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ORIGINAL RESEARCH

Corticosteroid use beyond 1-year post heart transplantation is associated with worse outcomes: A contemporary analysis of the ISHLT registry

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KEYWORDS:
Heart transplant;
Steroid;
Corticosteroid;
Withdrawal;
Discontinuation;
Survival

INTRODUCTION: Immunosuppressive drugs ensure graft survival in heart transplantation (HT). However, prolonged use can lead to significant morbidity and mortality, and the optimal immunosuppressive regimen is unknown. We compared outcomes in adult HT recipients with or without steroid use in the large, international ISHLT Registry.

METHODS: We included adults who underwent their first heart-only transplant between January 2010 and June 2018. We compared the risk-adjusted 2-, 3-, and 5-year survival as well as coronary allograft vasculopathy (CAV), treated rejection within 2 years, severe renal dysfunction, diabetes and malignancy rates between those with and without steroids by 1-year post-HT follow-up.

RESULTS: We included 17,483 HT recipients, steroids were discontinued in 8750 (50.0%) recipients beyond 1-year post-HT. Unadjusted survival rates (conditional upon 1-year survival) were significantly lower in the cohort receiving steroids at 2-years (96.2% vs. 98.0%, $p < 0.001$), 3-years (93.3% vs. 96.5% $p < 0.001$), and 5-years (89.8% vs. 94.0%, $p < 0.001$). After adjustment, continued steroid use remained associated with a significantly higher risk of 2-year (HR 1.92, 95% CI 1.60–2.31), 3-year (HR 1.88, 95% CI 1.63–2.16), and 5-year mortality (HR 1.64, 95% CI 1.47–1.82). Furthermore, continuing steroid was associated with a significantly higher prevalence of CAV (OR 1.09, 95% CI 1.01–1.18), diabetes (OR 1.24, 95% CI 1.12–1.36), 2-year treated rejection (OR 2.50, 95% CI 2.25–2.73), and severe renal dysfunction (OR 1.66, 95% CI 1.50–1.84) but no difference in malignancy rates (OR 0.85, 95% CI 0.70–1.04).

Glossary of Abbreviations: BMI, Body mass index; BiVAD, Biventricular assist device; CAV, Coronary allograft vasculopathy; CI, Confidence interval; ECMO, Extracorporeal membrane oxygenation; HR, Hazard ratio; HT, Heart transplant/transplantation; IABP, Intra-aortic balloon pump; ICD, Implantable cardioverter defibrillator; ISHLT, International Society of Heart and Lung Transplant; OCS, Organ care system; OR, Odds ratio; PHM, Predicted heart mass; VAD, Ventricular assist device

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https://doi.org/10.1016/j.jhlto.2025.100214

CONCLUSIONS: Steroid use beyond 1year post heart transplant was associated with significantly lower survival, and worsened morbidity among adult recipients. Whether this observation indicates steroid use is a marker of higher risk or worsens prognosis warrants prospective investigation.
JHLT Open 2025;8:100214

INTRODUCTION

Corticosteroids (steroids) are an integral part of the maintenance immunosuppressive regimen in adult heart transplant (HT) recipients. With the advent of effective immunosuppression with calcineurin inhibitors-based regimens, however, minimization of steroid use is typically prioritized to avoid the long-term adverse effects on glucose and lipid metabolism and bone health.

Weaning of steroids is feasible without impacts on rejection and long-term graft survival.[1–3] Based on these studies, the latest International Society for Heart and Lung Transplantation (ISHLT) guideline indicates that steroid weaning is reasonable in recipients with significant adverse effects.[4] Moreover, an ISHLT Registry study involving recipients from 2000–2008 reported lower 10-year survival with the use of steroids beyond 5 years post-HT compared to early (< 2 years) or to late withdrawal (between 2 and 5 years).[5]

Protocols for steroid maintenance, minimization, or withdrawal vary among HT centers, and there is significant variation in contemporary approaches in the use of steroids in heart transplant recipients, which ranges from 7- day wean to late withdrawal and, not uncommonly, lifelong therapy. Over 75% and 50% of HT recipients were taking steroids at one and five years, respectively 1 year.[6] This may be explained by concerns regarding the changing profile of HT recipients undergoing transplant in the contemporary era with factors such as higher allosensitization. This is occurring even though tacrolimus-based immunosuppression affords lower rejection risk and is the predominant drug used for patients.

We examined the trend in steroid use in adult HT recipients across multiple centers, steroid use as a function of transplant center volume, the impact of steroid withdrawal on graft rejection, and recipient survival in a contemporary cohort in the ISHLT Registry.

METHODS

This report was written following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[7]

Data source

We used the ISHLT International Thoracic Organ Transplant Registry, provided from January 1st, 2010 through June 30th, 2018. As the ISHLT provided a dataset without patient or center identifiers, our center did not require Institutional Review Board approval.

Study population

We included all adults (≥18 years of age) who received an HT, who were receiving steroids at hospital discharge after transplant, and who survived to 1-year post-HT. We excluded multiorgan transplants and redo HT recipients. Recipients were categorized into groups with and without steroid use at their 1-year post-HT follow-up visit.

