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Steroid Avoidance in Pediatric Heart Transplantation Results in Excellent Graft Survival

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Abstract

Background—Maintenance steroid (MS) use in pediatric heart transplantation (HT) varies across centers. The purpose of this study was to evaluate the impact of steroid-free maintenance immunosuppression (SF) on graft outcomes in pediatric HT.

Methods—Patients younger than 18 years in the United States undergoing a first HT during 1990 to 2010 were analyzed for conditional 30-day graft loss (death or repeat HT) and death based on MS use by multivariable analysis. A propensity score was then given to each patient using a logistic model, and propensity matching was performed using pre-HT risk factors, induction therapy, and nonsteroid maintenance immunosuppression. Kaplan-Meier graft and patient survival probabilities by MS use were then calculated.

Results—Of 4894 patients, 3962 (81%) were taking MS and 932 (19%) SF. Of the 4530 alive at 30 days after HT, 3694 (82%) and 836 (18%) were in the MS and SF groups, respectively. Unmatched multivariable analysis showed no difference in 30-day conditional graft survival between MS and SF groups (hazard ratio=1.08, 95% confidence interval=0.93-1.24; $P=0.33$). Propensity matching resulted in 462 patients in each MS and SF group. Propensity-matched Kaplan-Meier survival analysis showed no difference in graft or patient survival between groups ($P=0.3$ and $P=0.16$, respectively).

Conclusions—We found no difference in graft survival between SF patients and those taking MS. An SF regimen in pediatric HT avoids potential complications of steroid use without compromising graft survival, even after accounting for pre-HT risk factors.

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All authors were involved in the conception and design of the analysis, in the interpretation of data, in revising the article critically for important intellectual content, and in the final approval of the article submitted. S.R.A. was responsible for drafting of the article and revising it critically for important intellectual content. J.G. was responsible for performing statistical analysis.

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Keywords

Pediatric heart transplantation; Immunosuppression; Steroids; Graft survival; Organ Procurement and Transplantation Network

Maintenance immunosuppression regimens for the prevention of rejection in pediatric heart transplant (HT) recipients commonly include the use of corticosteroids. Despite the side effects associated with maintenance steroid (MS) use, the International Society for Heart and Lung Transplantation registry reports that 63% of pediatric HT recipients received MS at 1 year after HT and univariable conditional 1-year survival analysis showed better survival in patients not taking MS (1). Single- and dual-center reports of pediatric HT protocols that avoid MS have shown survival equivalent to what has been published in registry reports and an acceptable incidence of rejection (1-3). However, none of these studies have directly evaluated a survival advantage based on MS use. The purpose of this study was to determine whether the use of MSs in pediatric HT recipients impacts graft outcomes. Our hypothesis was that there would be no difference in graft survival between patients who received steroids and those who did not as part of their maintenance immunosuppression regimen.

RESULTS

There were 4894 patients with available data who underwent HT during the study period. Baseline patient characteristics can be viewed in Table S1 (see **SDC**, <http://links.lww.com/TP/A887>). Indication for HT was cardiomyopathy (CM) in 2368 (51%), congenital heart disease in 2109 (45%), and other in 162 (4%). There were 3962 (81%) in the MS group and 932 (19%) in the steroid-free (SF) group. There were 4530 alive at 30 days after HT, of which there were 3694 (82%) in the MS group and 836 (18%) in the SF group. Baseline characteristics of patients who survived up to 30 days after HT are shown in Table 1. More MS patients underwent transplantation as adolescents, had a body mass index greater than 16 kg/m², had a diagnosis of CM, underwent transplantation between 1990 and 1999, had status 2 according to United Network of Organ Sharing (UNOS) at HT, had a waitlist time less than 30 days, had a previous sternotomy, underwent ABO-compatible transplant, were on a ventricular assist device at HT, had an ischemic time of 4 hours or less, had a glomerular filtration rate (GFR) of 40 or higher, had a panel reactive antibody (PRA) greater than 10%, and did not receive induction immunosuppression.

