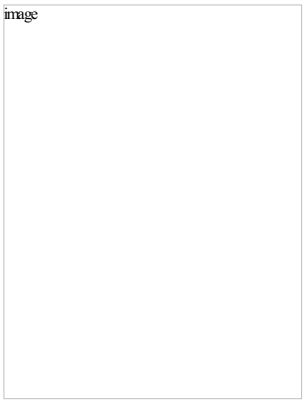

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www.elsevier.com/locate/bios

PII: S1053-2498(18)31438-4
DOI: https://doi.org/10.1016/j.healun.2018.04.00810.1161/CIR.000000000000035
6143.2008.02310.x10.1016/j.transproceed.2005.10.02110.1016/j.healun.201
Reference: HEALUN6745

To appear in: *Journal of Heart and Lung Transplantation*

Cite this article as: David Ouyang, Gunsagar Gulati, Richard Ha and Dipanjan Banerjee, Incidence of Temporary Mechanical Circulatory Support Prior to Heart Transplantation and Impact on Post-Transplant OutcomesTemporary Mechanical Circulatory Support Prior to Transplant, *Journal of Heart and Lung Transplantation,*doi:10.1016/j.healun.2018.04.008

Incidence of Temporary Mechanical Circulatory Support Prior to Heart Transplantation and Impact on Post-Transplant Outcomes

Running Title: Temporary Mechanical Circulatory Support Prior to Transplant

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Key Words - Mechanical Circulatory Support, Orthotopic Heart Transplant, UNOS allocation,

Background: Proposed changes to the United Network for Organ Sharing (UNOS) heart transplant allocation protocol will prioritize patients receiving temporary mechanical circulatory support (tMCS), including extracorporeal membrane oxygenation (ECMO), percutaneous ventricular assist devices (PVAD), and intra-aortic balloon pumps (IABP). We sought to evaluate contemporary trends in the incidence and outcomes of patients who required tMCS during the hospitalization prior to heart transplantation.

Methods: Using the National Inpatient Sample (NIS) from 1998 to 2014, we identified 6,892 patients who received an orthotopic heart transplant (OHT) and classified them based on either pre-transplant ECMO, PVAD, or IABP placement or no pre-transplant tMCS. We compared

baseline characteristics and in-hospital outcomes between patients who underwent pre-transplant ECMO, PVAD, or IABP and patients who did not receive tMCS prior to heart transplantation.

Results: Of patients who underwent heart transplantation, 456(6.6%) patients received tMCS prior to transplant. During the study time period, the use of tMCS more than doubled from 17 cases per year from 1998-2002 to 40 cases per year from 2012-2014 ($p < 0.001$ for trend). Of patients with tMCS, 341 (74.8%) were supported by IABP, 130 (28.5%) were supported by ECMO, and 21 (4.6%) were supported by PVAD. Prior to 2007, patients who required tMCS had higher in-hospital mortality than patients who did not require tMCS prior to transplant (14.3% vs. 7.5%, $p = 0.05$). In the subsequent era (2007 to 2014), there was no significant difference in mortality (4.7% vs. 5.1%, $p = 0.9$). There was an improvement in hospital mortality over time for all patients, but most significantly in patients who required tMCS (9.6% absolute risk reduction). Patients who received tMCS had increased lengths of stays and rates of acute renal, hepatic, and respiratory failure, sepsis, bleeding complications, and surgical reoperations.

Conclusions: The use of tMCS prior to cardiac transplantation is increasing, with no difference in inpatient post-transplant mortality in the recent era between patients who received tMCS and those who did not, but with increased complication rates among those receiving tMCS. These data support the use of tMCS prior to cardiac transplantation in appropriately selected patients; clinicians should balance the above outcomes when making decisions to implant temporary mechanical circulatory support, given the impending changes to the UNOS heart allocation protocol.

Introduction

Congestive heart failure is a highly morbid, common disease affecting 5.7 million people and contributing to over 300,000 deaths each year in the United States[1,2].For patients who are symptomatic despite maximal medical therapy, cardiac transplantation serves a crucial role in the treatment of end-stage heart failure. Appropriate patient selection balances morbidity on the transplant waitlist with the desire to maximize survival and clinical outcomes after cardiac transplantation.

Heart transplantation outcomes have continuously improved from 1-year survival of less than 50% to greater than 90% in some cohorts[3–5]. Heart transplant volumes have increased slowly, but the large number of heart transplant wait list candidates (3,928 in the United States in

2017) [6,7] means that 10% of patients on waitlist die every year due to the lack of available organs[8,9]. In part due to the mismatch between the number of donor organs and the number of transplant candidates, candidates in the most urgent classification (1A) now make up the majority of eventual transplant recipients (67% of adult heart transplants in 2014)[6].

