

Retrospective analysis of HLA mismatch burden and transplant outcomes after deceased-donor kidney transplantation in a setting without HLA-based allocation

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Abstract

Background

Human leukocyte antigen (HLA) matching influences kidney transplant outcomes, but its role in deceased donor transplantation has not been studied in Sri Lanka, where donor HLA typing is not used for allocation. Therefore, this study aimed to determine the association between HLA mismatch and transplant outcomes in a Sri Lankan deceased donor cohort.

Methods

We conducted a single-centre retrospective cohort study of adult recipients of deceased donor kidney transplants performed at the National Hospital of Sri Lanka between June 2017 and June 2024 who had complete donor and recipient HLA typing. Total mismatch at HLA-A, HLA-B and HLA-DRB1 (range 0–6) was dichotomised into low (0–3) and high (4–6) groups. Outcomes were acute rejection, rejection-free survival, death-censored graft survival and patient survival. Associations were assessed using Fisher's exact test, the Kaplan–Meier method with the log-rank test and Cox proportional hazards regression.

Results

A total of 87 recipients were included in the study, with a median follow-up period of 42.1 months. Acute rejection occurred in 33 recipients (38%) and 32 (37%) died. The incidence of rejection increased with the mismatch score ($p < 0.001$). Rejection-free survival was shorter in the high mismatch group and this association remained significant after adjustment (adjusted HR 7.38, 95% CI 1.72–31.62). Delayed graft function was also found to be an independent predictor of rejection. Graft failure occurred in eight recipients (9.2%), all of whom were in the high mismatch group (log-rank $p = 0.13$). HLA mismatch was not associated with patient survival (adjusted HR 2.96, 95% CI 0.90–9.75). Death was predicted independently by recipient aged ≥ 60 years (adjusted HR 2.59) and diabetic end-stage kidney disease (adjusted HR 3.47). Infection accounted for 30 of the 32 deaths.

Conclusions

Higher HLA mismatch was independently associated with acute rejection and shorter rejection-free survival. However, it was not associated with graft or patient survival, which were determined by infection and recipient factors. HLA mismatch data may help reduce rejection and sensitisation, but survival improvements are likely to depend on infection prevention in older and diabetic recipients.

Background

Chronic kidney disease is a major cause of illness and premature death in Sri Lanka. In addition to the conventional risk factors of diabetes and hypertension, the country bears the burden of chronic kidney disease of uncertain aetiology, affecting rural farming communities across several provinces (1, 2). A significant proportion of patients with the condition progress to end-stage kidney disease, becoming dependent on renal replacement therapy. For suitable patients, kidney transplantation offers a better quality of life and a better long-term prognosis than maintenance dialysis and is therefore the preferred treatment for end-stage disease (3).

Access to transplantation in Sri Lanka has depended largely on living donation, which is limited by donor availability and by long waiting times. Deceased donor transplantation is therefore essential if access is to expand and the number of deceased donor kidney transplants has risen since the national programme was established (4, 5). However, the volume remains low by international standards and the early outcomes could be better. A single-centre study at the National Hospital of Sri Lanka found that nearly a quarter of recipients of deceased donors died within the first year. The leading cause of death was infection, while delayed graft function and acute rejection were each common (5).

The most significant barriers to deceased donor transplantation are rejection and graft loss and the main factor in determining these is donor-recipient human leukocyte antigen (HLA) compatibility. HLA disparity drives alloimmune recognition and as reported in large registries the risk of rejection and graft failure rises steadily with each additional mismatch (6, 7). An analysis of 189,141 first deceased donor transplants revealed that the adjusted risk of allograft failure increased incrementally with each mismatch (8). The question of whether the benefit of matching still justifies its cost in modern allocation is debated in high-income settings (9, 10). It is unknown whether any of this applies to a Sri Lankan deceased donor population.

This question cannot be answered based on local practices because HLA mismatch is never measured. In Sri Lanka, deceased donor allocation is based on ABO compatibility and prospective T and B cell complement-dependent cytotoxicity crossmatching. This is carried out within the government programme, as all deceased donor transplants in the country are performed in government institutions (4). Crossmatching detects preformed donor-specific antibodies, but it does not quantify the degree of HLA disparity. HLA typing is low-resolution and the number of mismatches is neither calculated nor used in allocation (4). Local research has addressed living donor transplantation (3). The only dedicated deceased donor outcome study did not examine histocompatibility (5) and there is no data linking HLA mismatch to rejection or graft survival in this population. Therefore, this study aimed to determine the association between the degree of HLA mismatch and transplant outcomes in adult recipients of deceased donor kidney transplants at a national referral centre in Sri Lanka.

Methods

Study design and setting

This was a retrospective cohort study conducted at the renal transplant unit of the National Hospital of Sri Lanka (NHSL). The NHSL is one of the country's leading referral centres for deceased donor kidney transplants. All deceased donor kidney transplants performed at the centre between June 2017 and June 2024 were included in the study.

Participants

Adult recipients aged ≥ 18 years who received a kidney transplant from a deceased donor during the study period and who had complete HLA typing for both donor and recipient were included. Those with incomplete or unavailable HLA typing as well as those lost to follow-up were excluded. All eligible recipients were enrolled consecutively and a formal sample size calculation was not performed as the study included all eligible recipients treated during the study period.

HLA typing and mismatch definition

The primary exposure was the degree of HLA mismatch between the donor and the recipient, which was counted as the number of donor antigens that the recipient did not share. Total HLA mismatch was calculated as the sum of mismatches at the HLA-A, HLA-B, and HLA-DRB1 loci. Each locus contributed 0, 1, or 2 mismatches, giving a score from 0 to 6. Mismatches at the HLA-DQB1 locus were recorded separately and were not included in the total score.