Outcomes

We included the baseline characteristics either at the time of organ donation consideration (for donors) or at the time of transplant (for recipients), including demographic and transplant characteristics of the recipients and donors. The primary outcomes were mortality 2-, 3-, and 5 years after HT. Secondary outcomes included rates of coronary allograft vasculopathy (CAV), treated rejection within 2 years, severe renal dysfunction after transplant (defined as a serum creatinine > 2.5 mg/dL, dialysis, or need for renal replacement therapy), diabetes and malignancy post-HT.

Statistical analyses

We used standard statistical methods to describe all demographics and clinical variables, stratified by 1-year steroid usage. We compared baseline characteristics between groups using either Pearson's chi-square for categorical or the Wilcoxon rank sum test for continuous variables. Kaplan-Meier survival analysis with log-rank test compared time from transplantation to death between groups.

We used multiple imputations with chained equations, with missingness assumed to be random, using predictive mean matching with the "mice" package (version 3.16.0) in R (The R Foundation, https://www.r-project.org/). All predictors and outcomes were included in each imputation model. The number of imputed datasets we generated corresponded to the highest percent missingness for each outcome. We examined convergence through visual inspection of plots and diagnostics. Analyses were performed on each imputed dataset and pooled using Rubin's rules.

To evaluate risk-adjusted mortality and graft failure between study groups, a Cox proportional hazards model

was created using the 'rms' package (version 6.8–0) in R. Characteristics shown in the 38th ISHLT Registry report on adult heart transplantation to be associated with mortality were used in the model and included recipient age, body mass index (BMI), history of DM, and transplant year.[8] We also adjusted for LVAD use, ischemic time, transplant center volume, predicted heart mass ratio, and donor-recipient sex mismatch. Continuous variables were flexibly modeled using restricted cubic splines (4 knots). Results are reported as adjusted hazard ratios (HR) with a corresponding 95% confidence interval (CI). We evaluated the Schoenfeld residuals to determine the robustness of the proportionality assumption of each Cox model.

The association between steroid discontinuation at 1 year and the occurrence of the secondary outcomes was assessed using multiple logistic regression, controlling for known confounders, and reported as adjusted odds ratios (OR) with a corresponding 95% CI. When analyzing post-transplant CAV, we controlled for recipient age, BMI, gender, history of diabetes, ischemic HF etiology, donor age, donor brain death modality, and ischemic time.[9] When analyzing post-transplant DM, we controlled for recipient age, BMI, gender, history of diabetes, ischemic heart failure etiology, pre-transplant dialysis, and tacrolimus use at 1 year.[10] When analyzing post-transplant malignancy, we controlled for recipient age, history of malignancy, diabetes, and ischemic HF etiology.[11] When analyzing post-transplant severe renal dysfunction, we controlled for recipient age, BMI, gender, history of diabetes, ischemic HF etiology, pre-transplant use of dialysis, left ventricular assist device (LVAD) use at the time of listing, and tacrolimus use at 1-year.[12] Lastly when analyzing acute rejection within 2 years of transplant, we controlled for recipient age, BMI, gender, history of diabetes, ischemic HF etiology, donor age, ischemic time, and tacrolimus use at 1 year.[4]

We conducted subgroup analysis for each outcome of interest according to transplant center volume. The ISHLT database categorizes annual center volume as <25 transplants/year, 21–50 transplants/year, 51–75 transplants/year, and >75 transplants/year.

We performed data management using SAS 9.4 (SAS Institute, Cary, NC) and data analysis using R 4.4.0 using RStudio version 2024.04.0, with a p-value < 0.05 considered statistically significant.

RESULTS

Patient characteristics

We included 17,483 adult HT recipients, of whom 8750 (50.0%) had steroids discontinued by the one-year post-HT time point (Figure 1). Characteristics of the study groups are described and compared in Table 1. Transplant recipients who discontinued steroid use at 1 year were significantly more likely to be female (28% vs. 25%; $p<0.001$), more often had HF etiologies of hypertrophic cardiomyopathy (3.1% vs. 2.4%; $p<0.001$), and ischemic cardiomyopathy (35% vs. 33%; $p<0.001$), more likely to have an implantable cardioverter defibrillator (ICD) (91% vs. 88%; $p<0.001$), were less likely to have hypertension (52% vs. 56%; p=0.001), and were less likely to be supported on an intra-aortic balloon pump (IABP) (5.3% vs. 7.0%; $p<0.001$) and BiVAD pre-transplant (1.6% vs. 2.7%, $p<0.001$).

Patients who had steroids continued at 1 year were significantly more likely to be receiving calcineurin inhibitors (97% vs. 93%; $p<0.001$) or antiproliferative maintenance immunosuppressive drugs (95% vs. 90%; $p<0.001$). They were also more likely to be transplanted at a high-volume (>75 transplants/year) center (7.4% vs. 6.1%; $p<0.001$).