Patients in the MS group were more likely than those in the SF group to receive no induction immunosuppression, an IL-2 receptor antagonist, or OKT3 than antithymocyte globulin (ATG) while those in the SF group were more likely to receive induction immunosuppression with ATG ($P<0.001$; Table 1). Immunosuppression data were missing for 2.3% of the total study population, with data missing in 58 (1.5%) of the MS group and 57 (6.1%) of the SF group. Of those surviving 30 days after HT, immunosuppression data were missing for 1.5% of the study population, with 1.3% missing in the MS group and 2.3% missing in the SF group. Maintenance immunosuppression in the MS group was more likely to include cyclosporine and azathioprine, tacrolimus and mycophenolate mofetil, and tacrolimus and azathioprine, whereas the SF group was more likely to receive cyclosporine

and mycophenolate mofetil or other maintenance immunosuppression regimen ($P<0.001$; Table 1).

Characteristics of MS and SF patients after propensity matching are shown in Table 1. There were no statistically significant differences in baseline characteristics between groups after propensity matching, including donor factors, recipient risk factors, use of induction therapy, and nonsteroid maintenance immunosuppression at 30 days after HT. The number of MS patients in the propensity-matched group with a PRA greater than 50% was 27 (6%) versus 18 (4%) in the SF group ($P=0.15$). After propensity matching, the groups were also balanced with regard to use of azathioprine (MS 43% vs. SF 39%, $P=0.25$), mycophenolate mofetil (MS 55% vs. SF 61%, $P=0.07$), and sirolimus (MS 4% vs. SF 4%, $P=0.73$).

Graft and Patient Survival—Unmatched

Unmatched conditional 30-day graft survival was significantly lower in the MS group. Freedom from graft loss in the MS group was 91%, 74%, 56%, and 42% at 1, 5, 10, and 15 years, respectively, whereas unmatched graft survival in the SF group was 93%, 79%, 62%, and 47% at 1, 5, 10, and 15 years, respectively ($P=0.004$; Fig. 1A). Reasons for unmatched graft loss in both groups are shown in Table S2 (see **SDC**, <http://links.lww.com/TP/A887>). Unmatched conditional 30-day patient survival was significantly lower in the in the MS group as well. Freedom from death in the MS group was 91%, 76%, 63%, and 53% at 1, 5, 10, and 15 years, respectively, whereas in the SF group, it was 93%, 82%, 70%, and 63% at 1, 5, 10, and 15 years, respectively ($P=0.001$; Fig. 1B). Unmatched Cox proportional hazard analysis for risk factors for conditional 30-day graft and patient survival in univariable and multivariable analysis are shown in Table 2. After controlling for diagnosis, age, sex, race, era, mechanical ventilation, listing status, previous sternotomy, GFR, PRA greater than 10%, and induction immunosuppression, there was no difference in the risk of graft loss between MS and SF groups (conditional 30-day graft survival: hazard ratio [HR]=1.08, 95% confidence interval [CI]=0.93-1.24, $P=0.33$; conditional 30-day patient survival: HR=1.09, 95% CI=0.95-1.26, $P=0.23$; Table 2). Independent risk factors for conditional graft loss and death in unmatched multivariable analysis included age 11 to 17 years, female sex, black ethnicity, GFR less than 40, and PRA greater than 10% (Table 2).

Graft and Patient Survival—Propensity-Matched Analysis

Propensity-matched Kaplan-Meier analysis of 30-day conditional graft and patient survival stratified by MS use are shown in Figure 2A and B, respectively. There was no difference in graft or patient survival between groups ($P=0.30$ and $P=0.16$, respectively). Propensity-matched conditional 30-day graft survival in the MS group was 91%, 77%, 63%, and 51% at 1, 5, 10, and 15 years, respectively, whereas in the SF group, it was 94%, 82%, 64%, and 46% at 1, 5, 10, and 15 years, respectively ($P=0.004$, Fig. 1A). Reasons for propensity-matched graft loss in propensity both groups are shown in Table S2 (see **SDC**, <http://links.lww.com/TP/A887>). Freedom from death in the MS group was 91%, 79%, 70%, and 60% at 1, 5, 10, and 15 years, respectively, whereas in the SF group, it was 95%, 85%, 71%, and 60% at 1, 5, 10, and 15 years, respectively ($P=0.001$; Fig. 1B). When induction was removed from the propensity matching and patients were stratified by both induction therapy and MS use, we found no difference in graft or patient survival (Fig. 3A–D).

