**Incidence and In Hospital Mortalityof Acute Circulatory Support Prior to Heart Transplantation**

**Running Title: Circulatory Support Prior to Transplant**

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**Background**: Proposed changes to the UNOS heart transplant allocation protocol would prioritize patients receiving acute circulatory support, 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 acute circulatory support during the hospitalization prior to heart transplantation.

**Methods**: Using the Nationwide Inpatient Sample (NIS) from 1998 to 2014, we identified 6,892 patients who underwent orthotopic heart transplant (OHT) and determined whether the patient underwent pre-transplant ECMO, PVAD, or IABP. We calculated baseline characteristics and in hospital outcomes of patients who underwent acute circulatory supportcompared to patients who did not require acute circulatory support prior to heart transplantation.

**Results**:Of patients who underwent heart transplantation, 456 (6.6%) patients received acute circulatory support prior to transplant. During the study time period, the use of acute circulatory support increased (p < 0.001 for trend), more than doubling from 17 cases per year from 1998–2002 to 40 cases per year from 2012- 2014. Of patients with acute circulatory support, 341(74.8%) were supported by IABP, 130 (28.5%) were supported by ECMO, and 21(4.6%) were supported by PVAD. Patients who required acute circulatory support had increased length of stay (69.7vs. 41.3 days, p < 0.001) and in-hospital mortality (8.6% vs. 6.2%, p = 0.05). Over time, there was an improvement in in-hospital mortality rate for all patients, but most significantly in patients who require acute circulatory support (4.7% for acute circulatory support vs 5.1% for those without support prior to transplant from 2007-2014). Patients who had acute circulatory support had less comorbid diabetes, hypertension, or pre-existing renal dysfunction, but during the hospitalization had increased rates of complications including acute renal, hepatic, andrespiratory failure, cardiac complications, bleeding complications, and surgical complications requiring reoperation.

**Conclusions**: In this cohort, we found anincreasing proportion of patients receiving acute circulatory support prior to heart transplantation over time. These patients exhibited increased inpatient mortality, longer lengths of stays, and increased frequency of complications compared to those without acute circulatory support, but mortality in the more recent era was not significantly different from those not receiving acute circulatory support prior to transplantation.. Changes to the UNOS heart allocation protocol could accelerate this trend of increased use and should take the increased morbidity of these patients after transplantation into consideration.

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

**Introduction**

Congestive heart failure is a highly morbid, common disease affecting 5.7 million people and contributes to over 300,000 deaths each year in the United States1,2. 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 survival 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 cohorts3–5. Heart transplant volumes have plateaued, yet there has been a tremendous increase in the number of active transplant candidates from 1,203 candidates in 2006 to 3,008 candidates in 2013 6,7. 10% of patients on the heart transplant waitlist die every year due to the lack of available organs8,9. 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 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 ECMO6,10–14. Roughly 40% patients are being bridged to cardiac transplantation with durable mechanical circulatory support, but less data is available on temporary circulatory support prior to cardiac transplantation.

Given this 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 to the adult heart allocation system to further stratify high urgency patients6. 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 to be at the second highest priority, as these patients have the highest expected mortality on the waitlist.

Given the severity of illness in these patient populations, many recognize 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 suggest the need for further study of patients who require acute circulatory support 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 to assess the outcomes of patients who underwent acute circulatory support prior to heart transplantation, and compare their outcomes to patients who did not require acute circulatory support.

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

**Methods**

**Data Source and Study Design**

The Nationwide 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. Each NIS entry includes all diagnosis and procedure codes of activity during the patient’s hospitalization at the time of discharge, as well as patient demographics, hospital characteristics, and short-term complications of the hospitalization.

We identified all patients who underwent heart transplantation in the NIS from 1988 to 2014. This population was further divided by whether each patient underwent pre-transplant ECMO, PVAD, or IABP. 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. P-values were calculated by two-sided t-tests and Chi-squared tests, respectively, with significance thresholds of 0.05. Logistic regression was performed for the multivariate analysis.

**Results**

**Baseline Patient Characteristics**

Between 1998 and 2014, there were 6,892 patients who underwent cardiac transplantationin 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). 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%).

In this cohort, 456 transplant recipients required acute circulatory support prior to heart transplantation, of which 341 patients had an IABP placed, 130 patients were started on ECMO, and 21 patients underwent PVAD placement. Patients requiring acute circulatory support were of similar age, sex, and average household income compared to patients who did not require acute circulatory support. For patients requiring acute circulatory support, there was a decreased rate of diabetes (15.1% vs. 19.9%, p = 0.02), hypertension (23.2% vs. 30.2%, p = 0.002), and preexisting renal dysfunction (26.1% vs. 33.7%, p = 0.001), but similar rates of ischemic heart disease, peripheral vascular disease, obesity, and history of smoking.