Factors associated with continuing steroids at 1 year are shown in the Table 2. Older recipient age (OR 0.89, 95% CI

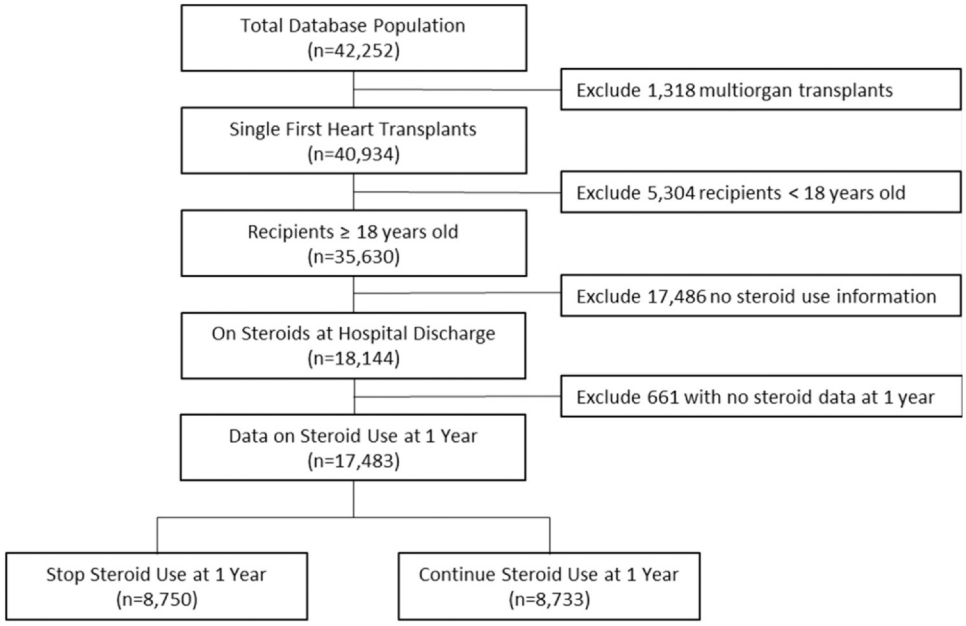

Figure 1 Selection of Study Cohort.

Table 1 Characteristics of Heart Transplant Recipients by Steroid Use at 1-Year

Characteristic	Total N = 17,483	Without Steroid N = 8750	With Steroid N = 8733	*p*-value
Recipient Characteristics				
Age, years	56 (46, 63)	56 (46, 63)	55 (45, 62)	< 0.001
Men	12,894 (74%)	6597 (75%)	6297 (72%)	< 0.001
Blood Type				0.3
A	7118 (41%)	3622 (41%)	3496 (40%)	
AB	1044 (6.0%)	513 (5.9%)	531 (6.1%)	
B	1559 (15%)	1256 (14%)	1303 (15%)	
O	6762 (39%)	3359 (38%)	3403 (39%)	
BMI, kg/m^2	26.9 (23.6, 30.5)	26.7 (23.5, 30.4)	27.1 (23.7, 30.7)	0.001
Heart Failure Etiology				< 0.001
Congenital diseases	492 (2.8%)	244 (2.8%)	248 (2.8%)	
Hypertrophic	482 (2.8%)	274 (3.1%)	208 (2.4%)	
Ischemic	5956 (34%)	3048 (35%)	2908 (33%)	
Miscellaneous	1088 (6.2%)	531 (6.1%)	557 (6.4%)	
Non-ischemic	8909 (51%)	4425 (51%)	4484 (51%)	
Restrictive	556 (3.2%)	228 (2.6%)	328 (3.8%)	
History of diabetes mellitus	4464 (27%)	2140 (28%)	2324 (27%)	0.3
History of hypertension	5217 (54%)	2305 (52%)	2912 (56%)	0.001
Prior cardiac surgery	8442 (52%)	4040 (53%)	4402 (51%)	0.063
Episode of ventilator support before transplant	3345 (21%)	1597 (21%)	1748 (20%)	0.6
Prior ICD	12,827 (89%)	6195 (91%)	6632 (88%)	< 0.001
Prior ECMO support	114 (0.7%)	54 (0.7%)	60 (0.7%)	> 0.9
Prior IABP	1016 (6.2%)	409 (5.3%)	607 (7.0%)	< 0.001
Durable VAD at listing				< 0.001
BiVAD	381 (2.2%)	144 (1.6%)	237 (2.7%)	
LVAD	6844 (39%)	3366 (38%)	3478 (40%)	
None	8872 (51%)	4101 (47%)	4771 (55%)	
TAH	167 (1.0%)	73 (0.8%)	94 (1.1%)	
Creatinine, mg/dL	1.16 (0.91, 1.41)	1.13 (0.90, 1.40)	1.19 (0.91, 1.45)	< 0.001
Bilirubin, mg/dL	0.7 (0.5, 1.1)	0.7 (0.5, 1.1)	0.7 (0.5, 1.1)	0.9
PCWP, mmHg	17 (11, 24)	17 (11, 24)	17 (11, 24)	0.011
PRA	0 (0, 6)	0 (0, 4)	0 (0, 9)	< 0.001
Maintenance Immunosuppression at Hospital Discharge				
Calcineurin Inhibitor	16,658 (95%)	8173 (93%)	8485 (97%)	< 0.001
Anti-proliferative agents	16,193 (93%)	7873 (90%)	8320 (95%)	< 0.001
Donor age, years	31 (23, 42)	31 (23, 43)	30 (23, 41)	< 0.001
Donor Male	12,098 (69%)	5908 (68%)	6190 (71%)	< 0.001
Donor blood type				0.2
A	6415 (37%)	3279 (37%)	3136 (36%)	
AB	449 (2.6%)	224 (2.6%)	225 (2.6%)	
B	1956 (11%)	970 (11%)	986 (11%)	
O	8663 (50%)	4277 (49%)	4386 (50%)	
Donor BMI, kg/m^2	26.2 (23.1, 30.2)	26.1 (23.1, 3.1)	26.2 (23.1, 3.2)	0.4
Donor history of diabetes mellitus	583 (3.6%)	289 (3.7%)	294 (3.4%)	0.3
Donor history of hypertension	2483 (15%)	1178 (15%)	1305 (15%)	> 0.9
Transplant Characteristics				
Ischemic time, h	3.12 (2.40, 3.83)	3.13 (2.45, 3.88)	3.12 (2.35, 3.78)	< 0.001
Donor-recipient PHM ratio	1.12 (1.00, 1.25)	1.11 (1.00, 1.24)	1.13 (1.01, 1.25)	< 0.001
Recipient-Donor Mismatch	4270 (24%)	2183 (25%)	2087 (24%)	0.11
Transplant center volume/year				< 0.001
< 25	8003 (46%)	4009 (46%)	3994 (46%)	
25–50	5713 (33%)	2944 (34%)	2769 (32%)	
51–75	2590 (15%)	1263 (14%)	1327 (15%)	
> 75	1177 (6.7%)	534 (6.1%)	643 (7.4%)	