Total mismatch was examined across its individual strata for the rejection outcome. For the survival and regression analyses, it was dichotomised at the midpoint of the scale into a low mismatch group of 0 to 3 and a high mismatch group of 4 to 6. This dichotomisation was pre-specified because the graded association between increasing mismatch and inferior graft survival is well established in large registry cohorts (7, 8) and because the size of the present cohort did not support stable estimation across all seven individual strata, several of which had a small number of recipients.

HLA-DRB1 mismatch was analysed separately because HLA-DR disparity has the most consistent effect on rejection and graft survival among the routinely typed loci (11). It was categorised as either no mismatch or one or two mismatches to contrast the presence or absence of DR disparity, since finer stratification was not feasible in a cohort of this size.

Covariate definitions and cut-offs

Recipient age at transplantation was categorised as under 60 years or ≥ 60 years, the conventional threshold above which recipient survival declines (12). Cold ischaemia time was categorised as ≤ 12 hours versus > 12 hours, above which the risks of delayed graft function and death increase (13).

Outcome definitions

Outcomes were defined each measured from the date of transplantation.

- Acute rejection was defined as an immune-mediated episode of allograft dysfunction, identified by a rise in serum creatinine and/or confirmed on allograft biopsy, which may occur at any point post-transplant (early or late).
- Delayed graft function was defined as kidney does not function adequately immediately after transplantation and patient requires dialysis within the first 7 days after transplantation.
- Graft failure was defined as permanent, irreversible loss of allograft function, defined as return to maintenance dialysis or re-transplantation.
- Death defined as patient mortality, recorded irrespective of graft function status at the time of death (with or without a functioning graft).

Data analysis

The analyses were performed in R. The distribution of the continuous variables was assessed using histograms. Continuous variables were summarised as medians with interquartile ranges, while categorical variables were summarised as frequencies with percentages. Associations between the degree of HLA mismatch and the occurrence of acute rejection were tested using Fisher's exact test. Time-to-event outcomes were described using the Kaplan–Meier method and compared between groups using the log-rank test and follow-up was measured from the date of transplantation.

The association between each candidate variable and each time-to-event outcome was estimated using univariable Cox proportional hazards regression and the results were reported as hazard ratios with 95% confidence intervals. For patient survival and rejection-free survival analysis a multivariable Cox model was fitted using pre-specified covariates. The number of covariates was limited to avoid an overfitted model, given the number of events observed.

Death-censored graft failure was analysed descriptively by reporting the number and group distribution of failures and by performing a log-rank comparison between mismatch groups. Rejection-free survival was compared between HLA mismatch groups using Kaplan–Meier estimation, the log-rank test and Cox regression. A p-value < 0.05 was considered statistically significant.

Results

Participant characteristics

Eighty-seven deceased donor kidney transplant recipients were included in this study. The median age at transplantation was 51.0 years (IQR 42.0–59.0), and 58 recipients (67%) were male. The most common causes of end-stage kidney disease were diabetes (45%) and hypertension (31%), followed by chronic glomerulonephritis (9.2%) and focal segmental glomerulosclerosis (5.7%). Most recipients (94%) had received dialysis before transplantation for a median of 16.5 months (IQR 7.0–24.0), and five patients

(5.7%) had received a previous transplant. Basiliximab was used for induction in 76 recipients (87%) and anti-thymocyte globulin in 11 (13%). The median cold ischaemia time was 5.0 hours (IQR 3.3–8.0) (Table 1).

Table 1. Baseline characteristics of kidney transplant recipients

Abbreviations:

Characteristic

Overall (N = 87)

Gender

Male

58 (67%)

Female

29 (33%)

Age at transplant (years)

51.0 (42.0–59.0)

Cause of CKD

Diabetes

39 (45%)

Hypertension

27 (31%)

Chronic glomerulonephritis

8 (9.2%)

FSGS

5 (5.7%)

Other

8 (9.2%)

Previous transplant

Yes

5 (5.7%)

No

82 (94%)

Pre-transplant dialysis

Yes

82 (94%)

No

5 (5.7%)

Pre-transplant dialysis duration (months)

16.5 (7.0–24.0)

Induction agent

Basiliximab

76 (87%)

ATG

11 (13%)

Cold ischemic time (hours) Before KT

5.0 (3.3- 8.0)

Post-transplant outcomes and clinical course

Over a median follow-up period of 42.1 months (IQR 20.5–60.8), 32 recipients (37%) died (Table 2). Infection was the leading cause. It accounted for 30 of the 32 deaths. The most common causes were pneumonia (69%), graft pyelonephritis (13%), meningitis (9.4%) and infective endocarditis (3.1%). The remaining two deaths (6.3%) were due to myocardial infarction. Graft failure, defined as a return to maintenance dialysis or re-transplantation occurred in eight recipients (9.2%). The remaining grafts had not failed by the final follow-up. Delayed graft function occurred in 15 recipients (17%), all of whom required dialysis within the first week, most commonly for a single session (9 patients). Acute rejection occurred in 33 recipients (38%) at any time and in 26 recipients (30%) within the first year. Of those affected, the most common type was T cell-mediated rejection (16 cases), followed by antibody-mediated rejection (9 cases) and mixed rejection (8 cases). Graft function remained stable with a median serum creatinine level ranging from 1.0–1.2 mg/dL from discharge to 12 months. Meanwhile, median tacrolimus trough levels fell from 10.0 ng/mL at discharge to 6.8 ng/mL at 12 months.