There is concern that 1A classification currently groups together patients on the waitlist with significantly disparate life expectancies. Among status 1A candidates for heart transplantation, 6-month waitlist mortality ranges from 4.8% in those with durable mechanical circulatory support(e.g. a left ventricular assist device) complicated by infection to 35.7% in candidates supported by extracorporeal membrane oxygenation (ECMO).[6, 10–14] Roughly 40% patients are now being bridged to cardiac transplantation with durable mechanical circulatory support, but less data is available on temporary mechanical circulatory support (tMCS) prior to cardiac transplantation. There are a variety of tMCS available including ECMO, percutaneous ventricular assist devices (PVAD) like Impella and TandemHeart, and intra-aortic balloon pumps (IABP).

Given the significant variation in prognosis for waitlist candidates at 1A status, the Thoracic Organ Transplantation Committee of Organ Procurement and Transplantation Network(OPTN) and United Network for Organ Sharing (UNOS) proposed changes in 2016 to the adult heart allocation system to further stratify high urgency patients.[6] By the proposed criteria, patients requiring support by ECMO or with temporary biventricular or right ventricular assist devices are given the highest priority, and the use of an intra-aortic balloon pump are among the criteria given the second highest priority, as these patients have the highest expected mortality on the waitlist.

There is some concern that this strategy could lead to worse outcomes post-transplant. For example, for patients undergoing ECMO support, the 6-month mortality after heart transplant is 24.0%[6]. The desire to balance the needs of critically ill patients with long-term outcomes after the receipt of a limited resource suggests the need for further study of patients who require tMCS prior to transplantation. There is significant interest in the outcomes of these patients, but there are few studies detailing either their short or long-term outcomes. In this study, we use the largest national database of hospitalizations in the United States, the National Inpatient Sample (NIS), to assess the outcomes of patients who underwent tMCS prior to heart transplantation and compare their outcomes to patients who did not require tMCS.

We hypothesized that patients who underwent tMCS prior to heart transplantation would exhibit significantly higher morbidity and mortality after cardiac transplantation than those patients who did not require tMCS, and that those outcomes would vary by type of support (ECMO vs. PVAD vs. IABP). We also sought to describe trends in the prevalence of tMCS prior to cardiac transplantation over time, as well as changes in outcomes.

Methods

Data Source and Study Design

The National Inpatient Sample (NIS), from the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, is the largest database of all-payer inpatient discharge information, sampling approximately 20% of all non-federal US hospitals and including approximately 9 million hospital admissions each year. It contains discharge data from over 5000 hospitals located across 45 states, of which approximately 1,200 hospitals are sampled each year to create a stratified sample of United States hospitals. The NIS is a stratified two-stage cluster design with hospitals as clusters sampled at about 20% and discharges sampled at 100% for chosen hospitals. Each NIS entry includes all diagnosis and procedure codes of activity during the patient's hospitalization (including the date of each procedure), as well as patient demographics, hospital characteristics, and short-term complications of the hospitalization. The person-level data is de-identified and thus exempt from institutional review board approval.

We identified all patients who underwent heart transplantation in the NIS from 1998 to 2014. This population was further divided by whether each patient underwent pre-transplant ECMO, PVAD, or IABP. Surgically implanted but non-durable mechanical circulatory support such as TandemHeart devices as well as centrally cannulated ECMO were included in the study population. Patients for whom the date of procedures were not available or the temporal relationship between temporary mechanical circulatory support and heart transplantation could not be established were excluded. Comorbidities including diabetes, ischemic heart disease, hypertension, renal dysfunction, obesity, peripheral vascular disease, and history of smoking were identified by International Classification of Diseases 9th edition (ICD-9) code (Supplementary Table A). In-hospital complications including acute renal failure, acute respiratory failure, redo sternotomy or reoperation, sepsis, bleeding complications, stroke, liver failure, and device failure were also identified by ICD-9 code (Supplementary Table B).