Data are presented either as n (%) or median (25th, 75th percentile) and compared using either Pearson's chi-squared test or Wilcoxon rank sum test, respectively. BiVAD: biventricular assist devices; BMI: body mass index, ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump, ICD: implantable cardioverter defibrillator; LVAD: left ventricular assist device; PCWP: pulmonary capillary wedge pressure; PHM: predicted heart mass; PRA: panel-reactive antibody; TAH: total artificial heart.

Table 2 Factors Associated with 1-Year Steroid Continuation

Factor	Odds Ratio (95% CI)
Age, per year	0.89 (0.85–0.94)*
Male	0.83 (0.75–0.91)*
BMI, per kg/m^2	1.00 (1.00, 1.00)
History of diabetes mellitus	1.01 (0.94–1.09)
Prior cardiac surgery	1.02 (0.94–1.09)
Prior ICD	0.81 (0.73–0.91)
Episode of ventilator support before transplant	0.97 (0.89–1.05)
Prior ECMO support	0.83 (0.57–1.20)
Prior IABP	1.40 (1.22, 1.60)*
Durable VAD at listing	
None	Referent
BiVAD	1.29 (1.03–1.61)*
LVAD	0.93 (0.86–1.00)
TAH	0.97 (0.71–1.33)
Calcineurin Inhibitor at discharge	1.31 (1.04, 1.65)*
Anti-proliferative agents at discharge	1.10 (0.93, 1.29)
Donor age, per year	1.01 (0.94, 1.07)
Donor Male	1.20 (1.10, 1.31)*
Donor BMI, per kg/m^2	1.00 (1.00, 1.00)
Donor history of diabetes mellitus	0.90 (0.76, 1.07)
Donor history of hypertension	1.03 (0.94, 1.14)
Ischemic time, per hour	0.96 (0.92, 1.01)
Transplant center volume/year	
< 25	Referent
25–50	0.88 (0.82, 0.95)*
51–75	1.02 (0.93–1.12)
> 75	1.23 (1.08, 1.39)*

BiVAD: biventricular assist devices; BMI: body mass index, ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump, ICD: implantable cardioverter defibrillator; LVAD: left ventricular assist device; TAH: total artificial heart.

0.85–0.94), male recipient (OR 0.83, 95% CI 0.75–0.91), and low-volume (< 25 transplants/year) centers (OR 0.88, 95% CI 0.82–0.95) were associated with lower odds of steroid continuation. Whereas use of an IABP at listing (OR 1.40, 95% CI 1.22–1.60), biventricular assist devise at listing (OR 1.29, 95% CI 1.003–1.61), those receiving a calcineurin inhibitor (OR 1.31, 95% CI 1.04–1.65), male donors (OR 1.20, 95% CI 1.10–1.31), and high-volume (> 75 transplants/year) centers (OR 1.23, 95% CI 1.08–1.39) were associated with higher odds of steroid continuation.

