ELSEVIER

https://www.jhltopen.org/

ORIGINAL RESEARCH

Induction therapy confers survival advantage in mechanically supported patients regardless of peak CPRA in heart transplantation

Nataliya Bahatyrevich, MD, MS,[a] Reid Dale, PhD,[b] Matthew Leipzig, BSc,[b] Katharine Casselman Pines, MPH,[b] Shirin Jimenez, MD,[c] and Maria Currie, MD, PhD[b,*]

[a]*Department of Surgery, University of California, Davis, Sacramento, California*
[b]*Department of Cardiothoracic Surgery, Stanford University School of Medicine, Stanford, California*
[c]*Division of Cardiovascular Medicine, University of California, Davis, Sacramento, California*

KEYWORDS:
immunosuppression;
induction therapy;
T-cell depleting agents;
interleukin-2 receptor antagonists;
mechanical circulatory support;
heart transplantation;
calculated panel reactive antibody

BACKGROUND: There is no consensus regarding induction therapy in patients on mechanically circulatory support (MCS) listed for heart transplantation. We sought to elucidate differences in outcomes between no induction and induction.

METHODS: A total of 3,987 patients were analyzed from the UNOS database from January 2018 through December 2022. Patients on Extracorporeal Membrane Oxygenation (ECMO), HeartMate 3, Impella 5.0 or 5.5, and intra-aortic balloon pump (IABP) and receiving no induction, anti-IL2R antibodies, or T cell depleting agent (TCDA) were included.

RESULTS: Of 3,987 patients, 1,288 (32.3%) received no induction, 1,566 (39.3%) received anti-IL2R antibodies, and 1,133 (28.4%) received TCDA. A total of 1,895 (47.5%) were supported with IABP; 1,098 (27.5%) with HeartMate 3; 489 (12.3%) with Impella 5.0 or 5.5; 351 (8.8%) with ECMO; and 154 (3.9%) with combination of the above devices. Comparison of 1-year survival between no induction, anti-IL2R, and TCDA groups in all MCS patients revealed significantly worse survival among those receiving no induction ($p < 0.0001$). Subgroup analysis of peak CPRA 0% patients revealed that no induction had significantly worse survival at 1 year ($p=0.002$). Analysis of acute rejection at 1 year showed a significantly decreased number of rejection episodes in the TCDA group compared to no induction (OR 0.65, CI 0.47-0.88, $p=0.006$).

CONCLUSIONS: Patients requiring MCS prior to heart transplantation have significantly improved post-transplant survival with induction therapy, regardless of their peak CPRA. TCDA confers decreased number of acute rejection episodes at 1 year in this patient population.

JHLT Open 2025;8:100246

Background

Heart transplantation remains the gold standard therapy for end-stage heart failure. There have been numerous efforts to expand the donor pool to increase access to heart

*Corresponding author: Maria Currie, MD, PhD, Center for Academic Medicine, 453 Quarry Road, Room 267, MC 5661, Stanford, CA 94304.
E-mail address: mecurrie@stanford.edu.

https://doi.org/10.1016/j.jhlto.2025.100246

transplantation. Despite these efforts and discovery of new immunosuppression treatments, optimal immunosuppression regimen remains undefined. Induction immunosuppression therapy was developed in an effort to lower the risk of acute rejection in the early postoperative period via profound effects on immune system suppression.[1] Currently, approximately 50% of heart transplantation programs use induction therapy with either interleukin-2 receptor antagonists (anti-IL2R), such as basiliximab or daclizumab, or T-cell depleting agents (TCDA) such as alemtuzumab, and antithymocyte globulin/ATGAM.[2] Risks and benefits of induction therapy in heart transplantation recipients remain unclear. Therefore, there is marked variability in the utilization of induction therapy and the type of induction therapy used among transplantation centers. This is partly due to lack of vigorous randomized control trials and concerns of implications for mortality, rejection, infection, and malignancy. Prior studies show conflicting results on the effects of induction therapy on rejection rates, mortality, and infection.[3-9]

Patients with mechanical circulatory support (MCS) represent a large proportion of heart transplantation recipients. Additionally, since the 2018 allocation policy change and development of novel MCS devices, there have been changes in utilization rates of different devices before heart transplantation. Specifically, Liu et al have shown that the new allocation system resulted in significant changes in MCS bridging strategy with increased use of temporary MCS devices, such as intra-aortic balloon pump (IABP), and decreased use of durable MCS devices, such as HeartMate 3.[10] Furthermore, the most common complications of MCS use are bleeding with rates as high as 60% depending on the patient and device and infection with rates up to 30% to 40%.[11] Bleeding could potentially lead to the need for transfusion, which could impact patient's calculated panel reactive antibody (CPRA). CPRA plays a crucial role in defining a recipient's level of sensitization with common thresholds for desensitization being CPRA >50%.[12] Sensitization is also associated with increased post-transplantation mortality, graft loss, rejection, and cardiac graft vasculopathy.[12] Additionally, each mechanical circulatory device has unique properties in terms of its mechanics (pulsatile vs nonpulsatile) and effects on the circulatory system, such as platelet activation and inflammatory response.[13,14] Given changes in utilization of MCS and distinct properties of each device, importance of CPRA, and lack of consensus on use of induction therapy, we performed an in-depth analysis of the impact of induction therapy on survival and rejection in MCS recipients, including subgroup analysis of CPRA 0% and device type.

Methods

Study design

This retrospective cohort study compared the outcomes of patients receiving induction and no-induction therapies. A subgroup analysis of no induction, TCDA, and anti-IL2R in heart transplant patients was also performed. We selected patients in the United Network for Organ Sharing (UNOS) database from January 1, 2018 to December 31, 2022. Only patients on extracorporeal membrane oxygenation (ECMO), HeartMate 3, Impella 5.0 or 5.5, and IABP, including combination of these devices pretransplant, were included in the analysis (Table 1). Other MCS devices were excluded due to limited sample size, unknown device type, or limited current clinical use (Table 1). OKT3 therapy was excluded due to limited sample size. We also excluded patients under 18 at the time of waitlist, multiorgan transplant recipients, and retransplant candidates. Pairwise standardized mean differences (SMDs) were compared between the groups to evaluate for balance and those above 0.2 were considered significant.

Table 1 Number of Patients Between January 2018 and December 2022 With Other Types of Devices That Were Excluded From Analysis and Number of Patients and Types of Combination of Included Devices

Type of device	Number of patients
Excluded devices	
Protek Duo	10
Tandem Heart	2
CentriMag	13
HeartMate II	23
Heartware HVAD	26
Impella CP	34
Impella Recover 2.5	2
Impella RP	2
Included combinations	
IABP + ECMO	83
HeartMate 3 + IABP	7
HeartMate 3 + ECMO	7
Impella 5.0/5.5+ IABP	23
Impella 5.0/5.5 + ECMO	31
Impella 5.0/5.5 + IABP + ECMO	3

Abbreviations: ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

Statistical analysis

Baseline characteristics were summarized using descriptive statistics and compared across groups using chi-square tests for categorical variables and Analysis of Variance (ANOVA) or Kruskal-Wallis tests for continuous variables, as appropriate. We also provided the pairwise SMDs for each of our 3 comparisons. Cardinality matching with a 0.1 SMD tolerance was used for matching induction and no-induction groups for recipient and donor age, sex, transplant year, peak CPRA, most recent CPRA, human leukocyte antigen (HLA) mismatch, creatinine, dialysis before transplantation, and ECMO use. Outcome analyses used Kaplan-Meier estimated survival curves for time-to-event outcomes and logistic or linear regression models for binary and continuous outcomes, respectively. The significance level

was set at $\alpha = 0.05$, and all analyses were performed using R version 4.3.0 (GNU General Public License).