DISCUSSION

In this analysis of the Organ Procurement and Transplantation Network (OPTN) database, we found no graft survival advantage to the use of MS in pediatric HT recipients. Differences in pre-HT risk of graft loss could have played a role in graft outcomes between SF and MS groups; however, we found no difference in graft or patient survival based on MS use in multivariable analysis. Variables other than MS that we found to be independent risk factors for graft loss have been shown to be independent risk factors in previous studies (4-8). The results of our multivariable model were confirmed by our propensity-matched analysis, which similarly showed that there is no graft or patient survival advantage to the use of MS. Propensity-matched analysis did not show that induction therapy influenced outcomes or that a combination of induction therapy or no induction with or without MS use made a difference in graft outcomes, which is consistent with data from the International Society for Heart and Lung Transplantation registry (1). However, we did not differentiate between the type of induction agent used and it is not known whether any combination of a particular induction agent with an MS or SF regimen would affect graft outcomes.

The lack of graft and patient survival benefit to MS use differs from the unmatched univariable graft and patient survival data, likely due to the higher proportion of patients who underwent transplantation during infancy in the SF group. Patients who underwent transplantation during infancy have a higher risk of perioperative mortality, but those who survive the post-transplant period have better long-term survival when compared to children older than 1 year (1). Other explanations for the worse univariable outcomes in the MS group include a higher proportion of African Americans, a higher proportion of patients who underwent transplantation in the earlier era, and a higher proportion of patients with a previous sternotomy, all of which have been associated with a higher risk of graft loss (1, 9, 10). The successful use of SF maintenance immunosuppression in our analysis is consistent with single-center and dual-center reports of SF maintenance immunosuppression in heart, liver, and renal transplantation (2, 3, 11, 12). While there are no other studies in pediatric HT directly comparing graft survival in patients with and without MS use, multiple single-center studies of pediatric HT have reported outcomes with an SF maintenance immunosuppression protocol with excellent results (2, 8, 13-16). Our propensity matching addresses the limitations of those reports by creating two groups with similar baseline characteristics and comparing MS and SF groups directly. Why additional immunosuppression did not result in improved graft survival is unclear. We speculate that medication nonadherence may have been more common in the MS group because of the many side effects of corticosteroids, and any benefit of the additional immunosuppression could have been countered by a higher likelihood of nonadherence (17). However, we were unable to analyze nonadherence patterns with the available data. Whether pediatric HT recipients on MS are more likely to be nonadherent requires further study. It is also possible that triple-drug immunosuppression is more than is necessary for good outcomes in pediatric HT.

Limitations

There are several limitations to this study. We found incomplete data entry in the OPTN data set, the most notable of which was acute rejection, with 45% of the data missing in both the

MS and SF groups. Therefore, we were unable to evaluate for differences in the incidence, frequency, and severity of rejection between groups. Because consistent data were only available at the time of hospital discharge from HT, we were not able to analyze differences in outcomes based on steroid withdrawal or change in calcineurin inhibitor and/or antiproliferative medication type at various times after HT. Although our model was able to control for pretransplant risk factors for graft loss, it cannot control for a clinician's perceived increased risk of poor post-HT outcomes in an individual. This type of clinical perception could affect the decision of whether to use MS in a particular patient. Also, the different methods of reporting of PRA values before and after 2004 may have influenced which patients qualified as having a PRA greater than 10% and, therefore, underestimating the influence of PRA on graft outcomes. Finally, as in any retrospective registry study, the data analysis supports associations between variables and outcomes, but causal relationships cannot be determined. Risk factors for graft loss may be surrogates for poor clinical status before HT rather than a direct cause of graft loss.

