**Incidence and Outcomes of 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 allocation protocol could prioritize patients with 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**: From the Nationwide Inpatient Sample (NIS) from 1998 to 2011, we identified 5,381 patients who underwent orthotopic heart transplant (OHT) and determined whether the patient underwent pre-transplant ECMO, PVAD, or IABP. We calculated baseline characteristics and compared patients who underwent acute circulatory support with patients who did not require acute circulatory support prior to heart transplantation.

**Results**: Of patients who underwent heart transplantation, 337 (6.3%) patients required acute circulatory support prior to transplant. During the study time period, the use of acute circulatory support has increased (p = 0.003 for trend) from 17 cases per year from 2008-2010 to 33 cases per year from 2009 - 2011. In this population, 253 (75.1%) patients were supported by IABP, 102 (30.3%) were supported by ECMO, and 4 (1.2%) were supported by PVAD. Patients who required circulatory support had increased length of stay (69.2 vs. 40.9 days, p < 0.001) and increased in-hospital mortality (10.1% vs. 6.3%, p = 0.009). Patients who had acute circulatory support had less comorbid diabetes, hypertension, or pre-existing renal dysfunction, however during the hospitalization had increased acute renal failure, liver failure, respiratory failure, cardiac complications, bleeding complications, and surgical complications requiring reoperation.

**Conclusions**: In this cohort, we found an increasing proportion of patients receiving acute circulatory support prior to heart transplantation. These patients exhibited significantly increased inpatient mortality, longer lengths of stays, and increased frequency of complications compared to those without acute circulatory support. Changes to the UNOS heart allocation protocol should take both this increased mortality and mortality and the trend of increased support use over time into consideration.

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

**Introduction**

Congestive heart failure is a highly morbid, common disease affecting 5.8 million people and contributes to 300,000 deaths each year in the United States [ 1,2 ]. 11.6% of Americans greater than 80 years of age have heart failure

Heart failure contributes to 35% of cardiovascular disease deaths and 7%

Despite significant advances in medical therapy and progress in advanced mechanical circulatory support, cardiac transplantation has a crucial role in the treatment of end-stage heart failure for appropriately selected patients. Starting almost fifty years ago, human heart transplantation outcomes have continuously improved from 1-year survival of less than 50% to greater than 90% in the vast majority of transplant centers [3,4,5]. The most recent data from the International Society of Heart and Lung Transplantation indicates a current 1-year survival of XX and 5-year survival of XX. In addition to advances in mechanical circulatory support, surgical technique, and immunosuppressive regimens, better understanding of transplant physiology and patient selection has allowed for heart transplant to be the gold standard in human organ transplantation.

The bottleneck in the volume of cardiac transplantation continues to be the mismatch between need and available of donor organs, and patient selection has been a dynamic area of discussion in light of advances in heart failure treatment. Although transplant volumes have plateaued, there has been a tremendous increase in the number of active transplant candidates from 1,203 candidates in 2006 to 3,008 candidates to 2013 [11]. XX% of patients in the transplant list continues to die every year due to the lack of available organs. In particular, candidates in the most urgent classification, 1A, now make up the majority of eventual transplant recipients (67% of adult heart transplants by 2014) [1].

With advances in durable mechanical circulatory support devices, the role of mechanical circulatory support prior to transplantation as greatly expanded over the last three decades [6]. Over time, a greater proportion of transplant recipients has had a ventricular assist device prior to transplantation [ ] even as there is more long-term data for durable MCS therapy. With MCS device related criteria being an increasingly higher proportion of transplant candidates (from 16.2% in 2007 to 35.8% in 2014),  there is concern that the most urgent classification currently groups together patients with disparate life expectancies. Even among status 1A candidates, 6 month mortality ranges from 4.8% in candidates with MCS complicated by infection to 35.7% in candidates supported by ECMO.

Under the current adult heart allocation system, candidates are stratified in the  highest urgency classification if they require multiple inotropes and hemodynamic monitoring, are supported by total artificial heart, IABP, ECMO, mechanical ventilation, or a ventricular assist device, or are experiencing a MCS device related complication.

Recently, the Thoracic Organ Transplantation Committee of Organ Procurement and Transplantation Network / UNOS proposed changes to the adult heart allocation system to further stratify high urgency patients. In the proposed criteria, patients supported by ECMO, on mechanical ventilation, supported with temporary biventricular or right ventricular assist devices, or MCS with life-threatening ventricular arrhythmias are

There is significant discussion on how to prioritize stable outpatient transplant candidates with a ventricular assist device in compared to hospitalized patients.

in response to increased use of mechanical circulatory support (MCS) devices. With an increasing proportion of heart transplants occurring in patients on MCS,

There exists a variety of acute circulatory support options for decompensated heart failure before and after transplantation. Intra-aortic balloon pump counterpulsation is used as a bridge to heart transplantation with similar 1 year survival outcomes [16,17] and novel approaching including axillaryIABP prior to transplant as been proposed [15].