Statistical Analysis

Python 2.7 (Python Software Foundation, www.python.org) and R 2.13 (R Foundation, www.r-project.org) were used for statistical analysis. The R packages ggplot2, plyr, stringr, survey, and survival were used for data processing and statistical analysis. P-values were calculated by stratified t- tests and ANOVA tests with significance thresholds of 0.05. Logistic regression was performed for the multivariable analysis, which included the number of comorbid conditions but not individual diagnoses. Patients who received heart-kidney transplants were excluded from our analysis of renal failure. To determine the effect of time on outcomes in this cohort, we divided the cohort into two eras: 1998 to 2006 and 2007 to 2014 (the modern era). Additionally, univariate analysis for trend over time was performed for mortality rates. We followed the latest published research guidelines with regard to analysis using the NIS dataset,[15] including identifying observations as hospitalization events rather than unique patients, not performing state, physician, or hospital level analyses, avoiding use of nonspecific secondary diagnosis codes to infer in-hospital events, using survey-specific analysis methods that account for clustering, stratification and weighting (the R 'survey' package above), and accounting for data changes in trend analyses spanning major transition periods in the data set by using trend analysis using the TRENDWT variable.

Results

Baseline Patient Characteristics

Between 1998 and 2014, there were 6,892 patients who underwent cardiac transplantation in the NIS (Table 1). The patients were predominantly male (72.0%) and white (57.0%) and had a mean age of 46.5 years (SD 19.0). Most patients were hospitalized at large, urban, academic hospitals, and the median day of heart transplant was hospital day 17 (interquartile range from day 2 to day 36). Mechanical support was initiated a median of 18 days prior to transplantation (IQR 7 to 45 days). There was no statistically significant difference between eras in the time from initiation of mechanical support to transplantation. Consistent with the demographics of congestive heart failure overall, patients had a high proportion of ischemic

heart disease (42.9%), hypertension (29.7%), diabetes (19.5%), and pre-existing renal dysfunction (33.2%). Patients receiving ECMO and PVAD were younger than patients receiving IABP, but otherwise these three cohorts did not substantially differ (Supplemental Table 1).

Temporal Trends

Between 1998 and 2014, the use of tMCS prior to cardiac transplantation increased over time, from 5.9% of transplants from 1998-2006 to 8.2% from 2007-2014 ($p < 0.001$ for pairwise comparison). In this cohort, 456 transplant recipients required tMCS prior to heart transplantation (Figure 1), of which 341 patients had an IABP placed, 130 patients were started on ECMO, and 21 patients underwent PVAD placement. Twenty-seven patients had both IABP and ECMO, 9 patients had both IABP and subsequent PVAD, and 3 patients had both PVAD and ECMO. Patients requiring tMCS were of similar age, sex, and average household income compared to patients who did not require tMCS. For patients requiring tMCS, there was a decreased rate of diabetes, hypertension, and preexisting renal dysfunction, but similar rates of ischemic heart disease, peripheral vascular disease, obesity, and history of smoking (Table 1).

Transplant outcomes

Mortality

In-hospital mortality in the entire cohort decreased over time from 7.9% from 1998-2006 to 5.1% from 2007-2014. In-hospital mortality decreased for both patients who required tMCS ($p < 0.001$ for trend), as well as patients who did not require tMCS ($p = 0.012$ for trend), though the decline in mortality was more pronounced in patients who required tMCS (Figure 2). In the earlier era, patients who received tMCS prior to transplant had increased mortality compared to those who did not (14.3% vs. 7.5%, $p = 0.05$). In the modern era, patients who received tMCS prior to transplant had similar mortality to those who did not (4.7% vs. 5.1%, $p = 0.90$).

In a multivariable analysis of predictors of mortality, increasing number of comorbid conditions was associated with increased mortality, while transplantation during the modern era and PVAD support appeared protective (Table 3). Duration of tMCS support did not independently affect mortality.

In-hospital complications

In the entire study cohort, in-hospital complications were more common in patients who required tMCS, with an increased risk of acute renal failure (55.5% vs. 36.0%, $p < 0.001$), acute liver failure (11.6% vs. 3.1%, $p < 0.001$), and acute respiratory failure (27.4% vs. 10.2%, $p < 0.001$) as well as bleeding complications (31.8% vs. 18.3%, $p < 0.001$), surgical complications requiring reoperation (28.3% vs. 15.4%, $p < 0.001$), and sepsis (11.4% vs. 5.2%, $p < 0.001$).

The frequency of strokes in both groups increased over time in general, with the rate of stroke increasing from 0.5% to 7% in those requiring tMCS, and from 1.6% to 3% in those without tMCS (Figure 3). In multivariable analysis, female gender and increasing number of comorbid conditions were associated with increased risk of stroke (Table 4). Increasing age was statistically associated with stroke, but not at a clinically significantly level (RR 0.99, $p < 0.001$). There was no independent risk of stroke based on the type of tMCS received.