Survival outcomes

Our study cohort survival rates (conditional upon available information on steroid use at 1- year) at 2-, 3-, and 5 years were 97.1%, 94.9%, and 91.9%, respectively. Kaplan-Meier analysis showed that transplant recipients who were maintained on steroids 1-year after HT had significantly higher unadjusted 2- (3.8% vs. 2.0%, log-rank $p < 0.001$), 3- (6.7% vs. 3.5%, log-rank $p < 0.001$) and 5-year mortalities (10.2% vs. 6.0%, log-rank < 0.001) (Figure 2). After adjustment, continuing steroids beyond 1 year after HT was still associated with a higher risk of 2- (HR 1.92, 95% CI 1.60–2.31), 3- (HR 1.88, 95% CI 1.63–2.16), and 5-year mortalities (HR 1.64, 95% CI 1.47–1.82).

Secondary post-transplant outcomes

The incidence of CAV, post-transplant DM, malignancy, severe renal dysfunction, and acute rejection within 2-years was 21.4%, 12.3%, 2.4%, 11.9%, and 16.6%, respectively. Continuing steroids at 1-year post-HT was associated with higher risk-adjusted CAV (OR 1.09, 95% CI 1.01–1.18), diabetes (OR 1.23, 95% CI 1.12–1.36), severe renal function (OR 1.66, 95% CI 1.50–1.84), and acute rejection within 2-years (OR 2.50, 95% CI 2.26–2.72) but no effect on malignancy (OR 0.85, 95% CI 0.70–1.04) (Figure 3).

Effect of center volume on outcomes

Results of the subgroup analyses by center volume are shown in Table 3. The association between steroid withdrawal and 2-year mortality was consistent, except for centers with > 75 transplants per year where no significant association was seen. Across the outcomes, similar associations were seen across the center volume, with some stronger relationships being seen in the higher volume centers.

DISCUSSION

Our findings add to the existing literature on steroid usage practice and associated outcomes in adult HT recipients. Prior analyses using the ISHLT Registry revealed increased withdrawal of steroids in 20% of patients in 2018 compared to approximately 6% in 2000.[13,14] Our analysis of the ISHLT Registry shows that this trend continues with the withdrawal of steroids at 1 year in 50% of contemporary HT recipients. These observations support the feasibility of a steroid-free immunosuppressive regimen without substantial risk of graft loss and survival in a significant proportion of adult HT recipients.

However, the reasons behind the continuation or withdrawal of steroids post-transplant were beyond our analysis due to a lack of data points in the ISHLT Registry database and remain elusive. One could argue that recipients in whom steroids were continued were fundamentally at higher risk of (or had sustained significant) rejections and hence this use was necessary. This is reflected in our findings of an increased association of treated rejections and steroid use in our analysis. By contrast, it is also possible that some transplant centers are likely rapid steroid weaners by protocol while other centers follow a slow or no withdrawal strategy. Indeed, we observed increased steroid use at high-volume transplant centers (> 75 transplants/year). Whether such observation could reflect a higher number of individuals receiving transplants in high-volume centers remains unclear. However, our finding of higher mortality rates in recipients who continue to receive long-term steroid use in low or medium-volume centers (< 75 transplants/

