increase in hepatic artery thrombosis in transplants without broad cross-reactive group (CREG) mismatches (which contain HLA-A antigens) has been reported.[51] Hepatic artery thrombosis occurred in 8/64 (12.5%) patients without CREG mismatches, compared with 3/144 (2.1%) with CREG mismatches. While this is in opposition to our findings, the method of determining matching differs between the studies and the overall number of hepatic artery thromboses was low in the earlier study.[51] However, together both studies raise the suggestion that the risk of hepatic artery thrombosis may be modulated by class I HLA matching in liver transplantation. Therefore, prospective assessment of the incidence of hepatic artery thrombosis in HLA-A–typed transplants is required to determine whether anticoagulation, antiplatelet agents, or specific immunomodulatory approaches may be able to reduce the risk.

Our observation of elevated rates of graft loss with sepsis in HLA-A–mismatched transplants fits with prior reports of higher rates of sepsis in poorly HLA-matched grafts.[26] It is conceivable that there is immune dysregulation or sequestration of immune effectors following receipt of an HLA-A–mismatched graft, or that those with HLA-A–mismatched grafts received higher doses of immunosuppression or had more significant graft dysfunction. We could find no evidence that those transplants with HAT or graft loss from sepsis were associated with the increased frequency of classical risk factors for HAT, nor with adverse donor risk characteristics[19] that would confound the association of HLA-A mismatching with these adverse outcomes.

We present data suggesting that HLA-A–mismatched liver transplantation carries an elevated hazard of graft loss and patient death, driven by events in the early period following transplantation. Although this analysis was retrospective, the HLA typing and ascertainment and recording of clinical outcomes were completed prospectively during routine monitoring. In addition, the level of patient exclusions was low and the data set was highly complete, minimizing the risk of bias. While we cannot ascribe causation between HLA-A mismatching and adverse patient outcomes in a retrospective study, this observation is important, illustrating a possible role for HLA-A typing in the prediction of hepatic artery thrombosis and sepsis.

In summary, HLA-A mismatching was significantly associated with graft loss and patient death in a large cohort of northern European liver transplant recipients, over a long period of follow-up. Graft loss predominantly occurred in the early months following liver transplantation and was associated with the occurrence of hepatic artery thrombosis and sepsis.

CONFLICT OF INTEREST

Nothing to report.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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