**Post-transplant outcomes**

Patients who required acute circulatory support had worse outcomes post-transplant compared to patients who did not require mechanical circulatory support prior to transplantation (Table 2). Patients who required acute circulatory support had longer overall lengths of stay (70 vs. 41 days, p < 0.001) and increased in-hospital mortality (8.6% vs. 6.2%, p = 0.05). The difference in in-hospital mortality decreased for both patients who required acute circulatory support (p < 0.001 for trend) as well as patients who did not require acute circulatory support (p = 0.012 for trend), though the decline in mortality was more pronounced in patients who required acute circulatory support (Figure 1). In modern era, the years 2007-2014, the difference in mortality was not statistically significant between the two groups (p = 0.80).

In a multivariate analysis of predictors of mortality, increased age and increasing number of comorbid conditions was associated with increased mortality, whereas transplantation during the modern era, a prior diagnosis of hypertension, chronic kidney disease, or diabetes appeared protective (Table 3). Consistent with the convergence in the mortality rate between patients who required acute circulatory support with patients who did not require acute circulatory support, there was no statistically significant association for any of the circulatory support modalities.

In-hospital complications were more common in patients who required acute circulatory support, 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), 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 complications in both groups increased over time in general, with the rate of stroke increasing from 0.5% to 7% in those requiring acute circulatory support, and from 1.6% to 3% in those without acute circulatory support (Figure 2). In multivariate analysis of predictors of renal failure, transplantation during the modern era, increasing age and increasing number of comorbid conditions were associated with decreased incidence of renal failure (Table 4). Female gender, diabetes, obesity, hypertension, smoking, chronic kidney disease, and ischemic heart disease were protective. In comparing the three acute circulatory support modalities, pre-transplant ECMO (OR 1.0972, p = 0.02) and IABP (OR 1.1045, p < 0.001) had statistically significant risk elevation in renal failure, although PVAD had a similar odds ratio but might be underpowered to show effect (OR 1.1089, p = 0.292).

**Prevalence of acute circulatory support prior to cardiac transplantation**

The use of acute circulatory support prior to cardiac transplantation increased significantlyover time, from 5.9% of transplants from 1998-2006 to 8.2% from 2007-2014 (p < .0001, Figure 3).

**Discussion**

In this cohort of heart transplant patients identified in the National Inpatient Sample, we discovered an increased use over time of acute circulatory support prior to heart transplantation. From 17 cases per year between 1998 to 2002 to an average of 40 cases per year between 2012 to2014, the rate of acute circulatory support prior to transplant has more than doubled. As a population, patients who underwent acute circulatory support were overall healthier, with decreased rates of diabetes, hypertension, and pre-existing renal disease. Despite this, they had increased in-hospital mortality, increased post-transplant length of stays, and a higher proportion of a variety of post-transplant complications. Over time, while mortality rates became similar between the two cohorts, the rate of post-transplant complications remained significantly higher in those patients who received acute circulatory support prior to transplantation.

The question of when and whether patients are "too sick" for heart transplantation is not explicitly described in the UNOS heart allocation proposal. If there were changes to UNOS heart allocation, there could be an acceleration of the number of patients who receive acute circulatory support prior to transplant. We saw over the last twenty years that more patients received acute circulatory support 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. Additionally, the question of when patients are “too sick” also depends on the state of the art in transplantation and has changed over time. As the in-hospital mortality rates of transplant patients who required acute circulatory support converges with the mortality rate of patients who did not require acute circulatory support, advances in circulatory support might allow patients to overcome critical cardiac failure.The new allocation scheme does suggest the use of hemodynamics to determine whether a patient can remain a candidate for cardiac transplantation while on acute circulatory support, and these and other measures could further refine our evaluation of patients’ candidacy while on the waitlist, potentially improving morbidity rates post transplantation.

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 acute circulatory support, we can confidently assume that patients were status 1A prior to transplantation. The NIS only lists same hospitalization complications and mortality, and does not have information of post-hospital follow-up. With an in-hospital mortality rate of 8.6% for patients requiring acute circulatory support, the mortality rate already exceeds the overall 1-year mortality of some large academic transplant centers4,5. Given the high rates of complications while hospitalized, including increased acute renal failure, liver failure, respiratory failure, cardiac complications, and bleeding complications, it is likely these patients would have a more challenging post-hospitalization course.