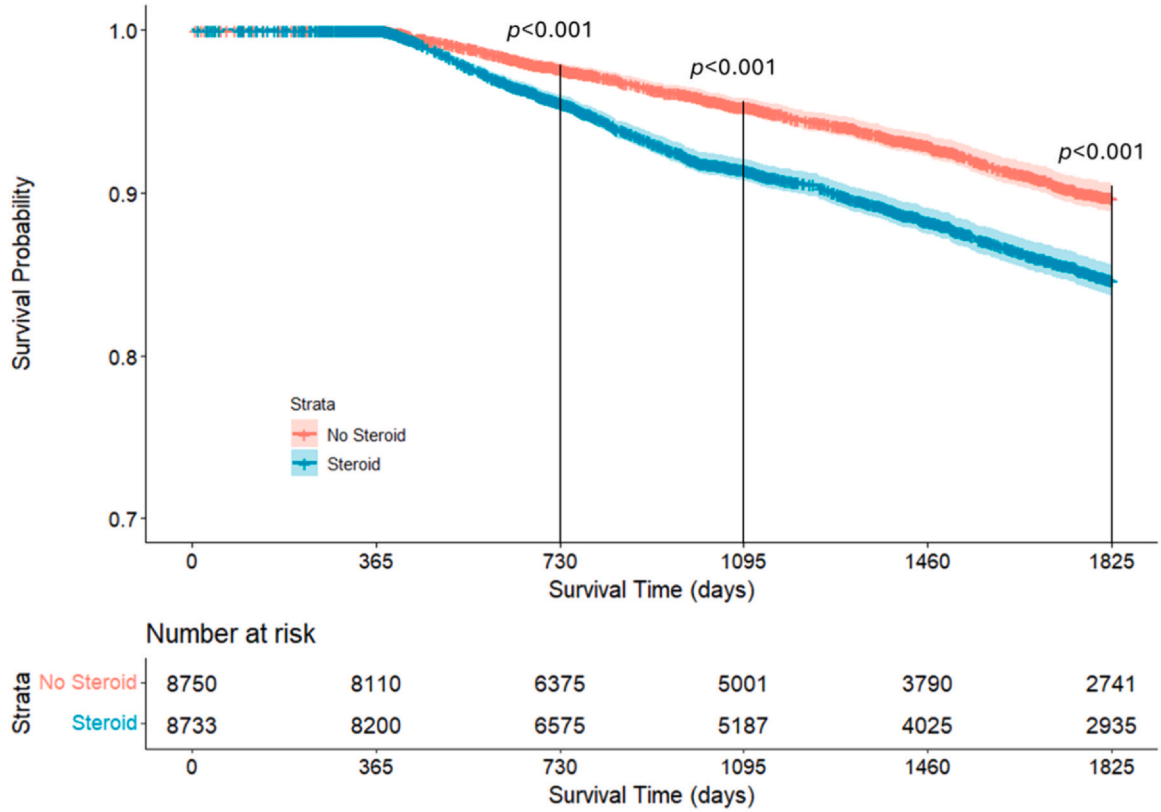

Figure 2 Post-transplant survival conditional on 1-year survival stratified by steroid usage.

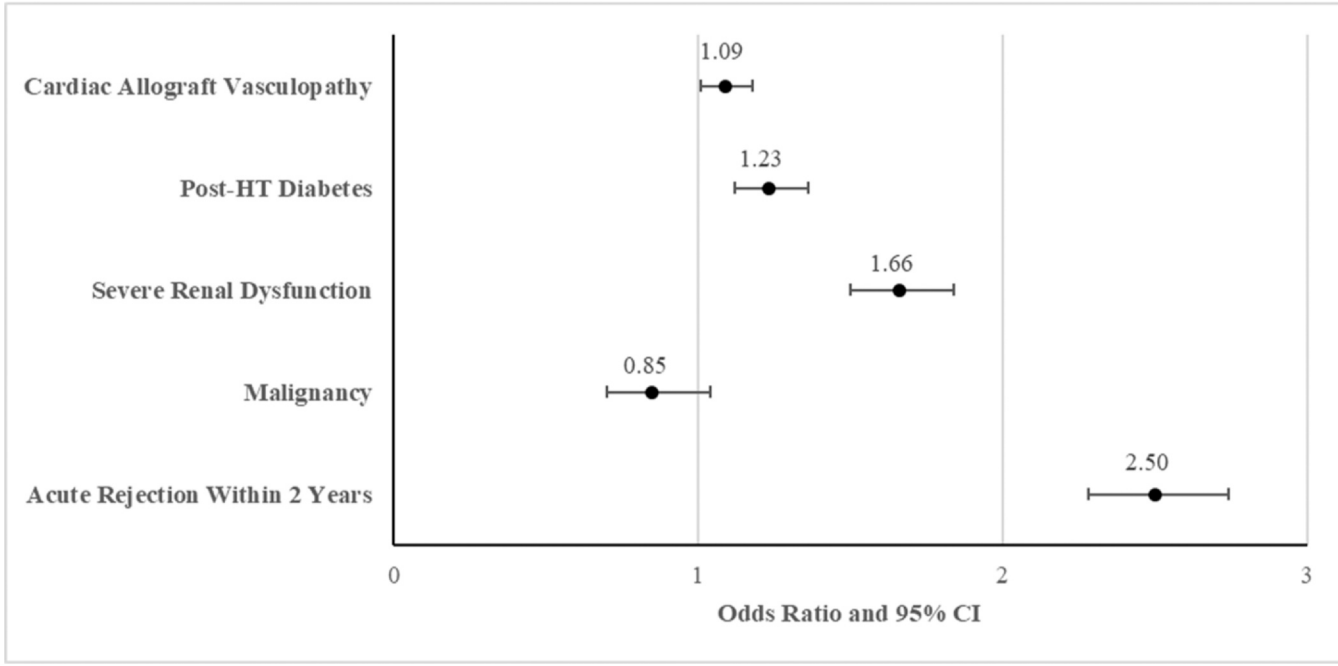

Figure 3 Association of steroid continuation with secondary post-transplant outcomes. CI = confidence interval; HT = heart transplant.

year) compared to high-volume centers suggests that a lack of standardization of steroid-weaning balancing the risk of rejection with the risk of steroid-sensitive comorbidities may be the issue at smaller-volume centers.