After transplantation, ECMO has been used to bridge and support patients with graft rejection or failure with variable success [12,13,14]. In this particularly sick population, clinical outcomes are poor despite ECMO support with 1 year survival ranging from 19% to 60%[13,14].

In addition

Acute circulatory support options

There is significant interest in the outcomes of transplant candidates who need acute circulatory support prior to transplantation, however there are no studies detailing their short or long-term outcomes. The desire to balance the acute needs of critically ill patients with long term outcomes of a limited and precious resource suggest further study of this subset of patients. In this study, we use the largest national database of hospitalizations in the United States to assess the outcomes of patients who underwent acute mechanical circulatory support prior to heart transplantation and compare these outcomes to published registry data of all heart transplant recipients.

With advances in

Patients who undergo heart transplantation can continue to expect

**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 2011. This population was further divided into cohorts by whether each patient underwent pre-transplant ECMO, or underwent placement of a PVAD, or had an IABP placed. In-hospital complications including acute renal failure, acute respiratory failure, redo sternotomy or reoperation, sepsis, bleeding complications, stroke, liver failure, and device failure were identified by associated International Classification of Diseases 9th edition (ICD-9) code. Comorbidities

**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.

**Results**

**Baseline Patient Characteristics**

Between 1998 and 2011, there were 5,381 patients who underwent cardiac transplantations sampled in the NIS (Table 1). The patients were predominantly male (72.8%) and white (56.7%) and had a mean age of 48.1 (SD 16.8). Most patients were hospitalized at large (83.8%), urban (99.8%), and academic (92.9%) hospitals and the median day of heart transplant was hospital day 17 (interquartile range from day 2 to day 36).

359 transplant recipients required acute circulatory support prior to heart transplantation, of which 253 patients had an IABP placed, 102 patients were started on ECMO, and 4 patients underwent PVAD placement. Patients who required acute circulatory support had longer overall lengths of stay (69.2 vs. 40.9 days, p < 0.001) and increased mortality (9.5% vs. 6.3%, p = 0.024).

**Discussion**

Diagnoses are not timed, but could speak to patient selection

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Figure 1: Time Trend of acute circulatory support prior to transplantation

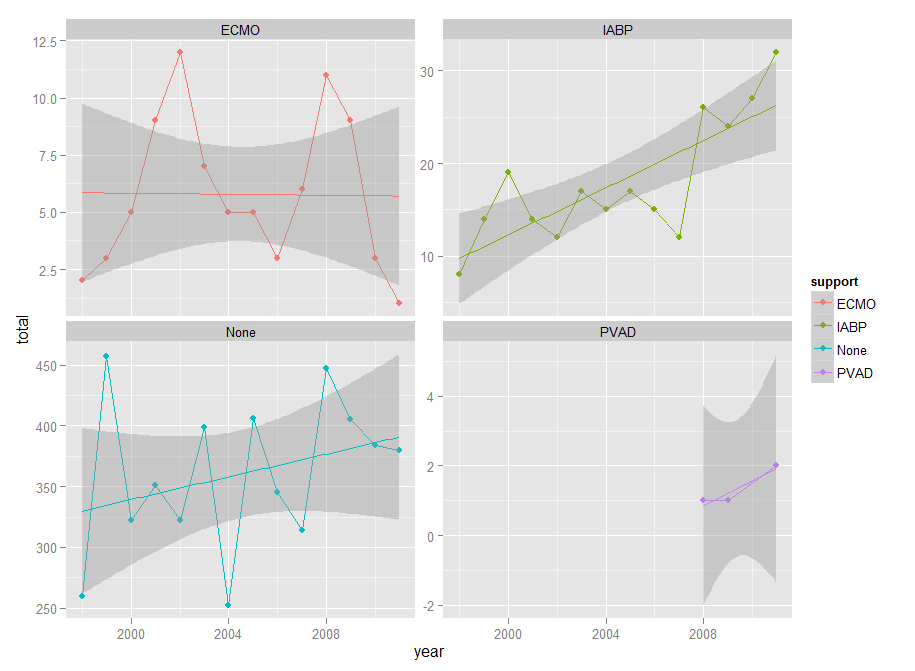


Table 1: Baseline characteristics of patients who underwent cardiac transplant from 1998 to 2011, divided by use of acute mechanical support prior to transplantation