Table 2
Post-transplant outcomes and follow-up characteristics of kidney transplant recipients

Characteristic	Overall (N = 87)
Follow-up duration (months) after KT	42.1 (20.5–60.8)
Patient status (alive/dead)	
Alive	55 (63%)
Dead	32 (37%)
Cause of death (among those who died)	
Graft pyelonephritis	4 (13%)
Infective endocarditis	1 (3.1%)
Meningitis	3 (9.4%)
Myocardial infarction	2 (6.3%)
Pneumonia	22 (69%)
Graft failure (loss of graft function at last follow-up)	
Yes	8 (9.2%)
No	79 (91%)
Delayed graft function After KT	
Yes	15 (17%)
No	72 (83%)
Dialysis first-week After KT	
1 HD session in first week	9 (60%)
2 HD sessions in first week	5 (33%)
3 HD sessions in first week	1 (6.7%)
Graft rejection during overall follow-up	
Yes	33 (38%)
No	54 (62%)
Graft rejection during 1st year follow-up	
Yes	26 (30%)
Abbreviations: KT- kidney transplant, HD- hemodialysis, TCMR- T cell-mediated rejection, ABMR- antibody-mediated rejection.	

Characteristic	Overall (N = 87)
No	61 (70%)
Rejection type (among those with rejection)	
TCMR	16 (48%)
ABMR	9 (27%)
Mixed (TCMR+ABMR)	8 (24%)
Number of graft rejection episodes during 1st year follow-up	
0	61 (70%)
1	22 (25%)
2	2 (2.3%)
3	1 (1.1%)
4	1 (1.1%)
Creatinine level after KT (mg/dL)	
At discharge	1.2 (1.0-1.9)
At 1 month	1.1 (0.8–1.3)
At 3 months	1.0 (0.8–1.3)
At 6 months	1.0 (0.8–1.2)
At 12 months	1.1 (0.8–1.4)
Current or at death	1.2 (0.9–1.5)
Tacrolimus level after KT (ng/mL)	
At discharge	10.0 (8.0-11.9)
At 1 month	7.8 (6.8–9.2)
At 3 months	7.2 (6.5–8.3)
At 6 months	6.8 (6.3–7.8)
At 12 months	6.8 (6.2–7.2)
Abbreviations: KT- kidney transplant, HD- hemodialysis, TCMR- T cell-mediated rejection, ABMR- antibody-mediated rejection.	

HLA mismatch and acute rejection

The total HLA mismatch score ranged from two to six. No recipient was matched for fewer than two antigens. Three recipients had two mismatches, 15 had three, 24 had four, 42 had five, and three had six. Sixty-nine recipients (79%) were categorised as having a high mismatch (four to six), and 18 (21%) as having a low mismatch (zero to three). At the individual loci, eight recipients (9.2%) had no HLA-DRB1 mismatch, four had no HLA-A mismatch, and two had no HLA-B mismatch.

The proportion of recipients developing acute rejection increased steadily as the total mismatch score rose, from none at two mismatches to all three at six. Over the entire follow-up period, the rejection rate increased progressively across ascending tiers, reaching 100% at six mismatches ($p < 0.001$). A similar trend was observed within the first year, with rejection rates of 0%, 13%, 17%, 40%, and 100% ($p = 0.007$) (Table 3).

At the individual loci, only HLA-A mismatch was associated with rejection. The rejection rate increased from 0% with no HLA-A mismatch, to 27% with one mismatch, and to 55% with two mismatches ($p = 0.008$ over the whole follow-up period, and $p = 0.058$ within the first year). HLA-B mismatch showed no association ($p = 0.500$). HLA-DRB1 mismatch showed a graded, though non-significant, increase: from 13% with no mismatch, to 34% with one mismatch, and to 46% with two mismatches ($p = 0.200$) (Table 3).

Table 3
HLA mismatch distribution in relation to acute rejection (N = 87)

Characteristic	Rejection within 1 year			Rejection ever		
	No ¹	Yes ¹	p-value	No ¹	Yes ¹	p-value
Total HLA mismatch (0–6)			0.007			< 0.001
2	3 (100%)	0 (0%)		3 (100%)	0 (0%)	
3	13 (87%)	2 (13%)		13 (87%)	2 (13%)	
4	20 (83%)	4 (17%)		19 (79%)	5 (21%)	
5	25 (60%)	17 (40%)		19 (45%)	23 (55%)	
6	0 (0%)	3 (100%)		0 (0%)	3 (100%)	
HLA-A mismatches			0.058			0.008
0	4 (100%)	0 (0%)		4 (100%)	0 (0%)	
1	35 (78%)	10 (22%)		33 (73%)	12 (27%)	
2	22 (58%)	16 (42%)		17 (45%)	21 (55%)	
HLA-B mismatches			0.500			0.500
0	2 (100%)	0 (0%)		2 (100%)	0 (0%)	
1	27 (75%)	9 (25%)		24 (67%)	12 (33%)	
2	32 (65%)	17 (35%)		28 (57%)	21 (43%)	
HLA-DRB1 mismatches			0.300			0.200
0	7 (88%)	1 (12%)		7 (88%)	1 (12%)	
1	28 (74%)	10 (26%)		25 (66%)	13 (34%)	
2	26 (63%)	15 (37%)		22 (54%)	19 (46%)	
¹ n (row %) = number and percentage of patients within that HLA mismatch tier who experienced rejection						

Death-censored graft survival

During follow-up, eight death-censored graft-failure events occurred. All eight occurred in the high mismatch group and none occurred in the low mismatch group. Kaplan-Meier analysis revealed no significant difference between the two groups (log-rank $p = 0.13$) (Fig. 1). As there were no events in the low mismatch group, a hazard ratio for graft failure by mismatch group could not be estimated. All eight recipients who experienced graft failure also died during follow-up. Recipients who died without prior graft failure were censored at death. Therefore, the number of graft-failure events available for analysis

was small. With only eight events confined to a single mismatch group, regression modelling was not done.