Chronic steroid use promotes obesity, and components of metabolic syndrome including hyperglycemia, hyperlipidemia, and hypertension which in turn could lead to insulin resistance and diabetes, an increase in atherogenesis, and a risk of cardiovascular events. Up to 90% of individuals who received steroids for more than 60 days experienced at least one side effect in a large population-based study involving 6517 steroid users.[15] Hence, it is not surprising that we and others as well

Table 3 Clinical Outcomes by Center Volume Category

Outcome	Total Cohort N=17,483	< 25 HT/Year N=8003	25-50 HT/Year N=5713	51-75 HT/Year N=2590	> 75 HT/Year N=1177
2-Year Mortality	1.92 (1.60–2.31)	2.02 (1.55–2.64)	1.63 (1.16–2.28)	2.79 (1.70–4.60)	1.36 (0.66–2.81)
CAV	1.09 (1.01–1.18)	1.01 (0.89–1.14)	1.21 (1.06–1.38)	1.00 (0.79–1.26)	1.18 (0.89–1.56)
Post-HT Diabetes	1.23 (1.12–1.36)	1.18 (1.03–1.35)	1.28 (1.08–1.52)	1.19 (0.92–1.54)	1.42 (0.92–2.19)
Severe Renal Dysfunction	1.66 (1.50–1.84)	1.55 (1.34–1.78)	1.76 (1.46–2.11)	1.79 (1.40–2.28)	2.09 (1.36–3.22)
Malignancy	0.85 (0.70–1.04)	0.83 (0.60–1.15)	0.92 (0.67–1.26)	1.08 (0.60–1.93)	0.67 (0.25–1.80)
Acute Rejection Within 2 Years	2.48 (2.26–2.72)	2.31 (2.04–2.63)	2.69 (2.29–3.15)	2.28 (1.76–2.95)	4.01 (2.44–6.61)

Mortality data are presented as hazard ratios (95% confidence intervals) while all other outcomes are odds ratios (95% confidence interval). CAV = cardiac allograft vasculopathy; HT = heart transplant.

have found increased diabetes and CAV in HT recipients with continuation of steroids.[16] While CAV is largely perceived as an immune-mediated pathology, the worsening cardiometabolic profile could both accelerate and worsen it.[17] This suggests that steroid withdrawal might be beneficial in alleviating CAV. As CAV is a significant cause of long-term graft loss and mortality, we speculate that the increased mortality observed with steroid continuation could in part be mediated by increased CAV and associated complications in HT recipients.[1]

Our finding of increased renal dysfunction in recipients with the continuation of steroids is intriguing. While, on the one hand, it remains possible that there is no cause-and-effect relationship between steroid use and renal dysfunction and that this observation could reflect a lack of departure from steroid use to minimize rejection risk as likely these patients would have decreased or discontinuation of CNI-based agents. On the other hand, it also remains a possibility that chronic steroid use is associated with further worsening of renal dysfunction. Indeed, the continuation of steroids in patients with underlying renal dysfunction and proteinuria could further worsen outcomes by promoting hypertension, diabetes, obesity, fractures, and infections. Moreover, steroid exposure in individuals with proteinuria is associated with a 40% increase with every 1-mg/kg per day increase in steroid dose associated with a 2.5-fold increase in risk of any of these side effects.[18]

A concerning complication in the HT recipients is malignancies, including post-transplant lymphoproliferative disorders. Reduction in immunosuppression has the potential to reduce such complications. However, our observation of no associated risk of post-HT malignancies with steroid use is not surprising. Steroids are a basis of chemoimmunotherapy for some malignancies, including PTLD, and might provide allograft protection against rejection while used with other chemotherapeutic agents.[19]

While steroid weaning might be safe in a significant proportion of HT recipients, some might still benefit from ongoing use as a part of the immunosuppressive regimen to minimize graft loss. However, we must choose wisely to optimize outcomes while minimizing side effects arising from long-term use. While safety and long-term survival have not been inferior for HT recipients who underwent aggressive steroid weaning, some within 2 months post HT, current experiences fall short of identifying a cohort of post-transplant individuals who would derive benefit from the continuation of long-term steroid use.[1] This suggests that defaulting to steroid sparing approach rather than other way around might further mitigate morbidity arising from the default now of chronic steroid use in our HT recipients. Hence, there remains an urgent need to prospectively examine this in multicenter studies to identify patient populations who would benefit or derive harm from long-term steroid use as well as a timeline for a safe transition off steroids. Furthermore, in such individuals, targeted delivery of steroids using nanoparticle-mediated or liposomal encapsulated drug delivery to allograft or bone marrow could provide a favorable method to reduce side effects arising from systemic steroid use in the future.[20,21]

Limitations

Although the ISHLT Registry is of high-quality, limitations inherent to observational, retrospective analyses, such as uncontrolled confounding, apply to this study, and causality cannot be demonstrated. More than 17,000 patients did not have information on steroid use prior to discharge after heart transplant suggesting a major limitation to our findings. The follow-up duration differed between the groups, and survival analyses should be interpreted as hypothesis-generating. In addition, variables not recorded in the ISHLT database could have influenced post-transplant outcomes and cannot be accounted for. Similarly, data relating to information on listing status, time on the waitlist and geographic region were not available. This precluded us from further look into practices involving steroid use.

The ISHLT database contains limited information on steroid use at 3, 6, and 9-month follow-up periods, which prevents us from examining the optimal timing for steroid discontinuation. Moreover, we could not analyze whether the weaning of steroids was driven by patient-specific factors or center-specific protocol due to the lack of information at the center level in the ISHLT Registry.