Ethical considerations

This study protocol was reviewed by the Institutional Review Board and Ethics Committee at Stanford University under IRB number 74018 (approved February 7, 2024) and did not meet the criteria for human subjects research as defined in 45 CFR 46.102(e) or 21 CFR 50.3(g). All patient data were deidentified by UNOS before access by the research team to protect privacy in accordance with ethical guidelines.

Results

Trends, demographics, and comparison between induction and no-induction groups

Of 3,987 patients, 1,288 (32.3%) received no induction and 2,699 (67.7%) received induction with 1,566 (39.3%) receiving anti-IL2R antibodies and 1,133 (28.4%) receiving TCDA. A total of 1,098 (27.5%) were supported with HeartMate 3, 489 (12.3%) with Impella 5.0 or 5.5; 351 (8.8%) with ECMO; 1,895 (47.5%) with IABP; and 154 (3.9%) with a combination of the above devices. Trends in utilization of no induction, anti-IL2R, and TCDA therapies from 2018 through 2022 are shown in Figure 1A. Trends in utilization of 4 types of mechanical support devices evaluated in our study (ECMO, HeartMate 3, IABP, and Impella) from 2000 through 2022 are shown in Figure 1B.

Table 2 shows demographics of the 2 cohorts: no induction and induction before matching and Table 3 shows demographics after matching. Comparison of 1-year survival between matched no-induction and induction groups showed significantly worse survival for no-induction group ($p = 0.016$) (Figure 2). Identifiable causes of death from the database are listed in Table 4 from most common to least common in the overall cohort, no-induction therapy group, and induction therapy group.

Demographics, comparison between, and analysis of no-induction, anti-IL2R, and TCDA groups

Table 5 shows demographics of the 3 cohorts: no induction, anti-IL2R, and TCDA. Of note, the only significant variables based on SMDs cutoff between groups were peak

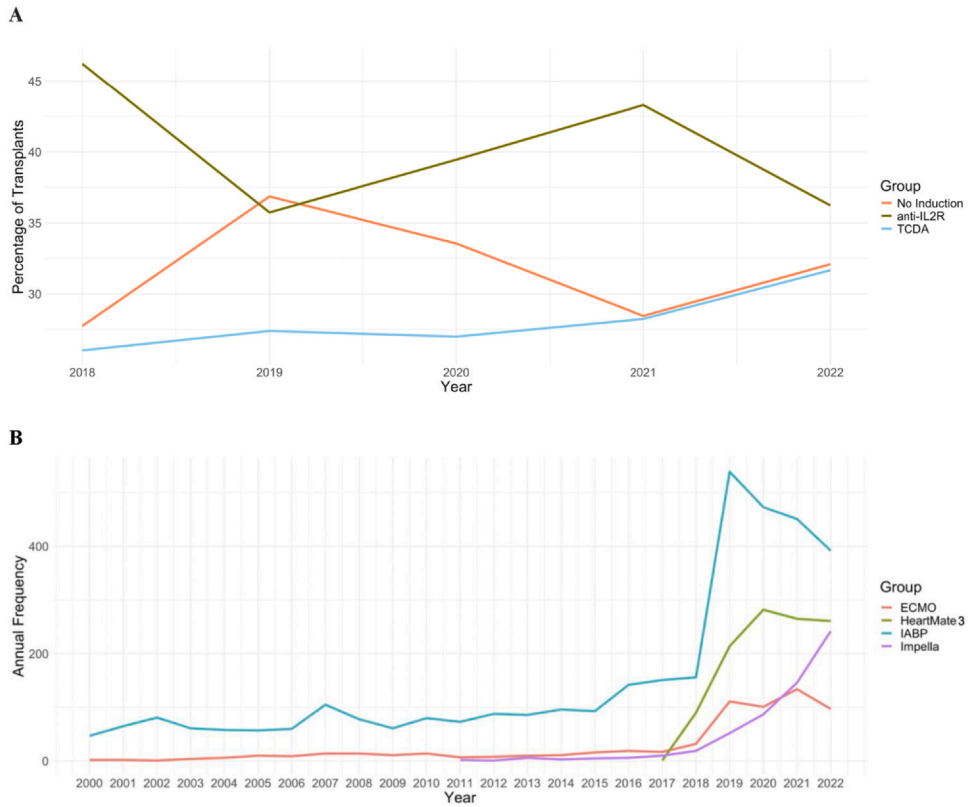

Figure 1 (A) Trends in utilization of no induction, anti-IL2R, and TCDA in MCS patients from 2018 through 2022. (B) Trends in utilization of different mechanical support such as ECMO, IABP, Impella 5.0 or 5.5, and HeartMate 3 from 2000 through 2022. ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IL2R, interleukin-2 receptor antagonists; TCDA, T-cell depleting agent.

Table 2 Demographics and Characteristics of No-Induction and Induction Groups With Pairwise SMDs and 95% Confidence Intervals Provided Before Matching