Figure 1. Death censored graft survival by HLA mismatch group

Patient survival

Thirty-two recipients (37%) died during the follow-up period. Kaplan-Meier analysis showed that patient survival was lower in the high mismatch group than in the low mismatch group (55% vs. 83%), though this difference was not statistically significant (log-rank $p = 0.058$) (Fig. 2). Of the 32 deaths, 29 occurred in the high mismatch group and 3 in the low mismatch group.

Figure 2

Patient survival by HLA mismatch group

Three factors were associated with death on univariable Cox regression (Table 4). The strongest association was found for a diabetic cause of end-stage kidney disease (HR 4.23, 95% CI 1.95–9.17, $p < 0.001$), followed by the recipient being aged ≥ 60 years (HR 3.55, 95% CI 1.77–7.14, $p < 0.001$). Female sex was associated with lower mortality, although the interval reached the null (HR 0.41, 95% CI 0.17–0.99, $p = 0.047$). High HLA mismatch was not significantly associated with death (HR 2.98, 95% CI 0.91 to 9.81, $p = 0.072$), which is consistent with the non-significant log-rank test for the same comparison. No association was found between patient survival and any HLA-DR mismatch, cold ischaemia time, delayed graft function, induction agent or acute rejection.

Table 4
Univariate Cox regression for patient survival

Factor	N	Deaths, n	No death, n	HR	95% CI	p-value
HLA mismatch group	87					
High (4–6)	69	29	40	2.98	0.91–9.81	0.072
Low (0–3)	18	3	15	1.00 (Ref)		
Any HLA-DR mismatch	87					
Yes	79	30	49	1.75	0.42–7.34	0.443
No	8	2	6	1.00 (Ref)		
Age at transplant	87					
≥ 60 years	21	15	6	3.55	1.77–7.14	< 0.001
<60 years	66	17	49	1.00 (Ref)		
Diabetic cause of ESKD	87					
Diabetic	39	23	16	4.23	1.95–9.17	< 0.001
Non-diabetic	48	9	39	1.00 (Ref)		
Sex	87					
Female	29	6	23	0.41	0.17–0.99	0.046
Male	58	26	32	1.00 (Ref)		
Cold ischaemic time	86					
>12 hours	7	3	4	1.12	0.34–3.70	0.848
≤12 hours	79	28	51	1.00 (Ref)		
Delayed graft function	87					
Yes	15	3	12	0.43	0.13–1.40	0.160
No	72	29	43	1.00 (Ref)		
Induction agent	87					
ATG	11	1	10	0.21	0.03–1.51	0.120
Basiliximab	76	31	45	1.00 (Ref)		
Acute rejection, ever	87					
Yes	33	15	18	1.57	0.78–3.15	0.203
No	54	17	37	1.00 (Ref)		

In the multivariable model both age (adjusted HR 2.59, 95% CI 1.27–5.30, $p = 0.009$) and diabetes (adjusted HR 3.47, 95% CI 1.57–7.66, $p = 0.002$) were found to be independently associated with death. However, high HLA mismatch was not found to be associated with death (adjusted HR 2.96, 95% CI 0.90–9.75 p -value = 0.075) (Table 5).

Table 5
Multivariable Cox regression for patient survival

Factor	Adjusted HR	95% CI	p-value
HLA mismatch group: High (4–6) vs Low (0–3)	2.96	0.90–9.75	0.075
Age at transplant: ≥ 60 vs < 60 years	2.59	1.27–5.30	0.009
Diabetic cause of ESKD: yes vs no	3.47	1.57–7.66	0.002

Rejection-free survival

Acute rejection occurred in 33 recipients during the follow-up period. Rejection-free survival was significantly poorer in the high mismatch group. Thirty-one out of 69 recipients with high mismatch developed rejection, compared to 2 out of 18 with low mismatch. The approximate rejection-free survival rate at the end of the follow-up period was 40% in the high mismatch group, compared to 89% in the low mismatch group (log-rank $p = 0.012$) (Fig. 3).

Two factors were associated with rejection on univariable Cox regression (Table 6). High HLA mismatch was associated with a significant increase in the hazard of rejection (HR 5.19, 95% CI 1.24–21.73, $p = 0.024$), and delayed graft function was also associated with rejection (HR 3.61, 95% CI 1.74–7.51, $p < 0.001$). Recipient age, sex, cold ischaemia time, sensitisation and induction agent were not associated with rejection.

In the multivariable model, both HLA mismatch (high mismatch adjusted HR 7.38, 95% CI 1.72–31.62, $p = 0.007$) and delayed graft function (adjusted HR 5.37, 95% CI 2.43–11.90, $p < 0.001$) were found to be independently associated with rejection, whereas age and induction agent were not (Table 7).