We also paradoxically found that pre-morbid conditions such as diabetes, hypertension, and chronic kidney disease were protective against post-transplant mortality and renal failure in multivariate analysis. These findings likely represent contemporary changes in management and the limitations of the dataset, which is a retrospective cohort and do not contain hemodynamic data or contemporaneous data on end-organ function at time of implant. In the modern era, hemodialysis was more common post-transplant regardless of whether patients who received pre-transplant acute circulatory support, potentially suggesting changing availability and threshold to initiate hemodialysis over time rather than worsening kidney failure in transplant patients over time. While the number of comorbid conditions was associated with worse outcomes, certain pre-existing diagnoses were protective in the model. This could be a result of variability in the practice of coding ICD9 codes (for example providers less likely coding for a history of smoking in a patient who had a complicated hospital stay requiring dialysis, suffering from infectious complications, and prolonged respiratory failure than a patient who had an uncomplicated hospitalization and relatively few comorbidities.) Going forward, it would be important to obtain such data to better risk stratify patients for better outcomes after transplantation..

In conclusion, we found that overall morbidity and mortality after heart transplantation was increased in patients who received acute circulatory support, though mortality rates were not significantly different in more recent years. As the use of acute circulatory support prior to heart transplantation has increased over time, further refinement of patient management and selection in those patients is required in order to improve outcomes.

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Figure 1: Time trend of mortality by presence of acute circulatory support prior to transplantation



Table 1: Baseline characteristics of patients who underwent cardiac transplant from 1998 to 2011, divided by use of acute mechanical support prior to transplantation

Table 2: Mortality, length of stay, complications in patients who underwent cardiac transplant from 1998 to 2014, divided by use of acute mechanical support prior to transplantation

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Supplement A: ICD-9 codes of comorbid conditions

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| **Comorbidities** | **ICD-9 codes** |
| Diabetes Mellitus | 250.00-250.93, 249.00-249.91 |
| Ischemic Heart Disease | 410.0-410.9, 411.0-411.8, 412, 413.0-413.9, 414.0-414.9, V45.8, V45.82 |
| Hypertension | 401.0-401.9, 402.0, 402.00-402.91, 403.0, 403.00-403.91, 404.0 404.00-404.93, 405.0, 405.01-405.91, 437.2 |
| Pre-existing renal dysfunction | 585.3, 585.4, 585.5, 585.6, 585.9, V42.0, V45.1, V45.11, V45.12, V56.0, V56.1, V56.2, V56.3, V56.31, V56.32, V56.8 |
| Peripheral vascular disease | 440.0-440.9, 443.1, 443.8,443.81, 443.82, 443.89, 443.9, 447.1, V43.4 |
| History of smoking | 305.1, V15.82 |
| BMI > 30 kg/m2 | 278.0, 278.01, 278.02 |

Supplement B: ICD-9 codes of complications

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| **Complication** | **ICD-9 codes** |
| Post Transplant Circulatory Support1 | 37.61, 37.68, 39.61 |
| Acute Renal Failure | 584.5, 584.6, 584.7, 584.8, 584.9 |
| Acute Liver Failure | 570 |
| Acute Respiratory Failure | 518.81 |
| Cardiac Complications | 997.1, 429.4, 432.0, 432.3, 426.0 |
| Sepsis | 995.91, 995.92 |
| Stroke | 433.0-433.9, 434.0-434.9 |
| Surgical Complication Requiring Reoperation | 340.3, 341, 347.9, 380.3 |
| Bleeding Complication | 530.21 ,456.0 ,530.7 ,530.82 ,578.0 ,578.1 ,578.9 ,456.20 ,531.00 ,531.01 ,531.20 ,531.21 ,531.40 ,531.41 ,531.60 ,531.61 ,532.00 ,532.01 ,532.20 ,532.21 ,532.40 ,532.41 ,532.60 ,532.61 ,533.00 ,533.01 ,533.20 ,533.21 ,533.40 ,533.41 ,533.60 ,533.61 ,534.00 ,534.01 ,534.20 ,534.21 ,534.40 ,534.41 ,534.60 ,534.61 ,535.01 ,535.11 ,535.21 ,535.31 ,535.41 ,535.51 ,535.61 ,535.71 ,537.83 ,562.02 ,562.03 ,562.12 ,562.13 ,569.3 ,569.85 ,537.84 ,569.86 |
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1Day of procedure past day of transplant