Characteristic	N	No induction, N = 1,288	Induction, N = 2,699	SMD	95% CI
Recipient age, years	3,987	55 (12)	53 (13)	0.17	0.10, 0.23
Donor age, years	3,987	32 (10)	32 (10)	0.01	−0.06, 0.07
Peak CPRA	3,028	8 (19)	16 (28)	−0.34	−0.42, −0.26
Unknown		410	549		
Recent CPRA	3,027	6 (16)	13 (25)	−0.32	−0.40, −0.24
Unknown		411	549		
Transplant year	3,987			−0.05	−0.12, 0.02
2018		81 (6.3%)	211 (7.8%)		
2019		327 (25%)	560 (21%)		
2020		307 (24%)	608 (23%)		
2021		270 (21%)	679 (25%)		
2022		303 (24%)	641 (24%)		
HLA mismatch	3,711			−0.01	−0.08, 0.06
0		3 (0.3%)	2 (< 0.1%)		
1		4 (0.3%)	7 (0.3%)		
2		29 (2.5%)	52 (2.1%)		
3		136 (12%)	281 (11%)		
4		296 (25%)	664 (26%)		
5		438 (37%)	950 (38%)		
6		275 (23%)	574 (23%)		
Unknown		107	169		
Creatinine, mg/ml	3,937	1.21 (0.50)	1.28 (0.59)	−0.12	−0.19, −0.05
Unknown		47	3		
Dialysis before transplant	3,987			0.26	0.19, 0.32
Unknown		49 (3.8%)	7 (0.3%)		
No		1,207 (94%)	2,600 (96%)		
Yes		32 (2.5%)	92 (3.4%)		
ECMO before transplant	3,987	136 (11%)	339 (13%)	−0.06	−0.13, 0.00
Etiology of heart failure	3,966			0.17	0.10, 0.24
Congenital		12 (0.9%)	51 (1.9%)		
Idiopathic		484 (38%)	1,032 (38%)		
Ischemic		400 (32%)	696 (26%)		
Exclude		20 (1.6%)	72 (2.7%)		
Other		351 (28%)	848 (31%)		
Unknown		21	0		
Donor/recipient PHM ratio	3,987	1.04 (0.18)	1.05 (0.18)	−0.07	−0.13, 0.00
Donor LV ejection fraction, %	3,986	62 (7)	62 (7)	0.01	−0.05, 0.08
Unknown		1	0		
Total bilirubin, mg/dl	3,932	1.08 (1.74)	1.11 (1.71)	−0.02	−0.08, 0.05
Unknown		49	6		
Weight, kg	3,987	86 (19)	85 (18)	0.02	−0.05, 0.08
Height, cm	3,987	175 (10)	175 (10)	−0.02	−0.09, 0.05
Donor sex	3,987			0.01	−0.06, 0.08
Female		284 (22%)	583 (22%)		
Male		1,004 (78%)	2,116 (78%)		
Transfusion	3,930			0.06	−0.01, 0.12
No transfusion		1,038 (84%)	2,193 (82%)		
Transfused between listing and transplant		202 (16%)	497 (18%)		
Unknown		48	9		
Hospitalization status at transplant	3,945			0.11	0.04, 0.18
Hospitalized, not ICU		80 (6.4%)	184 (6.8%)		
In ICU		870 (70%)	1,997 (74%)		
Not hospitalized		296 (24%)	518 (19%)		
Unknown		42	0		

Abbreviations: CI, confidence interval; CPRA, calculated panel reactive antibody; ECMO, extracorporeal membrane oxygenation; HLA, human leukocyte antigen; ICU, intensive care unit; LV, left ventricle; N (%), mean (SD) ,standard deviation; PHM, predicted heart mass; SMD, standardized mean differences.

Table 3 Demographics and Characteristics of Matched No-Induction and Induction Groups With Pairwise SMDs and 95% Confidence Intervals Provided

Characteristic	N	No induction, N = 790	Induction, N = 790	SMD	95% CI
Recipient age, years	1,580	55 (12)	56 (13)	−0.06	−0.16, 0.04
Donor age, years	1,580	32 (10)	33 (11)	−0.08	−0.18, 0.01
Peak CPRA	1,580	7 (17)	10 (22)	−0.14	−0.24, −0.04
Recent CPRA	1,580	5 (15)	7 (20)	−0.14	−0.24, −0.04
Transplant year	1,580			−0.10	−0.20, 0.00
2018		52 (6.6%)	76 (9.6%)		
2019		225 (28%)	172 (22%)		
2020		199 (25%)	169 (21%)		
2021		159 (20%)	183 (23%)		
2022		155 (20%)	190 (24%)		
HLA mismatch	1,580			−0.09	−0.19, 0.01
0		2 (0.3%)	1 (0.1%)		
1		3 (0.4%)	3 (0.4%)		
2		19 (2.4%)	20 (2.5%)		
3		98 (12%)	88 (11%)		
4		202 (26%)	182 (23%)		
5		287 (36%)	281 (36%)		
6		179 (23%)	215 (27%)		
Creatinine, mg/ml	1,580	1.21 (0.52)	1.27 (0.62)	−0.09	−0.19, 0.01
Dialysis before transplant	1,580			0.09	−0.01, 0.19
Unknown		1 (0.1%)	1 (0.1%)		
No		767 (97%)	754 (95%)		
Yes		22 (2.8%)	35 (4.4%)		
ECMO before transplant	1,580	93 (12%)	119 (15%)	−0.10	−0.20, 0.00
Etiology of heart failure	1,580			0.11	0.01, 0.21
Congenital		8 (1.0%)	11 (1.4%)		
Idiopathic		321 (41%)	284 (36%)		
Ischemic		250 (32%)	280 (35%)		
Exclude		12 (1.5%)	16 (2.0%)		
Other		199 (25%)	199 (25%)		
Donor/recipient PHM ratio	1,580	1.03 (0.18)	1.05 (0.18)	−0.12	−0.22, −0.02
Donor LV ejection fraction, %	1,580	62 (7)	61 (6)	0.05	−0.05, 0.15
Total bilirubin, mg/dl	1,579	1.15 (1.96)	1.19 (2.28)	−0.02	−0.12, 0.08
Unknown		0	1		
Weight, kg	1,580	86 (19)	84 (18)	0.11	0.01, 0.21
Height, cm	1,580	175 (10)	175 (10)	0.07	−0.03, 0.17
Donor sex	1,580			0.01	−0.09, 0.11
Female		174 (22%)	178 (23%)		
Male		616 (78%)	612 (77%)		
Transfusion	1,574			0.12	0.02, 0.22
No transfusion		667 (85%)	632 (80%)		
Transfused between listing and transplant		120 (15%)	155 (20%)		
Unknown		3	2		
Hospitalization status at transplant	1,580			0.06	−0.03, 0.16
Hospitalized, not ICU		46 (5.8%)	45 (5.7%)		
In ICU		576 (73%)	597 (76%)		
Not hospitalized		168 (21%)	148 (19%)		

Abbreviations: CI, confidence interval; CPRA, calculated panel reactive antibody; ECMO, extracorporeal membrane oxygenation; HLA, human leukocyte antigen; ICU, intensive care unit; LV, left ventricle; N (%), mean (SD), standard deviation; PHM, predicted heart mass; SMD, standardized mean differences.

CPRA and most recent CPRA. Comparison of 1-year survival between no-induction, anti-IL2R, and TCDA showed significantly worse survival for no-induction group ($p < 0.0001$) (Figure 3A). The pairwise differences in 1-year survival between groups were $p < 0.0001$ for no induction compared to TCDA, $p < 0.0001$ for no induction

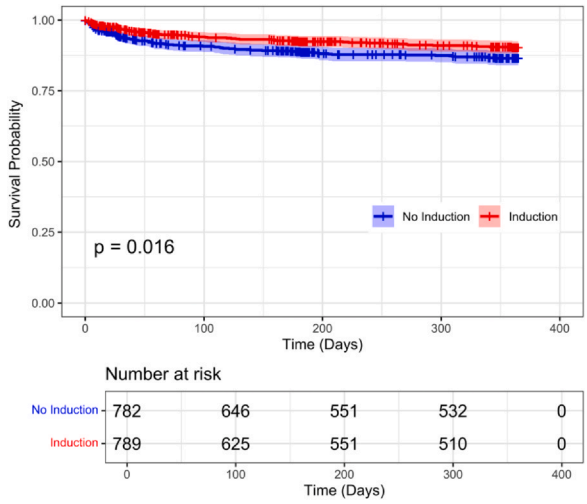

Figure 2 Kaplan-Meier 1-year survival curve for matched induction and no induction therapy groups.