Table 6
Univariable Cox regression for rejection-free survival

Factor	N	Rejection, n	No rejection, n	HR	95% CI	p-value
HLA mismatch group	87					
High (4–6)	69	31	38	5.19	1.24–21.73	0.024
Low (0–3)	18	2	16	1.00 (Ref)		
Age at transplant	87					
≥60 years	21	7	14	0.95	0.41–2.19	0.906
<60 years	66	26	40	1.00 (Ref)		
Sex	87					
Female	29	9	20	0.60	0.28–1.30	0.198
Male	58	24	34	1.00 (Ref)		
Cold ischaemic time	86					
>12 hours	7	2	5	0.68	0.16–2.85	0.599
≤12 hours	79	30	49	1.00 (Ref)		
Delayed graft function	87					
Yes	15	11	4	3.61	1.74–7.51	< 0.001
No	72	22	50	1.00 (Ref)		
PRA sensitised	87					
Yes	15	4	11	0.54	0.19–1.53	0.244
No	72	29	43	1.00 (Ref)		
Induction agent	87					
ATG	11	4	7	0.82	0.29–2.35	0.719
Basiliximab	76	29	47	1.00 (Ref)		

Table 7
Multivariable Cox regression for rejection-free survival

Factor	Adjusted HR	95% CI	p-value
HLA mismatch group: High (4–6) vs Low (0–3)	7.38	1.72–31.62	0.007
Delayed graft function: yes vs no	5.37	2.43–11.90	< 0.001
Age at transplant: ≥60 vs < 60 years	1.20	0.50–2.89	0.682
Induction agent: ATG vs Basiliximab	0.51	0.17–1.51	0.223

Discussion

This study aimed to determine whether the degree of HLA mismatch influences outcomes after deceased donor kidney transplantation in a Sri Lankan cohort, in a setting where donor HLA typing is not used for organ allocation. The main finding was that HLA mismatch was significantly associated with acute rejection. Rejection became more frequent as the mismatch score increased, with recipients having a high mismatch score experiencing substantially shorter rejection-free survival. This association persisted and strengthened after adjusting for delayed graft function, recipient age, and induction agent. However, HLA mismatch was not independently associated with either graft or patient survival. Mortality was driven by infection, older recipient age and diabetic end-stage kidney disease, rather than by the degree of donor-recipient matching.

The incidence of acute rejection increased steadily with the total mismatch score, ranging from none among the best-matched recipients to all those with six mismatches. This dose-response pattern is consistent with large registry analyses, in which each additional mismatch increases the risk of rejection and subsequent graft loss (7, 8, 14). Observing this gradient in only 87 patients suggests a strong immunological effect. The overall rejection rate was high, with 38% of recipients experiencing rejection at some point including 30% within the first year. This is higher than the rate of approximately one in five reported in the earlier NHSL deceased donor series (5) and higher than the roughly 10 to 20% first-year acute rejection reported in contemporary deceased donor cohorts (15, 16).

Rejection-free survival was significantly poorer in patients with high mismatch. High mismatch was associated with a more than fivefold hazard of rejection (HR 5.19) in the univariable model and strengthened (HR 7.38) in the adjusted model. Delayed graft function was also found to be independently associated with rejection. However, the confidence interval for the mismatch estimate was wide because only 2 of the 18 low mismatch recipients experienced rejection. Therefore, although the direction and significance are clear, the magnitude is uncertain. This finding should be interpreted as a strong signal rather than a precise estimate.

At the individual loci, HLA-A mismatch was associated with rejection, whereas HLA-DRB1 was not. This is the reverse of the usual pattern, in which DR carries the greatest weight (11). However, this observed reversal is unlikely to be true. The HLA-A association was based on just four recipients with no HLA-A

mismatch, none of whom experienced rejection. Similarly, only eight recipients had no DR mismatch. Therefore, both per-locus comparisons were based on very small reference groups. With rejection events spread thinly and strong linkage between neighbouring HLA genes, a genuine DR effect could be missed while an HLA-A association could emerge by chance. One of the largest analysis of deceased donors found that individual loci contribute to graft failure to a similar extent, rather than DR standing apart (8). The most reasonable interpretation is that total mismatch load, rather than any single locus could be a better marker of rejection risk in this cohort.

Although HLA mismatch had no measurable effect on death-censored graft survival, this should be interpreted as a result of limited statistical power rather than as evidence of no effect. Only eight grafts failed throughout the entire follow-up period and all of these failures occurred in the high mismatch group. Therefore, the reference group contained no events, no hazard ratio could be estimated and the log-rank test was not significant ($p = 0.13$). All eight recipients who lost their graft subsequently died. The graft failed in seven cases with return to dialysis before death and in one case at the time of death, so graft failure and death were closely linked rather than independent. With only eight graft failures against 32 deaths, there were few isolated graft failures, and a death-censored analysis under these conditions has little power to detect the effect of mismatch. Registries demonstrating a clear graded effect of mismatch on graft survival are based on tens of thousands of transplants and much longer follow-ups (7, 8, 14), which are not present in this cohort.

HLA mismatch was not independently associated with patient survival. Although Kaplan-Meier survival was lower in the high mismatch group than in the low mismatch group (55% vs. 83%), the difference was not statistically significant (log-rank $p = 0.058$). The univariable hazard ratio was also not significant (HR 2.98, $p = 0.072$), and this remained non-significant after adjustment (adjusted HR 2.96, $p = 0.075$). The point estimate was consistent across analyses, suggesting that this cohort was underpowered to confirm a possible effect given that only three deaths occurred among the 18 low mismatch recipients. Female sex was associated with lower mortality in the univariate analysis. However, the interval reached the null.