CONCLUSIONS

We have found that there is no graft survival advantage to MS use in pediatric HT recipients. Adoption of SF maintenance immunosuppression regimens in pediatric HT has the potential to minimize the known complications of steroid use without compromising graft outcomes. The likelihood of a multicenter, randomized, controlled trial of MS is low in pediatric HT owing to the many different maintenance immunosuppression protocols across institutions, the limited number of pediatric transplant patients, and a lack of equipoise. Therefore, analyses of more robust databases are needed to evaluate differences in the incidence of morbidities such as rejection, malignancy, hypertension, and diabetes.

MATERIALS AND METHODS

Patient Data and Study Population

All subjects 18 years or younger who underwent their first HT in the United States from January 1, 1990, through May 31, 2010, were identified in the OPTN database based on OPTN data as of June 30, 2011. The OPTN database was chosen because it includes data on all patients listed for an HT in the United States submitted by their transplant centers with a uniform data entry format for the entire country. These data are provided to investigators as deidentified data. The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the OPTN contractor, the UNOS. We excluded patients who were listed for a heart retransplantation or multiorgan transplantation. Recipients were stratified on the basis of MS use at the time of hospital discharge (MS group) or SF at the time of hospital discharge (SF group) after HT. Records with incomplete data on the outcome of graft survival or on MS use were excluded from the analysis. For the primary analysis, univariate analysis for risk of graft loss and death for those alive with a functioning graft at 30 days after transplant was performed using risk factors previously identified in the literature. This period was chosen to eliminate perioperative deaths not related to MS use and to ensure that patients who never had an opportunity to receive MS were not included. The variables included in the survival analyses

were diagnosis of CM, congenital heart disease, or other; recipient and donor age; cold ischemic time; sex; race; body mass index; era of HT; ABO mismatch; mechanical ventilation at the time of HT; UNOS listing status at HT; presence of previous sternotomy; estimated GFR less than 40 mL/min; most recent panel reactive antibody (PRA) greater than 10%; use of induction and maintenance immunosuppression; and waitlist time. The most recent PRA was used for the analysis. Because of the different methods of reporting the PRA in UNOS, the total PRA was used up to June 2004, while the maximum of the Class I and the Class II PRA was used from June 2004 onward. Immunosuppression data were provided separately by OPTN per our request. Missing covariate data were accounted for in the analysis by generating additional “missing” categories. Use of these data was consistent with the regulations of our university’s institutional review board.

Data Analysis

Data were analyzed using SAS 9.3 for Windows software (SAS Institute, Inc., Cary, NC). The primary outcomes were 30-day contingent graft survival (time to retransplantation or death) and patient survival. Continuous variables are reported as means and standard deviations and were compared by the Student *t* test. Dichotomous and categorical variables were compared by the χ^2 test. All *P* values are 2-sided. Kaplan-Meier analysis, log-rank test, and Cox proportional hazards regression were used for time-to-event analyses. Covariates that were significant for *P* < 0.10 in the univariate analysis were included in the respective multivariable analysis. HRs are reported with 95% CIs in parentheses. To further address potential confounding and bias due to differences in baseline characteristics between patients with and without MS use at 30 days after HT, we derived a propensity score that summarized the predictive probability of being prescribed MS using a logistic model that included all the covariates stated above. We matched each recipient in the SF group with a recipient from the MS group and then calculated Kaplan-Meier graft and patient survival probabilities by steroid use. For the analysis by induction therapy, we removed induction from the matching covariates and then analyzed on a four-group variable, based on steroid and induction therapy stratification. To account for the matched-pair data, we used the extended McNemar test (Bhapkar test, 1990) to compare categorical variables and the Wilcoxon signed rank test to compare continuous variables between matched groups (18).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Kaplan-Meier analysis of unmatched conditional 30-day graft (A) and patient (B) survival stratified by maintenance steroid use.

FIGURE 2.