Table 4 Identifiable Causes of Death Within 1 Year of Transplant in the Overall Cohort Compared to No-Induction and Induction Therapy Groups

Cause of death	Overall cohort (N)	No induction (N)	Induction (N)
Infection	86	44	42
Multiorgan failure	59	17	42
Unknown/other	47	25	22
Neurologic	44	19	25
Cardiac	41	19	22
Immunologic	31	12	19
Pulmonary	25	9	16
Malignancy	6	3	3
Hepatic	2	2	0
Suicide	2	1	1
Renal	1	1	0

N, number of patients.

compared to anti-IL2R, and $p = 0.088$ for TCDA compared to anti-IL2R. Analysis of overall survival for all MCS patients revealed statistically worse survival ($p < 0.0001$) for no-induction group compared to anti-IL2R and TCDA groups (Figure 3B) with survival curves appearing to start converging at the 3-year mark. To elucidate the effects of 1-year survival on the longer overall survival, conditional 1-year survival analysis was performed and showed no differences in survival between the 3 groups (Fig. 3C).

Subgroup survival analysis at 1 year of HeartMate 3, Impella 5.0 or 5.5, ECMO, and IABP supported patients showed statistically worse survival with no induction for ECMO ($p = 0.044$) and IABP ($p = 0.0002$) and statistically improved survival with TCDA for Impella 5.0 or 5.5 ($p = 0.015$) (Figure 4A-D). The HeartMate 3 subgroup did not reach statistically significant difference in survival at 1 year (Figure 4A).

Cox proportional hazard analysis for all MCS patients revealed protective effects for anti-IL2R (hazard ratio [HR] 0.64, confidence interval [CI] 0.50-0.81, $p < 0.001$) and TCDA (HR 0.50, CI 0.37-0.66, $p < 0.001$) compared to no-induction group for 1-year survival (Table 6A). Of note, ECMO (HR 2.35, CI 1.44-3.83, $p = 0.001$) and older age (HR 1.02, CI 1.01-1.03, $p < 0.001$) were identified as risk factors for decreased 1-year survival for all MCS patients compared to no-induction group (Table 6A). Similar analysis for treatment for acute rejection within 1 year showed TCDA (HR 0.65, CI 0.47-0.88, $p = 0.006$) and older age (HR 0.97, CI 0.97-0.98, $p < 0.001$) to be protective factors while HLA mismatch (HR 1.18, CI 1.06-1.32, $p = 0.004$) was a risk factor compared to no-induction group (Table 6B).

Subgroup analysis of peak CPRA = 0% patients

Given that the only significant SMD from Table 5 between no-induction, anti-IL2R, and TCDA groups were in regards to CPRA, subgroup analysis of peak CPRA = 0% patients was performed and revealed that no induction still had significantly worse survival at 1 year ($p = 0.002$) (Figure 5). Additionally, the median and interquartile range of the time between the most recent CPRA measurement and transplant was 32 (17-66) days.

Subgroup analysis of peak CPRA = 0% patients showed protective effect of TCDA (HR 0.45, CI 0.29-0.70, $p < 0.001$) in improved 1-year survival compared to no-induction group (Table 7A). However, anti-IL2R induction therapy was no longer significant in this subgroup. ECMO (HR 2.09, CI 1.08-.03, $p = 0.028$) and older age (HR 1.02, CI 1.00-1.03, $p = 0.016$) were risk factors for worse 1-year survival compared to no-induction group (Table 7A). Analysis of acute rejection at 1 year for peak CPRA = 0% subgroup showed a significantly decreased number of rejection episodes in the TCDA group (HR 0.40, CI 0.24-0.63, $p < 0.001$) and older age (HR 0.97, CI 0.96-0.98, $p < 0.001$) compared to no induction (Table 7B).

Discussion

Our analysis of UNOS database showed that induction therapy with either anti-IL2R or TCDA improved 1-year survival in patients on MCS. Furthermore, TCDA was associated with decreased incidence of treatment for acute

Table 5 Demographics and Characteristics of No-Induction, Anti-IL2R, and TCDA Groups With *p*-Values and Pairwise SMDs Provided

Characteristic	No induction N = 1,288	Anti-IL2R N = 1,566	TCDA N = 1,133	*p*-value	No induction vs anti-IL2R	No induction vs TCDA	Anti-IL2R vs TCDA
MCS type				0.012	0.074	0.136	0.081
HeartMate 3	393 (31%)	426 (27%)	293 (26%)				
Impella 5.0/5.5	157 (12%)	207 (13%)	182 (16%)				
ECMO	136 (11%)	161 (10%)	178 (16%)	< 0.001	0.009	−0.153	−0.162
IABP	639 (50%)	837 (53%)	535 (47%)	0.005	−0.077	0.048	0.125
Transfusion				< 0.001	0.001	0.132	0.131
No transfusion	1,038 (84%)	1306 (84%)	887 (79%)				
Transfusion between listing and transplant	202 (16%)	255 (16%)	242 (21%)				
Peak CPRA	0 (0, 5)	0 (0, 11)	0 (0, 41)	< 0.001	−0.151	−0.530	−0.392
Unknown number	410	395	154				
Most recent CPRA	0 (0, 0)	0 (0, 3)	0 (0, 25)	< 0.001	−0.162	−0.480	−0.331
Unknown number	411	394	155				
Recipient							
Age, years	58 (48, 65)	56 (46, 63)	55 (43, 62)	< 0.001	0.116	0.235	0.119
Sex				< 0.001	0.044	0.183	0.138
Female	254 (20%)	337 (22%)	311 (27%)				
Male	1,034 (80%)	1,229 (78%)	822 (73%)				
Diabetes mellitus	408 (32%)	466 (30%)	305 (27%)	0.015	0.056	0.119	0.062
Total waitlist time, days	17 (6, 91)	23 (8, 110)	19 (6, 96)	0.002	−0.001	0.021	0.025
Prior cardiac surgery	484 (38%)	647 (41%)	453 (40%)	0.12	−0.077	−0.049	0.027
Prior lung surgery	2 (0.2%)	5 (0.3%)	4 (0.4%)	0.7	0.032	0.038	0.006
Hospitalization status				0.020	0.108	0.118	0.035
Ward	80 (6.4%)	101 (6.4%)	83 (7.3%)				
Intensive care unit	870 (70%)	1,162 (74%)	835 (74%)				
Not hospitalized	296 (24%)	303 (19%)	215 (19%)				
Blood type				0.049	0.062	0.128	0.101
A	470 (37%)	599 (38%)	484 (43%)				
AB	51 (4.0%)	73 (4.7%)	40 (3.5%)				
B	209 (16%)	228 (15%)	159 (14%)				
O	555 (43%)	665 (42%)	449 (40%)				
Total bilirubin at time of transplant, mg/dl	1.08 (1.74)	1.09 (1.43)	1.13 (2.03)	0.11	−0.007	−0.025	−0.021
Weight, kg	84 (72, 98)	85 (73, 98)	84 (71, 96)	0.042	−0.029	0.076	0.108
Height, cm	175 (168, 183)	175 (168, 183)	175 (168, 180)	0.002	−0.079	0.060	0.142
Waitlist priority status					0.102	0.120	0.138
Adult status 1	180 (14%)	221 (14%)	195 (17%)				
Adult status 2	755 (59%)	926 (59%)	654 (58%)				
Adult status 3	162 (13%)	181 (12%)	111 (9.8%)				
Adult status 4	135 (10%)	155 (9.9%)	126 (11%)				
Adult status 6	0 (0%)	2 (0.1%)	0 (0%)				
Status 1A	49 (3.8%)	78 (5.0%)	42 (3.7%)				
Status 1B	7 (0.5%)	3 (0.2%)	5 (0.4%)				
Etiology of heart failure				< 0.001	0.134	0.241	0.172
Congenital	12 (0.9%)	31 (2.0%)	20 (1.8%)				
Idiopathic	484 (38%)	631 (40%)	401 (35%)				
Ischemic	400 (32%)	418 (27%)	278 (25%)				
Other	351 (28%)	456 (29%)	392 (35%)				
Creatinine at time of transplant, mg/dl	1.12 (0.92, 1.40)	1.20 (0.98, 1.50)	1.14 (0.90, 1.46)	< 0.001	−0.161	−0.059	0.096
Donor/recipient PHM	1.01 (0.92, 1.12)	1.03 (0.93, 1.15)	1.01 (0.92, 1.14)	0.034	−0.079	−0.049	0.030
Donor							
Age, years	31 (24, 39)	31 (24, 39)	32 (24, 39)	0.6	0.019	−0.014	−0.033
Sex				0.007	0.063	0.059	0.122
Female	284 (22%)	305 (19%)	278 (25%)				
Male	1,004 (78%)	1,261 (81%)	855 (75%)				
Weight, kg	83 (71, 96)	84 (73, 98)	82 (71, 95)	0.003	−0.094	0.051	0.147