In multivariable analysis, female gender, increasing age, and increasing number of comorbid conditions were associated with an increased risk of renal failure (Table 5). In comparing the three types of tMCS, pre-transplant ECMO (RR 1.12, $p = 0.01$) and IABP (RR 1.13, $p < 0.001$) placement conferred a statistically significant risk of renal failure. PVAD placement conferred a similar risk by odds ratio but was likely underpowered to show effect (RR 1.16, $p = 0.15$).

Length of stay

In both the earlier and modern eras, patients who received tMCS prior to transplant had an increased length of stay (71vs. 43 days and 69 vs. 39 days, respectively) but this was not statistically significant given the significant variance in LOS in both groups. Similarly, there was a longer length of stay after heart transplantation for patients who required tMCS (70 vs. 41 days), but again this difference was not statistically significant.

Outcomes by type of tMCS

The rate of complications and mortality did not differ significantly by type of tMCS apart from overall length of stay being longer in the ECMO group vs IABP group (89 vs 63 days, $p < 0.0001$); length of stay after transplant was similar (Supplemental Table 2). The multivariable analyses of the impact of type of tMCS on these outcomes are reported above.

Discussion

In this cohort of heart transplant patients identified in the National Inpatient Sample, in-hospital mortality decreased over time, and this trend in decreasing mortality persisted despite an increasingly elderly patient population, patients with more comorbidities, and increased use of tMCS prior to heart transplantation.

This trend held true for both patients who received tMCS before transplant and patients who did not. In fact, the most significant improvement in hospital mortality over time was in the cohort who received tMCS. Although not statistically significant, in the modern era there was a modest trend towards decreased mortality in the tMCS cohort.

During this time period, the use of tMCS prior to transplant increased, more than doubling from 2002 to 2014. While mortality rates became similar between the two cohorts, the rate of post-transplant complications remained significantly higher in those patients who received tMCS prior to transplantation, and the rates of important complications such as stroke and renal failure increased over time.

The question of when and whether patients are "too sick" for heart transplantation is not explicitly described in the UNOS heart allocation proposal. Given the reduction over time of mortality for patients who received tMCS, our data suggests the proposed changes may be justified. However, based on the proposed changes, there could be an acceleration of the number of patients who receive tMCS prior to transplant. This could shift the overall transplant candidate population towards sicker patients prior to transplantation and lead to longer wait times for other

patients on the transplant list, while also increasing post-transplant morbidity, mortality, and overall cost to the healthcare system.

The question of when patients are "too sick" also depends on the state of the art perioperative treatment of patients undergoing transplantation, which has changed over time. If, as we found, the in-hospital mortality rates of transplant patients who require tMCS converges with the mortality rate of patients who do not require tMCS, advances in circulatory support might allow more patients to overcome critical cardiac failure and become transplant candidates. Patients who would otherwise die waiting on the transplant list could instead be transplanted and have good outcomes.

Yet even if mortality remains similar between patients who receive tMCS prior to transplant and those who do not, our finding of increased complication rates in patients receiving tMCS gives one pause. As the field of mechanical circulatory support advances, the focus on improving outcomes has broadened beyond mortality to other complications, which negatively impact quality of life and cost. Thus we need ways to reduce complication rates, whether by improved management of these patients or improved technology. The new UNOS allocation scheme does suggest the use of serial hemodynamic evaluations to determine whether a patient can remain a candidate for cardiac transplantation while on tMCS, and these and other measures could further refine our evaluation of patients' candidacy while on the waitlist, potentially improving morbidity rates post transplantation in patients receiving tMCS. For example, if tMCS devices were implanted in patients earlier in their hospital course, the rates of complications could decline. The type of tMCS may also be important, as we found that PVAD support significantly reduced post-transplant mortality, but this finding can only be hypothesis generating.

There are a few limitations to our study based on the design of the NIS. We are not able to explicitly determine to priority of the patients in our cohort nor the time on the transplant waiting list. Given the use of tMCS, we can assume that patients were status 1A prior to transplantation. As a retrospective cohort, we are not able to ascertain why tMCS was initiated and the discussion around which modality of circulatory support was chosen. The lack of hemodynamic data in the NIS means we cannot assess changes in patient's clinical condition prior to transplant. Additionally, the NIS also only lists same hospitalization complications and mortality and does not have information of post-hospital follow-up. Given the increased length

of stay and the high rates of complications while hospitalized, it is possible these patients would have a more challenging post-hospitalization course.