Kaplan-Meier analysis of propensity-matched conditional 30-day graft (A) and patient (B) survival stratified by maintenance steroid use.

FIGURE 3.

Kaplan-Meier analysis of propensity-matched conditional 30-day graft survival stratified by maintenance steroid (MS) and induction therapy use. Comparisons include MS with induction versus steroid-free (SF) with induction (A), MS without induction versus SF without induction (B) MS with induction versus SF without induction (C), and MS without induction versus SF with induction (D).

TABLE 1
 Characteristics of recipients by steroid Use 30 days after transplant, before and after propensity matching

Characteristics	Before propensity matching			After propensity matching			<i>P</i> ^b
	MS (n=3694)	SF (n=836)	<i>P</i> ^a	MS (n=462)	SF (n=462)		
Donor age (yr)							
Mean (SD)	9.6 (10.5)	5.9 (8.5)	<0.001	7.2 (9.4)	7.0 (8.8)		0.94
Median (IQR)	6 (1–16)	2 (0–8)		2.5 (0–12)	3 (0–11)		
0 to <1	733 (20%)	279 (33%)	<0.001	135 (29%)	132 (29%)		0.87
1–10	1581 (43%)	372 (45%)		197 (43%)	208 (45%)		
11–17	695 (19%)	91 (11%)		62 (13%)	58 (13%)		
18	684 (18%)	91 (11%)		68 (15%)	64 (13%)		
Recipient age (yr)							
Mean (SD)	6.8 (6.2)	3.9 (5.5)	<0.001	5.0 (5.9)	4.9 (5.9)		0.79
Median (IQR)	6 (0–13)	0 (0–7)		2 (0–10)	2 (0–10)		
0 to <1	930 (25%)	424 (51%)	<0.001	189 (41%)	181 (39%)		0.36
1–10	1430 (39%)	264 (31%)		160 (35%)	178 (39%)		
11–17	1334 (36%)	148 (18%)		113 (24%)	103 (22%)		
Sex							
Male	2118 (57%)	457 (55%)	0.16	253 (55%)	259 (56%)		0.67
Female	1576 (43%)	379 (45%)		209 (45%)	203 (44%)		
Race							
White	2303 (62%)	474 (57%)	<0.001	270 (58%)	270 (58%)		0.96
Black	754 (21%)	100 (12%)		64 (14%)	67 (15%)		
Hispanic	437 (12%)	206 (24%)		96 (21%)	91 (20%)		
Other	200 (5%)	56 (7%)		32 (7%)	34 (7%)		
BMI (kg/m ²)							
<15	1215 (36%)	413 (54%)	<0.001	218 (47%)	214 (46%)		0.93
15–25	1934 (56%)	317 (41%)		216 (47%)	218 (47%)		
26–45	268 (8%)	40 (5%)		28 (6%)	30 (7%)		
Diagnosis							
Cardiomyopathy	2016 (54%)	320 (38%)	<0.001	202 (44%)	200 (43%)		0.89