(*continued on next page*)

Table 5 (*Continued*)

Characteristic	No induction N = 1,288	Anti-IL2R N = 1,566	TCDA N = 1,133	*p*-value	No induction vs anti-IL2R	No induction vs TCDA	Anti-IL2R vs TCDA
Height, cm	175 (168, 183)	178 (170, 183)	175 (168, 180)	< 0.001	−0.098	0.072	0.172
BMI	26.8 (23.5, 31.2)	27.1 (23.8, 31.6)	26.7 (23.8, 30.8)	0.2	−0.052	0.016	0.068
LVEF, %	60 (57, 65)	60 (55, 65)	60 (57, 65)	0.5	0.031	−0.009	−0.041
Ischemia time, hours	3.48 (2.88, 4.02)	3.52 (2.98, 4.08)	3.52 (2.97, 4.07)	0.10	−0.112	−0.019	0.100
Diabetes mellitus	43 (3.4%)	53 (3.4%)	38 (3.4%)	> 0.9	−0.002	−0.002	0.000
Hypertension	211 (17%)	214 (14%)	149 (13%)	0.049	0.077	0.089	0.012
Total bilirubin, mg/dl	0.7 (0.4, 1.1)	0.7 (0.4, 1.0)	0.7 (0.5, 1.2)	0.033	−0.032	−0.098	−0.052
Blood type				0.027	0.083	0.139	0.095
A	406 (32%)	536 (34%)	407 (36%)				
AB	14 (1.1%)	22 (1.4%)	7 (0.6%)				
B	133 (10%)	133 (8.5%)	82 (7.2%)				
O	735 (57%)	875 (56%)	637 (56%)				

Abbreviations: BMI, body mass index; CPRA, calculated panel reactive antibody; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IL2R, interleukin-2 receptor antagonists; LVEF, left ventricle ejection fraction; MCS, mechanical circulatory support; PHM, predicted heart mass; TCDA, T-cell depleting agent.

N (%); median (IQR); mean (SD), standard deviation.

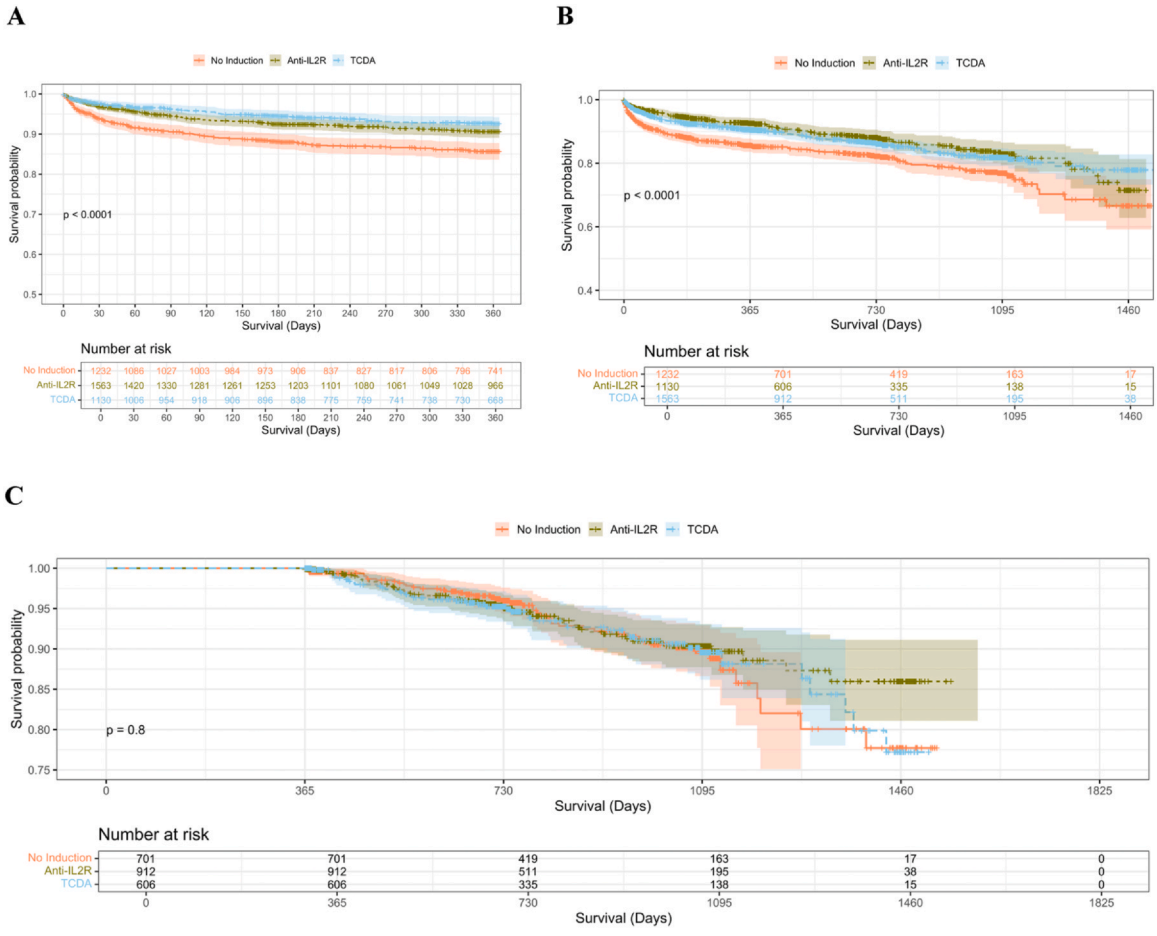

Figure 3 (A) Kaplan-Meier 1-year survival curve for all MCS patients. (B) Kaplan-Meier overall survival curve for all MCS patients. (C) Kaplan-Meier 5-year survival curve for all MCS patients conditioned on 1-year survival. IL2R, interleukin-2 receptor antagonists; MCS, mechanical circulatory support; TCDA, T-cell depleting agent.