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Acute Circulatory Support** | **None** | **Total** |  | |
| **n = 337** | **n = 5022** | **n = 5381** | p-value | |
| Age, mean ± SD | 47.2 ± 17.5 | 46.5 ± 18.7 | 48.1 ± 16.8 | 0.47 | |
| Sex, n (%) | | | |  | |
| Male | 257 (76.3) | 3660 (72.6) | 3917 (72.8) | 0.2 | |
| Female | 80 (23.7) | 1383 (27.4) | 1463 (27.2) |  | |
| Race, n (%) | | | |  | |
| White | 199 (61.6) | 2851 (69.9) | 3050 (56.7) | 0.006 | |
| Black | 47 (14.6) | 633 (15.5) | 680 (12.6) |  | |
| Hispanic | 34 (10.5) | 386 (9.5) | 420 (7.8) |  | |
| Asian/Pacific Islander | 12 (3.7) | 121 (3.0) | 133 (2.5) |  | |
| Native American | 0 (0.0) | 16 (0.4) | 16 (0.3) |  | |
| Other or unknown | 45 (13.4) | 1037 (20.6) | 1082 (18.2) |  | |
| Median household income, n (%) | | | |  | |
| $1-24,999 | 53 (14.8) | 797 (15.9) | 850 (15.8) | 0.8 | |
| $25,000-34,999 | 84 (23.4) | 1177 (23.4) | 1261 (23.4) |  | |
| $35,000-44,999 | 84 (23.4) | 1335 (26.6) | 1419 (26.4) |  | |
| $45,000 or more | 110 (30.6) | 1601 (31.9) | 1711 (31.8) |  | |
| Unknown | 6 (1.7) | 134 (2.7) | 140 (2.6) |  | |
| Comorbidities | | | |  | |
| Diabetes | 50 (14.8) | 999 (19.9) | 1049 (19.5) | 0.03 | |
| Ischemic Heart Disease | 156 (46.3) | 2248 (44.8) | 2404 (44.8) | 0.62 | |
| Hypertension | 71 (21.1) | 1447 (28.8) | 1518 (28.2) | 0.003 | |
| Preexisting Renal Dysfunction | 75 (22.2) | 1641 (32.7) | 1716 (31.9) | < 0.001 | |
| Peripheral Vascular Disease | 5 (1.5) | 83 (1.7) | 88 (1.6) | 0.99 | |
| History of smoking | 14 (4.2) | 297 (5.9) | 311 (5.8) | 0.22 | |
| BMI ≥ 30 kg/m2 | 7 (2.1) | 130 (2.6) | 137 (2.5) | 0.69 | |
| Location of Hospital, n (%) | | | |  | |
| Urban | 337 (100.0) | 4971 (99.8) | 5308 (99.8) | 0.99 | |
| Rural | 0 (0.0) | 8 (0.2) | 8 (0.2) |  | |
| Bedsize of Hospital, n (%) | | | |  | |
| Small | 6 (1.7) | 120 (2.4) | 126 (2.4) | 0.08 | |
| Medium | 59 (17.5) | 737 (14.9) | 796 (15.0) |  | |
| Large | 272 (80.7) | 4122 (83.2) | 4394 (82.6) |  | |
| Teaching Hospital, n (%) | | | |  | |
| Teaching | 323 (95.8) | 4547 (91.7) | 4870 (91.6) | 0.006 | |
| Non - Teaching | 14 (4.2) | 432 (8.7) | 446 (8.4) | |  |

Table 2: Mortality, length of stay, complications in patients who underwent cardiac transplant from 1998 to 2011, divided by use of acute mechanical support prior to transplantation

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Acute Circulatory Support** | **None** |  |
| **n = 337** | **n = 5022** | **p-value** |
| Length of stay, mean ± SD | 69.2 ± 50.6 | 40.9 ± 49.2 | < 0.001 |
| Mortality, n (%) | 34 (10.1) | 316 (6.3) | 0.009 |
| Post Transplant Circulatory Support | 2 (0.6) | 64 (1.3) | 0.4 |
| Acute Renal Failure | 168 (49.9) | 1616 (32.2) | < 0.001 |
| Acute Liver Failure | 31 (9.2) | 128 (2.5) | < 0.001 |
| Acute Respiratory Failure | 97 (28.8) | 474 (9.4) | < 0.001 |
| Cardiac Complications | 56 (16.6) | 620 (12.3) | 0.028 |
| Sepsis | 33 (9.8) | 201 (9.2) | < 0.001 |
| Stroke | 10 (3.0) | 98 (2.0) | 0.278 |
| Surgical Complication Requiring Reoperation | 90 (26.7) | 690 (13.7) | < 0.001 |
| Bleeding Complication | 117 (34.7) | 935 (18.6) | < 0.001 |

Supplement A: ICD-9 codes of comorbid conditions

|  |  |
| --- | --- |
| **Comorbidty** | **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

|  |  |
| --- | --- |
| **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 |
|  |  |

1Day of procedure past day of transplant