Characteristics	Before propensity matching			<i>P</i> ^a	After propensity matching			<i>P</i> ^b
	MS (n=3694)	SF (n=836)			MS (n=462)	SF (n=462)		
Congenital heart disease	1538 (42%)	500 (60%)			245 (53%)	249 (54%)		
Other	140 (4%)	16 (2%)			15 (3%)	13 (3%)		
Era of transplantation								
Era 1 (1990–1999)	1548 (42%)	315 (38%)		0.025	141 (31%)	140 (30%)		0.94
Era 2 (2000–2010)	2146 (58%)	521 (62%)			321 (69%)	322 (70%)		
UNOS listing status								
1	2916 (79%)	716 (86%)		<0.001	391 (85%)	386 (84%)		0.60
2	774 (21%)	120 (14%)			71 (15%)	76 (16%)		
Waitlist time (d)								
>30	2009 (55%)	485 (58%)			269 (58%)	279 (60%)		0.49
30	1671 (45%)	348 (42%)		0.06	193 (42%)	183 (40%)		
ABO compatibility								
Yes	3640 (99%)	815(97%)		0.03	451 (98%)	451 (98%)		1.00
No	54 (1%)	21 (3%)			11 (2%)	11 (2%)		
Mechanical ventilation								
Yes	666 (18%)	128 (15%)		0.06	68 (15%)	70 (15%)		0.85
No	3028 (82%)	708 (85%)			394 (85%)	392 (85%)		
Prior sternotomy								
Yes	2266 (61%)	468 (56%)		0.004	222 (48%)	231 (50%)		0.53
No	1428 (39%)	368 (44%)			240 (52%)	231 (50%)		
VAD at transplant								
Yes	256 (7%)	27 (3%)		<0.001	20 (4%)	20 (4%)		1.00
No	3438 (93%)	809 (97%)			442 (96%)	442 (96%)		
Ischemic time (h)								
0–4	2445 (70%)	451 (55%)		<0.001	287 (62%)	282 (61%)		0.70
>4	1029 (30%)	363 (45%)			175 (38%)	180 (39%)		
GFR								
<40	134 (5%)	79 (11%)		<0.001	40 (9%)	34 (7%)		0.44
40	2818 (95%)	609 (89%)			422 (91%)	428 (93%)		
PRA								

Characteristics	<u>Before propensity matching</u>		<i>p^a</i>	<u>After propensity matching</u>		<i>p^b</i>
	MS (n=3694)	SF (n=836)		MS (n=462)	SF (n=462)	
10%	2797 (86%)	635 (90%)	0.006	414 (90%)	410 (89%)	0.65
>10%	448 (14%)	70 (10%)		48 (10%)	52 (11%)	
Induction						
Yes	2234 (60%)	754 (90%)	<0.001	411 (89%)	413 (89%)	0.74
No	1460 (40%)	82 (10%)		51 (11%)	49 (11%)	
Maintenance immunosuppression			<0.001			0.42
Cyclosporine-based	1780 (49%)	461 (56%)		233 (50%)	230 (50%)	
Tacrolimus-based	1380 (38%)	184 (23%)		146 (32%)	136 (29%)	
Other	486 (13%)	172 (21%)		83 (18%)	96 (21%)	

^aWilcoxon signed rank sum test for continuous data; χ^2 test for categorical data.

^bWilcoxon signed rank sum test for paired continuous data; extended McNemar test (Bhapkar test) for paired categorical data.

BMI, body mass index; GFR, glomerular filtration rate; IQR, interquartile range; MS, maintenance steroid; PRA, panel reactive antibody; SD, standard deviation; SF, steroid-free; UNOS, United Network of Organ Sharing; VAD, ventricular assist device.