The factors that predicted death were recipient age and a diabetic cause of end-stage kidney disease. Each factor more than doubled the adjusted hazard of death (age ≥ 60 years, adjusted HR 2.59, diabetic cause, adjusted HR 3.47). This is consistent with a large United Kingdom registry analysis of over 12,000 deceased donor recipients. In this analysis, older recipient age and diabetic nephropathy as the primary renal diagnosis were found to independently predict death. Meanwhile, female recipients were found to be at lower risk, which mirrors the sex difference seen in this study (17). Furthermore, older recipient age is consistent with earlier work involving recipients aged ≥ 60 years (12). This pattern of death explains why matching had little bearing on survival. Infection caused 30 of the 32 deaths, with pneumonia accounting for 22. This is also consistent with the NHSL deceased donor series (5) and international data, in which infection is a leading non-cardiovascular cause of death after transplantation (18). These deaths arose from the infectious consequences of immunosuppression as well as from recipient age and comorbidity. None of these factors were influenced by donor-recipient HLA compatibility. The

immunological signal that mismatch produced for rejection therefore did not translate into a measurable effect on survival, because in this cohort death was governed by infection and recipient factors rather than by alloimmunity.

Delayed graft function was an independent predictor of acute rejection and was one of the most robust associations identified in the study (univariable HR 3.61; adjusted HR 5.37). This finding is consistent with existing evidence. A systematic review and meta-analysis found that delayed graft function increased the relative risk of acute rejection by 38%, as well as increasing the risk of graft loss by 41% (19). As expected in a small, single-centre cohort where individual estimates are less stable, our effect is larger than that pooled estimate. However, the direction and strength of the association are concordant with that body of work. Further, delayed graft function was not associated with patient death. This too is consistent with the meta-analysis, which found that delayed graft function affects graft outcomes and rejection without a clear effect on patient survival (19).

As survival in this group was determined by infection and recipient age rather than HLA matching, this centre is most likely to make significant progress by reducing infection-related mortality. As deaths were predominantly infection-related, interventions such as vaccination, infection surveillance and prophylaxis and individualised immunosuppression for older and diabetic recipients would be most likely to improve patient survival. Delayed graft function was a strong driver of acute rejection, and importantly, a modifiable one. Therefore, the transplant unit can reduce rejection by minimising the incidence and duration of delayed graft function through measures within its control, such as optimising donor haemodynamic and perioperative management and reducing cold ischaemia time (13).

To the best of our knowledge, this is the first study to relate HLA mismatch to transplant outcomes in a Sri Lankan deceased donor population and it included every eligible recipient with complete donor and recipient HLA typing over a seven-year period. However, the study also has several limitations. This was a single-centre, retrospective cohort study of just 87 recipients, which limits its generalisability to other Sri Lankan units. Another limitation is the small number of outcome events. Only eight death-censored graft failures occurred, all of which were in the high mismatch group. Furthermore, only eight recipients had no HLA-DR mismatch, which left too small a reference group for reliable estimation. Therefore, the graft survival and HLA-DR analyses should be regarded as exploratory. HLA matching was assessed at the antigen level at HLA-A, HLA-B and HLA-DRB1. Molecular or eplet-level typing was not available and HLA-DQ was not routinely typed. Antigen-level typing is less sensitive and misses differences that finer typing would detect, which is one reason the HLA-DR analysis may have failed to show an effect (4). Lastly, donor-specific data, including donor-specific antibody status, donor age and sex and the cause of death were not available, which prevented a fuller assessment of immunological and donor-related risk.

Conclusion

This is the first study to relate HLA mismatch to transplant outcomes in Sri Lankan deceased donor recipients, a setting where donor HLA is not considered at allocation. Despite not being considered at

allocation, the degree of HLA mismatch was independently associated with a graded increase in acute rejection and shorter rejection-free survival. However, HLA mismatch was not associated with graft or patient survival. Mortality was mainly due to infection and recipient factors, including older age (≥ 60 years) and diabetes, rather than the degree of matching. Incorporating HLA mismatch data into clinical practice could reduce acute rejection and sensitisation. However, improvements in survival are likely to depend primarily on preventing infection in older and diabetic recipients. Further research using molecular-level HLA typing and donor-specific antibody data is needed to confirm these findings.

Declarations

Ethical considerations

This study was approved by the Ethical Review Committee of National Hospital of Sri Lanka (AJ/ETH/COM/2026/April). All methods were carried out in accordance with the relevant guidelines and regulations, including the Declaration of Helsinki. As this was a retrospective study using existing clinical records, the requirement for individual informed consent was waived.

Consent for publication

NA

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Availability of data and material

The dataset is available with the Primary Investigator (TS) and can be provided upon request. Data are withheld from public deposit to protect patient confidentiality.

Competing Interests

The authors declare that they have no competing interests.

Authors Contribution

TS conceived the study and wrote the research proposal. AH, LN, EW and MS supervised the research. TS performed the data collection and organisation and CA supervised the data collection. CM performed the statistical analysis. TS and CM interpreted the data. TS wrote the manuscript. AH, LN, CM, EW, MS and CA critically reviewed the manuscript for publication. All authors discussed the results and implications, commented on the manuscript at all stages and read and approved the final manuscript.

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Table 1

Table 1 is available in the Supplementary Files section.