CONCLUSIONS

Half of adult HT recipients are weaned from steroids at 1-year post-transplant in the contemporary international cohort of adult transplant recipients. Continuation of steroids as part of the maintenance immunosuppressive regimen at 1 year after transplantation is associated with increased mortality and morbidity. Factors driving steroid use in adult HT recipients vary by transplant centers and are not clear. There also remains a need to examine recipient and center-level factors that might be driving the weaning or continuation of steroids in contemporary practice. Immunosuppression should be individualized to avoid overtreating some patients while undertreating others. In addition, prospective multicenter studies are needed to identify individuals who would benefit or harm from long-term steroid use after heart transplantation.

Author Contributions

All authors contributed to the manuscript.

Funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Not applicable.

Conflicts of Interest and Source of Funding

Dr. Baran has received funds (modest) for consulting with the following firms: Past: Livanova, Getinge, Abiomed, and Abbott: steering Committee Procyrion, CareDx, XVIVO, NirSense. Dr. Jaiswal is on the speaker's bureau for Bristol Myers Squibb and has been on the speaker's bureau for Novartis in the past. The remaining authors have nothing to disclose. No funding was provided for this work.

Disclosure

None by the authors.

References

1. Baran DA, Kapoor S, Grewal J, Andries G, Camacho M. Long term follow-up of the tacrolimus in combination, tacrolimus alone compared (TICTAC) trial. J Heart Lung Transplant 2023;42(6):838-45.
2. Heegaard B, Nelson LM, Gustafsson F. Steroid withdrawal after heart transplantation in adults. Transpl Int 2021;34(12):2469-82.
3. Elboudwarej O, Phan D, Patel JK, et al. Corticosteroid wean after heart transplantation-Is there a risk for antibody formation? Clin Transplant 2017;31(4).
4. Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2023;42(5):e1-141.
5. Goldraich LA, Stehlik J, Cherikh WS, et al. Duration of corticosteroid use and long-term outcomes after adult heart transplantation: A contemporary analysis of the International Society for Heart and Lung Transplantation Registry. Clin Transplant 2018;32(8):e13340.
6. Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report–2013; focus theme: age. J Heart Lung Transplant 2013;32(10):951-64.
7. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. Ann Intern Med 2007;147(8):573-7.
8. Khush KK, Hsich E, Potena L, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-eighth adult heart transplantation report - 2021; Focus on recipient characteristics. J Heart Lung Transplant 2021;40(10):1035-49.
9. Chih S, Chong AY, Mielniczuk LM, Bhatt DL, Beanlands RS. Allograft vasculopathy: The Achilles' heel of heart transplantation. J Am Coll Cardiol 2016;68(1):80-91.
10. Newman JD, Schlendorf KH, Cox ZL, et al. Post-transplant diabetes mellitus following heart transplantation. J Heart Lung Transplant 2022;41(11):1537-46.
11. Baker WL, Moore TE, Baron E, Jennings DL, Jaiswal A. Development and validation of a model to predict malignancy within the first year after adult heart transplantation. Prog Transplant 2023;33(1):69-77.
12. Skanthan C, Wang J, Liyanage I, et al. Renal dysfunction after heart transplant. Transplant Proc 2023;55(7):1681-7.
13. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth adult heart transplant report–2011. J Heart Lung Transplant 2011;30(10):1078-94.

14. Khush KK, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth Adult Heart Transplantation Report-2018; Focus Theme: Multiorgan Transplantation. J Heart Lung Transplant 2018;37(10):1155-68.
15. Curtis JR, Westfall AO, Allison J, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum 2006;55(3):420-6.
16. Yamani MH, Taylor DO, Czerr J, et al. Thymoglobulin induction and steroid avoidance in cardiac transplantation: results of a prospective, randomized, controlled study. Clin Transplant 2008;22(1):76-81.
17. Mehra MR, Boulet J, Pelletier-Galarneau M. The panvascular interplay in pathophysiology and prognosis of cardiac allograft vasculopathy. J Am Coll Cardiol 2022;80(17):1629-32.
18. Oh GJ, Waldo A, Paez-Cruz F, et al. Steroid-associated side effects in patients with primary proteinuric kidney disease. Kidney Int Rep 2019;4(11):1608-16.
19. Tsung I, Worden FP, Fontana RJ. A pilot study of checkpoint inhibitors in solid organ transplant recipients with metastatic cutaneous squamous cell carcinoma. The Oncologist 2020;26(2):133-8.
20. van Alem CMA, Schmidbauer M, Rong S, et al. Liposomal delivery improves the efficacy of prednisolone to attenuate renal inflammation in a mouse model of acute renal allograft rejection. Transplantation 2020;104(4):744-53.
21. Jiang S, Prozeller D, Pereira J, et al. Controlling protein interactions in blood for effective liver immunosuppressive therapy by silica nanocapsules. Nanoscale 2020;12(4):2626-37.