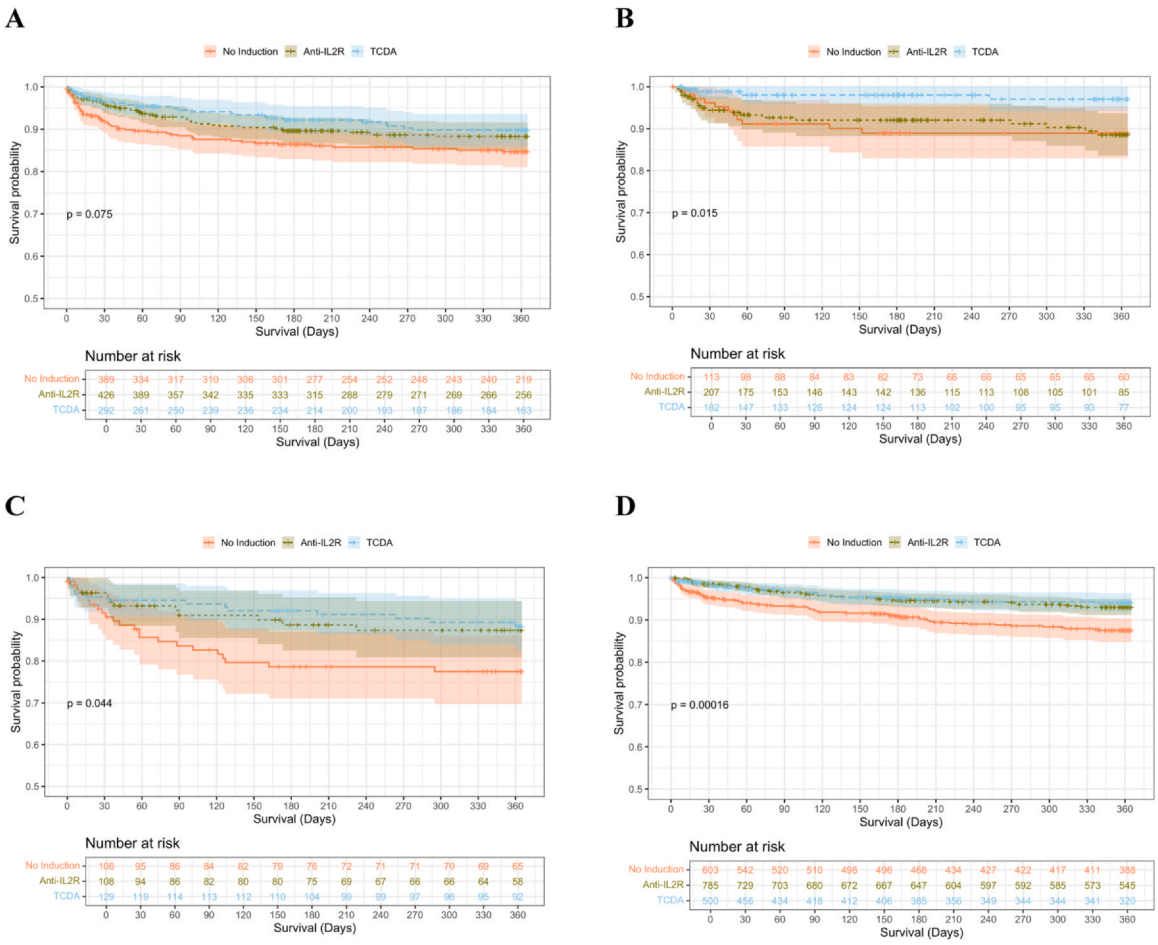

Figure 4 Kaplan-Meier 1-year survival curves for (A) HeartMate 3, (B) Impella 5.0 or 5.5, (C) ECMO, and (D) IABP patients only. ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IL2R, interleukin-2 receptor antagonists; TCDA, T-cell depleting agent.

rejection at 1 year. Others have reported benefits of TCDA in reducing rejection but with no effects on survival.[3,8,15,16] Given lack of optimal treatment consensus, contrasting reported findings in the literature, and heterogeneity of heart transplantation recipients in terms of illness acuity and function, we specifically focused on MCS patients and subgroup analysis of specific devices such as HeartMate 3, Impella 5.0 or 5.5, ECMO, and IABP before transplantation to investigate a more homogeneous group. Furthermore, given increased risks of bleeding and transfusion associated with MCS use as well as potential effects on the immune system,[11,13,14] we hypothesized that in this patient population, induction therapy could offer a survival advantage, which was validated with our database analysis. Of note, in our analyzed cohorts, the rates of transfusion between listing and transplant were comparable between the 3 groups at 16% in no-induction group, 16% in anti-IL2R group, and 21% in TCDA group. Although the most common identifiable cause of death within 1 year in our cohort was infection related (86 patients), there did not appear to be a significant difference in the number of patients who died due to infection-related causes between induction and no-induction therapy groups. Additionally, benefits of induction therapy and TCDA therapy continued to maintain significance in peak CPRA = 0% patients, suggesting that the benefits of the induction therapy in survival and prevention of rejection could not be explained by sensitization alone.

Our analysis of trends in MCS utilization was consistent with previously reported increased use of IABP since 2018 UNOS policy change.[10] However, Impella use has grown exponentially since 2019, potentially correlating to approval

Table 6 The Cox Proportional Hazards Model in All MCS Patients for (A) 1-Year Survival and (B) Treatment for Rejection Within 1 Year

Predictors	Odds ratios	CI	*p*
A			
No induction as the reference category			
Anti-IL2R	0.64	0.50-0.81	< 0.001
TCDA	0.50	0.37-0.66	< 0.001
ECMO	2.35	1.44-3.83	0.001
IABP	1.04	0.61-1.76	0.896
HeartMate 3	1.71	0.97-3.03	0.063
Impella 5.0/5.5	1.09	0.61-1.97	0.764
Recipient age	1.02	1.01-1.03	< 0.001
HLA mismatch	0.98	0.89-1.08	0.692
Observations	3677		
R^2 Nagelkerke	0.028		
B			
No induction as the reference category			
Anti-IL2R	1.05	0.81-1.36	0.729
TCDA	0.65	0.47-0.88	0.006
ECMO	0.78	0.38-1.46	0.470
IABP	0.71	0.33-1.41	0.352
HeartMate 3	0.58	0.26-1.20	0.158
Impella 5.0/5.5	0.61	0.27-1.25	0.195
Recipient age	0.97	0.97-0.98	< 0.001
HLA mismatch	1.18	1.06-1.32	0.004
Observations	2354		
R^2 Tjur	0.028		

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HLA, human leukocyte antigen; IABP, intra-aortic balloon pump; IL2R, interleukin-2 receptor antagonists; MCS, mechanical circulatory support; TCDA, T-cell depleting agent.

of Impella 5.5 by Food and Drug Administration (FDA) in 2019,[17] which has reduced complication rates compared to the Impella 5.0.[18] Our study population is limited to modern era of 2018-2022 to eliminate temporal bias and differences in management in earlier decades and also accommodate availability of newer generation devices, such as HeartMate 3. Furthermore, given potential future UNOS continuous distribution changes for heart transplantation as well as technological improvements in percutaneous support devices, it will be important to re-evaluate utilization trends and optimal therapies in the future.