Figures

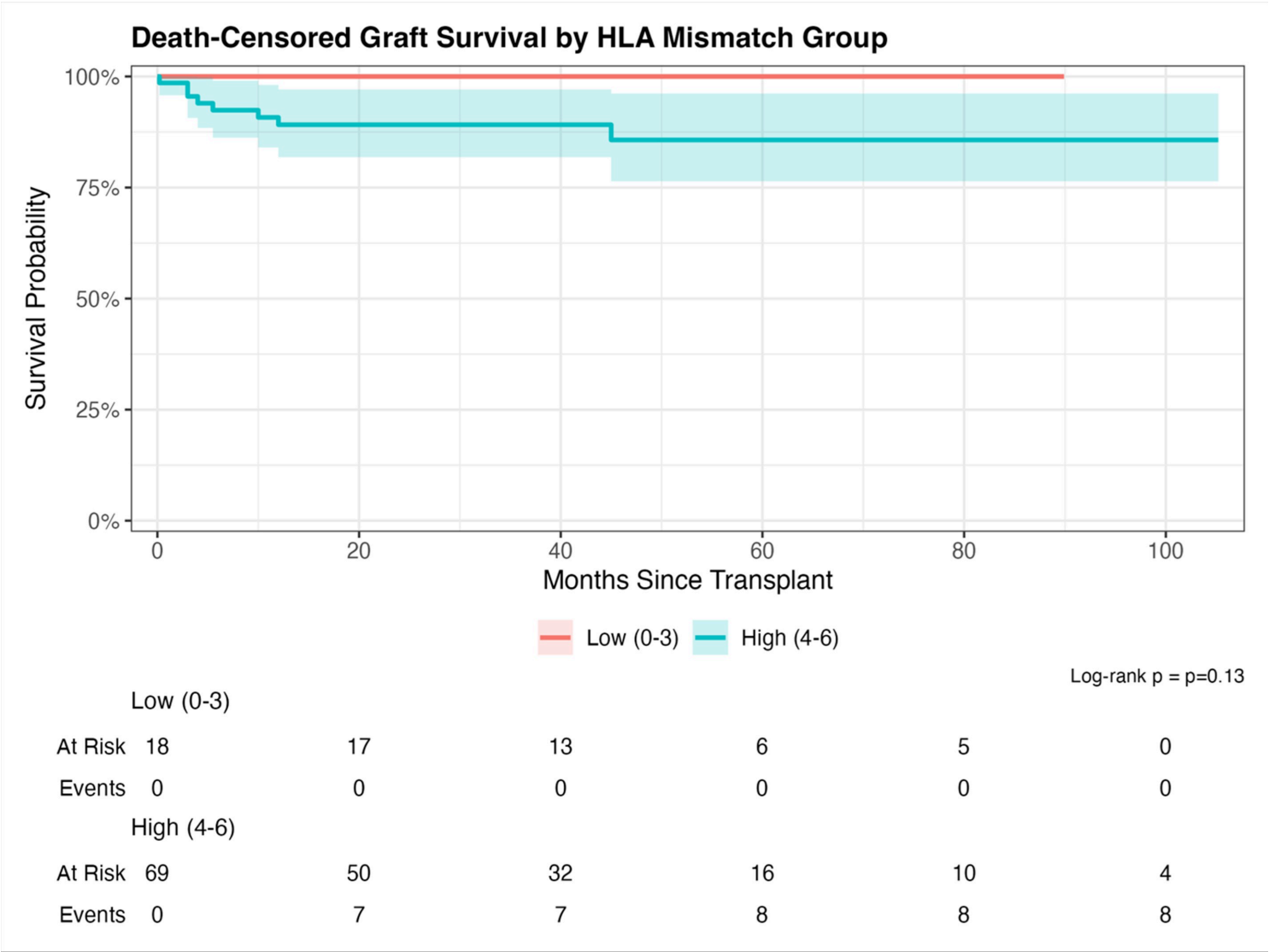


Figure 1

Death censored graft survival by HLA mismatch group

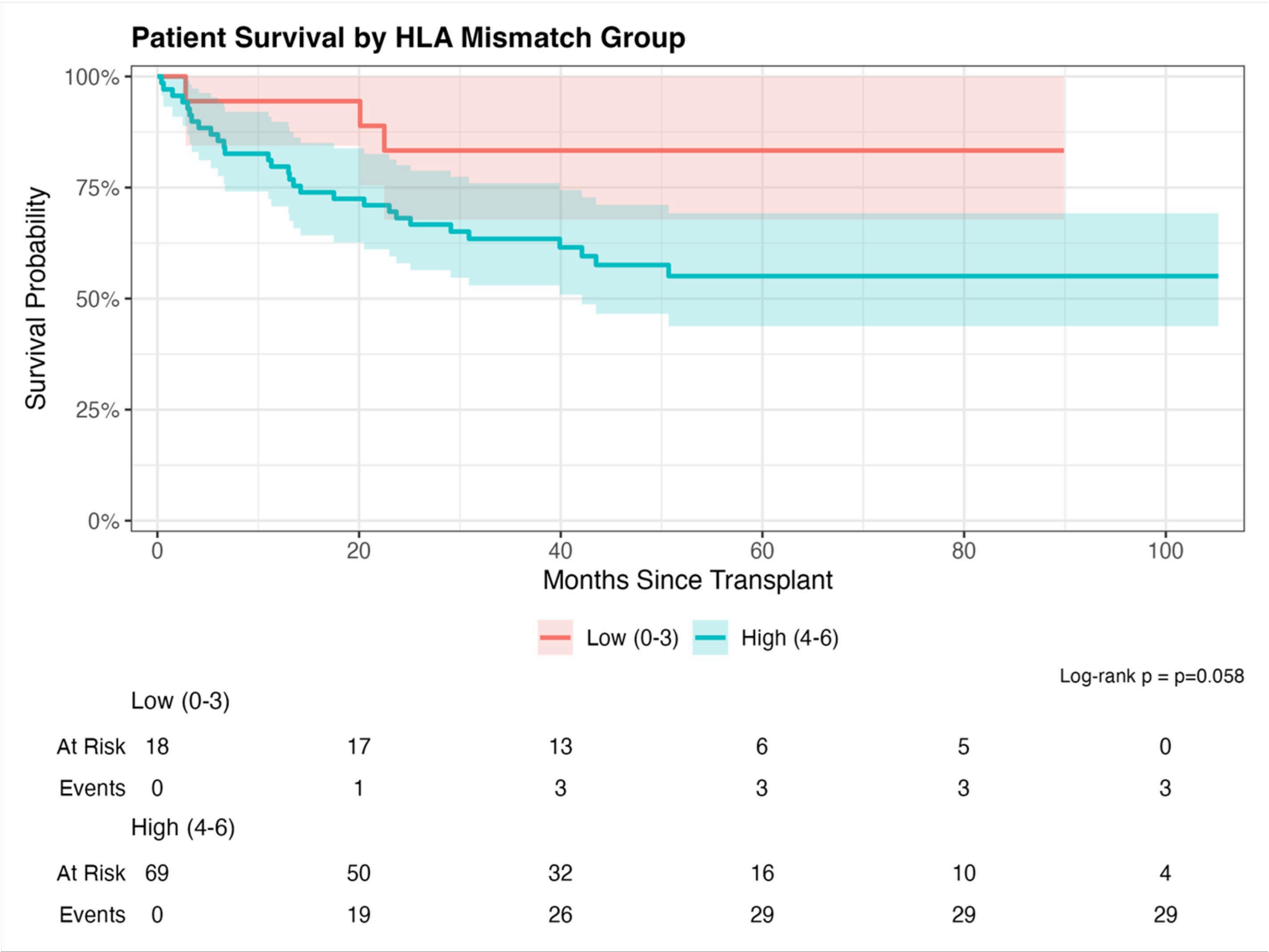


Figure 2

Patient survival by HLA mismatch group