TABLE 2

Thirty-day conditional graft and patient survival prior to propensity matching

Variable	30-d conditional graft survival			30-d conditional patient survivalcenter		
	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	Univariable HR (95% CI)	P	Multivariable HR (95% CI)
Maintenance steroids	1.22 (1.06–1.40)	0.004	1.08 (0.93–1.24)	1.34 (1.14–1.56)	<0.001	1.09 (0.95–1.26)
Donor age 1–10 vs. <1 yr	1.08 (0.94–1.23)	0.29	0.98 (0.82–1.17)	1.05 (0.90–1.21)	0.54	0.98 (0.82–1.17)
Donor age 11–17 vs. <1 yr	1.23 (1.05–1.44)	0.011	0.92 (0.72–1.18)	1.20 (1.00–1.43)	0.045	0.91 (0.71–1.17)
Donor age >18 vs. <1 yr	1.50 (1.29–1.75)	<0.001	1.09 (0.84–1.40)	1.55 (1.31–1.84)	<0.001	1.08 (0.84–1.39)
Age 1–10 vs. <1 yr	1.06 (0.94–1.20)	0.35	0.98 (0.83–1.17)	0.99 (0.86–1.14)	0.85	0.99 (0.83–1.17)
Age 11–17 vs. <1 yr	1.45 (1.28–1.64)	<0.001	1.33 (1.06–1.67)	1.47 (1.28–1.68)	<0.001	1.33 (1.06–1.67)
Female sex	1.18 (1.07–1.30)	<0.001	1.22 (1.11–1.35)	1.11 (1.00–1.24)	0.054	1.23 (1.11–1.36)
Black vs. Caucasian	1.92 (1.71–2.15)	<0.001	1.89 (1.68–2.12)	1.96 (1.72–2.22)	<0.001	1.88 (1.67–2.12)
Hispanic vs. Caucasian	1.03 (0.89–1.21)	0.67	1.09 (0.93–1.28)	0.95 (0.80–1.14)	0.59	1.10 (0.94–1.29)
Other vs. Caucasian	1.17 (0.92–1.49)	0.20	1.19 (0.93–1.52)	1.20 (0.92–1.56)	0.17	1.21 (0.95–1.54)
BMI <15 vs. 15–25 kg/m ²	0.81 (0.73–0.91)	<0.001	0.93 (0.82–1.05)	0.82 (0.73–0.92)	<0.001	0.94 (0.83–1.06)
BMI 26–45 vs. 15–25 kg/m ²	1.20 (0.99–1.45)	0.067	1.06 (0.87–1.30)	1.19 (0.97–1.47)	0.097	1.04 (0.85–1.27)
CHD vs. CM	1.02 (0.92–1.12)	0.73		1.04 (0.94–1.17)	0.45	
Other vs. CM	1.14 (0.88–1.48)	0.33		1.16 (0.87–1.55)	0.31	
Era 1 vs. Era 2	1.15 (1.03–1.28)	0.012	1.08 (0.95–1.23)	1.15 (1.02–1.29)	0.021	1.13 (1.00–1.28)
UNOS status 1 vs. 2	0.84 (0.75–0.94)	0.002	0.86 (0.76–0.97)	0.87 (0.76–0.98)	0.021	0.86 (0.76–0.97)
Waited >30 vs. 30 d	1.06 (0.96–1.17)	0.24		1.10 (0.99–1.23)	0.090	1.06 (0.95–1.17)
ABO incompatible vs. identical/compatible	1.14 (0.70–1.87)	0.60		1.29 (0.79–2.11)	0.32	
Mechanical ventilation	1.04 (0.91–1.18)	0.57		1.10 (0.96–1.27)	0.17	
Sternotomy	1.12 (0.99–1.27)	0.071	1.13 (0.98–1.31)	1.09 (0.96–1.25)	0.19	
VAD	1.04 (0.85–1.28)	0.71		1.12 (0.90–1.40)	0.32	
Ischemic time >4 h	0.94 (0.84–1.04)	0.22		0.91 (0.80–1.02)	0.11	
GFR: <40	1.23 (0.99–1.53)	0.064	1.53 (1.22–1.93)	1.31 (1.04–1.66)	0.025	1.54 (1.22–1.94)
PRA: >10%	1.28 (1.09–1.49)	0.002	1.34 (1.15–1.57)	1.19 (1.00–1.42)	0.046	1.31 (1.12–1.54)
PVRI 6 vs. 0–6 units	1.07 (0.85–1.34)	0.58		1.07 (0.83–1.37)	0.61	
No induction therapy	0.95 (0.85–1.05)	0.30		0.91 (0.81–1.03)	0.13	
Tacrolimus-based vs. cyclosporine-based	1.00 (0.88–1.13)	0.96		1.02 (0.90–1.17)	0.75	1.00 (0.88–1.14)

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Variable	30-d conditional graft survival			30-d conditional patient survivalcenter		
	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	Univariable HR (95% CI)	P	Multivariable HR (95% CI)
Other maintenance vs. cyclosporine-based	1.09 (0.95–1.25)	0.21		1.19 (1.03–1.38)	0.021	1.12 (0.97–1.28)

0.12

CHD, congenital heart disease; CI, confidence interval; CM, cardiomyopathy; GFR, glomerular filtration rate; HR, hazard ratio; PRA, panel reactive antibody; UNOS, United Network of Organ Sharing; VAD, ventricular assist device.