While the number of comorbid conditions was associated with worse outcomes in our multivariable model, due to the nature of the NIS dataset we could not precisely examine the effect of clinical factors such as renal function, blood pressure, and serum glucose levels on outcomes. The NIS dataset contains instead diagnoses such as chronic kidney disease, hypertension, and diabetes. Hemodynamic data or contemporaneous data on end-organ function at time of implant would provide incremental benefit to our analysis. Such data would also potentially aid in patient selection for tMCS, defining to some extent patients who should and should not receive tMCS prior to transplantation (e.g. because the latter would have poor outcomes after cardiac transplantation).

In conclusion, we found that while overall morbidity after heart transplantation increased over time in patients who received temporary mechanical circulatory support, in-hospital mortality rates did not significantly differ in more recent years between patients who received tMCS prior to cardiac transplantation and those who did not. These data support the use of tMCS prior to cardiac transplantation in appropriately selected patients, and if the use of tMCS prior to heart transplantation continues to increase over time, further refinement of patient management and selection may be required in order to improve outcomes.

Acknowledgements: None

Funding Sources: No study specific funding was used to support this work. The authors are solely responsible for the study design, conduct, and analyses, drafting and editing of the manuscript and its final contents.

Conflict of Interest Disclosures: None of the listed authors have any disclosures or potential conflicts of interest.

Figure and Table Captions

Figure 1: Number of heart transplant patients who had tMCS between 1998 and 2014 by type of tMCS.

Figure 2: Time trend of mortality rate by presence of tMCS prior to transplantation between 1998 and 2014

Figure 3: Time trend of stroke rate by presence of tMCS prior to transplantation between 1998 and 2014

Table 1: Baseline characteristics of patients who underwent cardiac transplant from 1998 to 2014, stratified by use of tMCS prior to transplantation

Table 2: Mortality, length of stay, complications in patients who underwent cardiac transplant from 1998 to 2014, by transplantation era

Table 3: Multivariable analysis of risk factors for mortality

Table 4: Multivariable analysis of risk factors for renal failure

Table 5: Multivariable analysis of risk factors for stroke

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	Acute Circulatory Support	**None**		**Total**
	n = 456	**n = 6436**	**p-value***	**n = 6892**
Age, mean ± SD	47.1 ± 17.5	46.5 ± 19.1	0.60	46.5 ± 19.0
Length of Stay, mean ± SD	69.7 ± 51.6	41.3 ± 49.2	0.95	43.1 ± 49.9
Length of stay after OHT, mean ± SD	23.4 ± 22.0	19.5 ± 19.1	0.36	19.8 ± 19.4
Length of time on ACS, median ± SD	18.0 ± 47.8	NA		18.0 ± 47.8
Sex, n (%)			0.24	
Male	339 (74.3)	4621 (71.8)		4960 (72.0)
Female	117 (25.7)	1814 (28.2)		1931 (28.0)
Race, n (%)			0.61	
White	272 (59.6)	3655 (56.8)		3927 (57.0)
Black	75 (16.4)	894 (13.9)		969 (14.1)
Hispanic	40 (8.8)	501 (7.8)		531 (7.8)
Asian/Pacific Islander	17 (3.7)	163 (2.5)		180 (2.6)
Native American	0 (0.0)	22 (0.3)		22 (0.3)
Other or unknown	52 (11.4)	1101 (18.7)		1253 (16.1)
Median household income, n (%)			0.36	
$1-24,999	84 (18.4)	1111 (17.3)		1195 (17.3)
$25,000-34,999	113 (24.7)	1508 (23.4)		1621 (23.5)
$35,000-44,999	114 (25.0)	1679 (26.1)		1793 (26.0)

$45,000 or more	137 (30.0)	1985 (30.8)		2122 (30.8)
Unknown	8 (1.8)	153 (2.3)		161 (2.3)
Bedsize of Hospital, n (%)			0.40	
Small	43 (9.4)	479 (7.4)		522 (7.6)
Medium	75 (16.4)	1024 (15.9)		1099 (15.9)
Large	338 (74.1)	4933 (76.6)		5271 (76.5)
Comorbidities				
Diabetes	69 (15.1)	1278 (19.9)	< 0.01	1347 (19.5)
Ischemic Heart Disease	194 (42.5)	2760 (42.9)	0.88	2954 (42.9)
Hypertension	106 (23.2)	1943 (30.2)	< 0.01	2049 (29.7)
Preexisting Renal Dysfunction	119 (26.1)	2169 (33.7)	< 0.01	2288 (33.2)
Peripheral Vascular Disease	8 (1.8)	103 (1.6)	0.78	111 (1.6)
History of smoking	16 (3.5)	354 (5.5)	0.02	370 (5.4)
BMI $\geq$ 30 kg/m^2	11 (2.4)	192 (3.0)	0.40	203 (3.0)