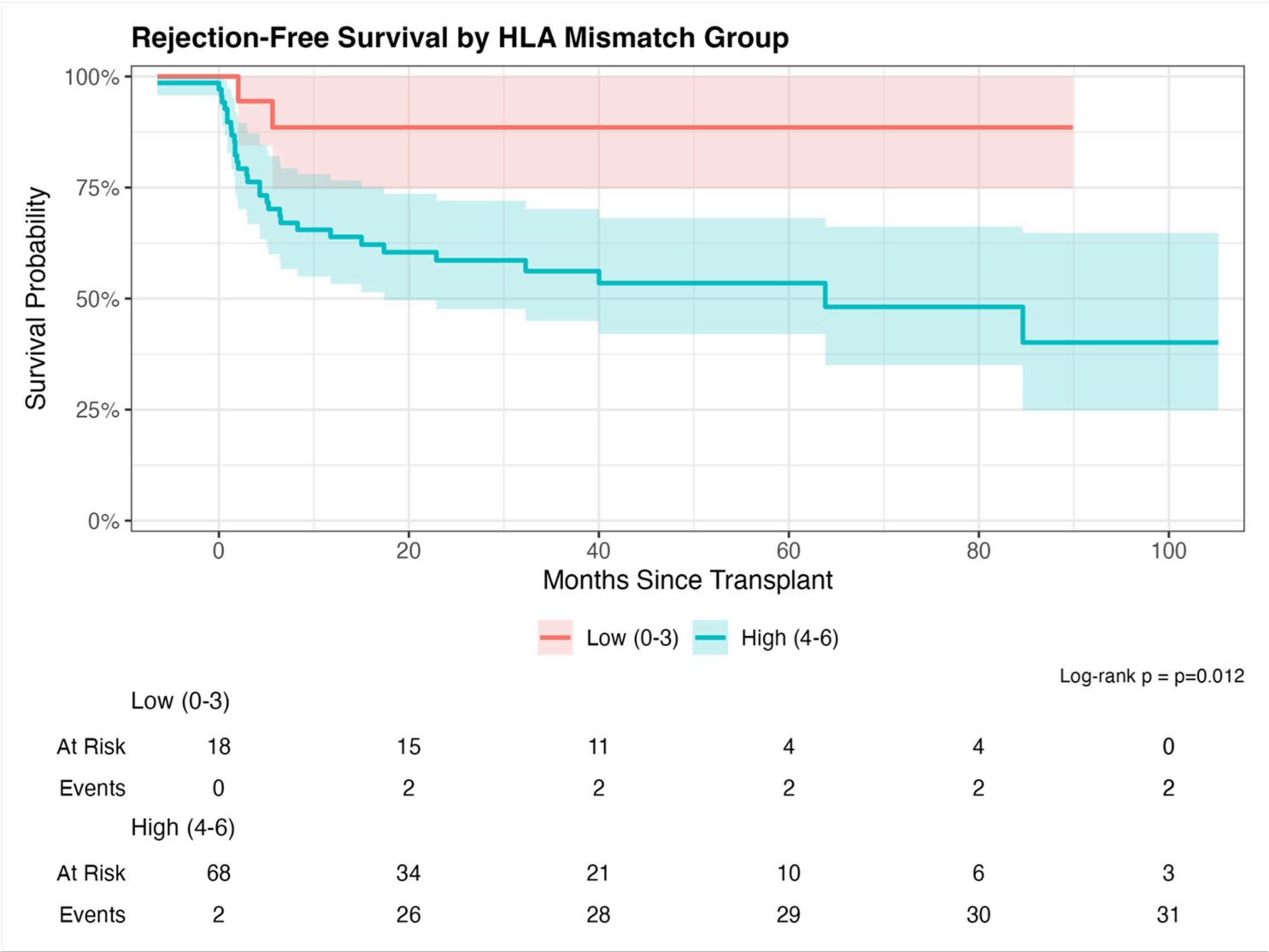


Figure 3

Rejection-free survival by HLA mismatch group

Supplementary Files

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- [Table1.docx](#)