Since each MCS device has unique hemodynamic support profiles, pulsatility, and shear stress, we performed subgroup analysis to identify optimal management for each type of device. Aside from HeartMate 3, other devices such as ECMO, IABP, and Impella favored induction therapy for improved survival at 1 year. These results are consistent with previous reports looking at induction therapy in contemporary left ventricular assist devices, showing no differences in survival with the use of induction therapy but increased freedom from transplant coronary artery disease.[19] Interestingly, Kaplan-Meier 1-year survival analysis also revealed that TCDA might offer a survival advantage in Impella-assisted patients compared to anti-IL2R induction therapy. For the ECMO and IABP groups, TCDA and anti-IL2R appeared to be comparable in terms of 1-year survival. These differences in therapies can likely be explained by the unique mechanical properties of each device, patient selection differences, and differences in their acuity, as well as risks, such as bleeding, infection rates, and transfusion rates. Future studies with larger sample size could evaluate the potential benefit of either TCDA or anti-IL2R in device-specific setting as well as extent of

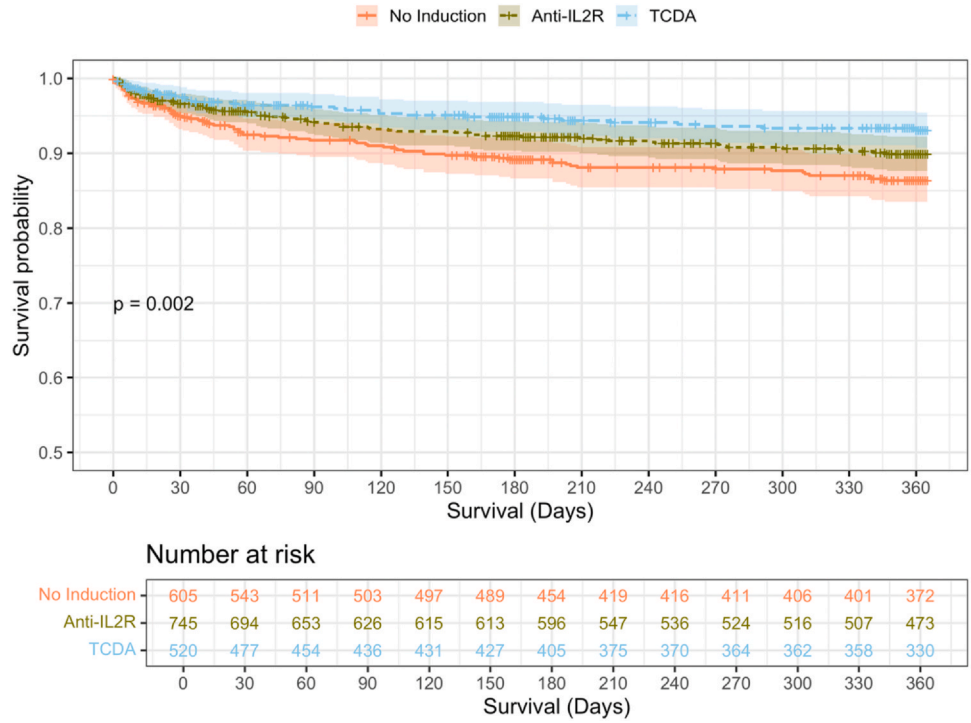

Figure 5 Kaplan-Meier 1-year survival curve for peak CPRA 0% patients only receiving no induction, anti-IL2R, or TCDA therapies. CPRA, calculated panel reactive antibody; IL2R, interleukin-2 receptor antagonists; TCDA, T-cell depleting agent.

Table 7 The Cox Proportional Hazards Model in CPRA = 0% Only Oatients for (A) 1-Year Survival and (B) Treatment for Rejection Within 1 Year

Predictors	Odds ratios	CI	p
A			
No induction as the reference category			
Anti-IL2R	0.73	0.52-1.03	0.075
TCDA	0.45	0.29-0.70	< 0.001
ECMO	2.09	1.08-4.03	0.028
IABP	0.93	0.45-1.92	0.849
HeartMate 3	1.33	0.61-2.90	0.480
Impella 5.0/5.5	1.10	0.49-2.47	0.814
Recipient age	1.02	1.00-1.03	0.016
HLA mismatch	1.05	0.90-1.21	0.537
Observations	1801		
R^2 Nagelkerke	0.023		
B			
No induction as the reference category			
Anti-IL2R	1.07	0.75-1.53	0.717
TCDA	0.40	0.24-0.63	< 0.001
ECMO	0.88	0.34-1.98	0.780
IABP	0.75	0.27-1.88	0.558
HeartMate 3	0.72	0.24-1.93	0.527
Impella 5.0/5.5	0.80	0.27-2.18	0.681
Recipient age	0.97	0.96-0.98	< 0.001
HLA mismatch	1.19	1.02-1.40	0.030
Observations	1195		
R^2 Tjur	0.038		

Abbreviations: CI, confidence interval; CPRA, calculated panel reactive antibody; ECMO, extracorporeal membrane oxygenation; HLA, human leukocyte antigen; IABP, intra-aortic balloon pump; IL2R, interleukin-2 receptor antagonists; CDA, T-cell depleting agent.

cardiovascular support provided. Interestingly, Cox proportional hazard analysis of all patients and patients with peak CPRA = 0% identified ECMO as a risk factor for worse 1-year survival, which could be explained by likely confounding of ECMO to more critically ill patients with comorbidities. Of note, in Cox proportional hazard analysis, increased age significantly increased the risk of mortality while also decreasing the risk of acute rejection at 1 year following heart transplantation. Increased mortality can likely be explained by the association of increased age with other comorbidities. The decreased risk of acute rejection could likely be explained by aging of the immune system and moving toward immunosenescence, which reduces the ability of the immune system to recognize pathogens but also could potentially reduce the ability to reject donor organs.[20]

We also analyzed the temporal effects of induction therapy on survival. Even though analysis of the overall survival among no induction, anti-IL2R, and TCDA showed improved survival for induction therapy group, the survival curves begin to converge around 3 years. Analysis of survival based on conditional 1-year survival revealed no differences in the overall survival among various treatment groups. This suggests that induction therapy offers advantage in the early postoperative period. The lack of difference in survival beyond 1 year could potentially be explained by adjustments in the maintenance immunotherapy regimen. Given the lack of data recorded in the UNOS database on maintenance immunotherapy, we were not able to examine closely the reason for survival curve convergence at long-term follow-up. Future studies should be able to elucidate whether adjustment in maintenance immunotherapy could potentially extend the induction therapy benefit long-term.