*Stratified t-test or ANOVA

	1998 - 2006			2007 - 2014		
	Acute Circulatory Support	**None**		**Acute Circulatory Support**	**None**	
	n = 182	**n = 3114**	**p-value**	**n = 274**	**n = 3322**	**p-value**
Length of stay, mean ± SD	70.8 ± 52.4	43.4 ± 52.6	0.52	68.9 ± 51.1	39.2 ± 45.7	0.82
Length of stay after OHT, mean ± SD	24.6 ± 27.9	18.3 ± 17.5	0.70	22.6 ± 17.1	20.6 ± 20.4	0.37
Mortality, n (%)	26 (14.3)	233 (7.5)	0.05	13 (4.7)	169 (5.1)	0.90
Post-Transplant Circulatory Support	1 (0.6)	31 (1.0)	0.48	3 (1.1)	59 (1.8)	0.25
Acute Renal Failure	78 (42.9)	837 (26.9)	< 0.001 *	175 (64.3)	1478 (44.5)	< 0.001 *
Acute Liver Failure	12 (6.6)	50 (1.6)	0.005 *	41 (15.1)	148 (4.5)	< 0.001 *
Acute Respiratory Failure	40 (22.0)	223 (7.2)	< 0.001 *	85 (31.0)	433 (13.0)	< 0.001 *
Cardiac Complications	28 (15.4)	367 (11.8)	0.32	48 (17.6)	452 (13.6)	0.09
Sepsis	8 (4.4)	57 (1.8)	0.16	44 (16.1)	275 (8.3)	< 0.001 *
Stroke	1 (0.5)	50 (1.6)	0.03 *	19 (7.0)	101 (3.0)	0.009 *
Complication Requiring Reoperation	41 (22.5)	407 (13.1)	0.002 *	88 (32.1)	581 (17.5)	< 0.001 *
Bleeding Complication	60 (33.0)	549 (17.6)	< 0.001 *	85 (31.0)	630 (19.0)	0.002 *

*p < .05; stratified t-test or ANOVA

Variable	**OR**	**2.5%**	**97.5%**	**P value**
Decade of Age	1.00	0.9996	1.0004	0.99
Not White	1.01	1.00	1.02	0.18
Female	1.00	0.99	1.03	0.39
Prior to Transplant ECMO	1.04	0.99	1.10	0.13
Prior to Transplant IABP	0.99	0.93	1.05	0.74
Prior to Transplant PVAD	0.94	0.92	0.97	< 0.001 *
Modern Era	0.95	0.93	0.97	< 0.001 *
Number of Comorbidities	1.01	1.00	1.01	< 0.001 *

Logistic Regression Model: death, age, race, sex, type of tMCS, era, number of comorbidities

*p < 0.05

Variable	**OR**	**2.5%**	**97.5%**	**P value**
Decade of Age	0.999	0.9991	0.9996	< 0.001 *
Not White	0.99	0.987	1.002	0.16
Female	1.01	1.001	1.02	0.03 *
Prior to Transplant ECMO	1.02	0.98	1.06	0.31
Prior to Transplant IABP	1.01	0.99	1.02	0.49
Prior to Transplant PVAD	1.05	0.92	1.20	0.46
Modern Era	1.01	0.998	1.014	0.16
Number of Comorbidities	1.003	1.002	1.005	< 0.001 *

Logistic Regression Model: stroke, age, race, sex, type of tMCS, era, number of comorbidities

*p < 0.05

Variable	**OR**	**2.5%**	**97.5%**	**P value**
Decade of Age	1.003	1.002	1.004	< 0.001 *
Not White	1.01	0.99	1.04	0.38
Female	0.97	0.94	0.99	0.01 *
Prior to Transplant ECMO	1.12	1.02	1.21	0.01 *
Prior to Transplant IABP	1.13	1.08	1.19	< 0.001 *
Prior to Transplant PVAD	1.16	0.95	1.43	0.15
Modern Era	1.04	0.99	1.09	0.13
Number of Comorbidities	1.04	1.03	1.04	< 0.001 *

Logistic Regression Model: renal failure, age, race, sex, type of tMCS, era, number of comorbidities

*p < 0.05