Limitations

This is a retrospective database study that carries all inherent limitations associated with such analysis. There are significant limitations in the type and granularity of data available in the UNOS database. For example, there was no data included before listing in terms of duration and types of MCS used, infection rates, transfusion rates, and timing of CPRA measurements. The utilization of induction therapy and the type of induction therapy are frequently center-specific, and therefore, there could be regional and center-specific bias involved. Certain device subgroups contained a limited sample size, making comparison among therapy groups difficult to interpret.

Conclusions

From large retrospective analysis of UNOS database, we found that patients requiring MCS before heart transplantation have significantly improved post-transplant survival with induction therapy, regardless of their peak CPRA at 1 year. These trends were supported in device-specific subgroup 1-year survival analysis. However, future studies with larger sample size and detailed postoperative maintenance therapy data are needed to identify optimal regimen specific to device and MCS type. Furthermore, TCDA confers decreased number of acute rejection episodes at 1 year in this patient population. Randomized controlled studies are needed to confirm these findings.

CRediT authorship contribution statement

Nataliya Bahatyrevich: Conceptualization, Methodology, Investigation, Writing – original draft & editing, Visualization, Supervision, Project administration, Funding acquisition. **Reid Dale:** Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing. **Matthew Leipzig:** Software, Validation, Formal analysis, Resources, Data curation. **Katharine Casselman Pines:** Supervision, Writing – review & editing. **Shirin Jimenez:** Conceptualization, Writing – review & editing, Supervision. **Maria Currie:** Conceptualization, Writing – review & editing, Visualization, Supervision.

Data availability

The data can be requested and are readily available from the United Network for Organ Sharing.

Disclosure statement

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.

Nataliya Bahatyrevich was supported with postdoctoral T32 HL086350 grant and received type 2 travel award from ISHLT for oral presentation of this abstract at the 44th ISHLT Annual Meeting in Prague, Czech Republic.

References

1. Chang DH, Youn JC, Dilibero D, Patel JK, Kobashigawa JA. Heart transplant immunosuppression strategies at Cedars-Sinai Medical Center. Int J Heart Fail 2020;3:15-30. https://doi.org/10.36628/ijhf.2020.0034.
2. Briasoulis A, Inampudi C, Pala M, Asleh R, Alvarez P, Bhama J. Induction immunosuppressive therapy in cardiac transplantation: a systematic review and meta-analysis. Heart Fail Rev 2018;23:641-9. https://doi.org/10.1007/s10741-018-9691-2.
3. Bellumkonda L, Oikonomou EK, Hsueh C, Maulion C, Testani J, Patel J. The impact of induction therapy on mortality and treated rejection in cardiac transplantation: a retrospective study. J Heart Lung Transplant 2022;41:482-91. https://doi.org/10.1016/j.healun.2022.01.008.
4. Tzani A, Van den Eynde J, Doulamis IP, et al. Impact of induction therapy on outcomes after heart transplantation. Clin Transplant 2021;35:e14440. https://doi.org/10.1111/ctr.14440.
5. Nozohoor S, Stehlik J, Lund LH, Ansari D, Andersson B, Nilsson J. Induction immunosuppression strategies and long-term outcomes after heart transplantation. Clin Transplant 2020;34:e13871. https://doi.org/10.1111/ctr.13871.
6. Kobashigawa J, David K, Morris J, et al. Daclizumab is associated with decreased rejection and no increased mortality in cardiac transplant patients receiving MMF, cyclosporine, and corticosteroids. Transplant Proc 2005;37:1333-9. https://doi.org/10.1016/j.transproceed.2004.12.135.
7. Jarmi T, Patel N, Aslam S, et al. Outcomes of induction therapy with rabbit anti-thymocyte globulin in heart transplant recipients: a single center retrospective cohort study. Ann Transplant 2018;23:422-6. https://doi.org/10.12659/AOT.907984.
8. Whitson BA, Kilic A, Lehman A, et al. Impact of induction immunosuppression on survival in heart transplant recipients: a contemporary analysis of agents. Clin Transplant 2015;29:9-17. https://doi.org/10.1111/ctr.12469.
9. Emin A, Rogers CA, Thekkudan J, Bonser RS, Banner NR. Antithymocyte globulin induction therapy for adult heart transplantation: a UK national study. J Heart Lung Transplant 2011;30:770-7. https://doi.org/10.1016/j.healun.2011.01.716.
10. Liu J, Yang BQ, Itoh A, Masood MF, Hartupee JC, Schilling JD. Impact of new UNOS allocation criteria on heart transplant practices and outcomes. Transplant Direct 2020;7:e642. https://doi.org/10.1097/TXD.0000000000001088.
11. Hunt SA, Frazier OH. Mechanical circulatory support and cardiac transplantation. Circulation 1998;97:2079-90. https://doi.org/10.1161/01.cir.97.20.2079.
12. Colvin MM, Cook JL, Chang PP, et al. Sensitization in heart transplantation: emerging knowledge: a scientific statement from the American Heart Association. Circulation 2019;139:e553-78. https://doi.org/10.1161/CIR.0000000000000598.
13. Crow S, John R, Boyle A, et al. Gastrointestinal bleeding rates in recipients of nonpulsatile and pulsatile left ventricular assist devices. J Thorac Cardiovasc Surg 2009;137:208-15. https://doi.org/10.1016/j.jtcvs.2008.07.032.
14. Radley G, Pieper IL, Ali S, Bhatti F, Thornton CA. The inflammatory response to ventricular assist devices. Front Immunol 2018;9:2651. https://doi.org/10.3389/fimmu.2018.02651.
15. Carrier M, Leblanc MH, Perrault LP, et al. Basiliximab and rabbit anti-thymocyte globulin for prophylaxis of acute rejection after heart transplantation: a non-inferiority trial. J Heart Lung Transplant 2007;26:258-63.
16. Zuckermann AO, Grimm M, Czerny M, et al. Improved long-term results with thymoglobuline induction therapy after cardiac transplantation: a comparison of two different rabbit-antithymocyte globulines. Transplantation 2000;69:1890-8.
17. Rock JR, Kos CA, Lemaire A, et al. Single center first year experience and outcomes with Impella 5.5 left ventricular assist device. J Cardiothorac Surg 2022;17:124.
18. Ramzy D, Soltesz E, Anderson M. New surgical circulatory support system outcomes. ASAIO J 2020;66:746-52. https://doi.org/10.1097/MAT.0000000000001194.
19. Truby LK, Batra J, Jennings DL, et al. Impact of induction immunosuppression on post-transplant outcomes of patients bridged with contemporary left ventricular assist devices. ASAIO J 2020;66:261-7.
20. Weyand CM, Goronzy JJ. Aging of the immune system. Mechanisms and therapeutic targets. Ann Am Thorac Soc 2016;13(Suppl 5):S422-8. https://doi.org/10.1513/AnnalsATS.201602-095AW.