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**Extracorporeal Membrane Oxygenation (ECMO) in Adults in the United States
from 2006-2011**

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

By

Christopher Mark Sauer

2014

Abstract

Objective: Recent studies have shown the benefits of extracorporeal membrane oxygenation (ECMO) in supporting adults with severe respiratory or cardiac failure refractory to conventional treatments. The purpose of this investigation was to analyze the utilization of ECMO in adults to identify recent trends within the United States.

Methods: In a serial cross-sectional study, the utilization rate of ECMO in adults in the United States from 2006 to 2011, as well as the survival rates and costs of hospitalization were analyzed using the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP). The survival rates were further analyzed by grouping the hospitals by size, type, or volume of adult ECMO cases.

Results: The rate of ECMO cases per million adult discharges increased 433% from 11.4 (95% CI, 6.1-16.8) in 2006 to 60.9 (95% CI, 28.1-93.7) in 2011 (p for trend = 0.001). Throughout this six-year period, there were no statistically significant changes in the survival rates (p for trend = 0.14), costs per day (p for trend = 0.07), or total costs per patient (p for trend = 0.87). Hospitals that were small, nonteaching, or had few adult ECMO cases were more likely to transfer their patients to other acute care hospitals.

Conclusion: From 2006 to 2011, there was a huge increase in the utilization of ECMO in adults with no significant changes in survival rates or hospitalization costs. ECMO as a therapeutic modality should be given consideration in critically ill patients with reversible cardio-respiratory collapse.

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a type of mechanical cardiopulmonary support that can be used for temporary life support of patients suffering from severe, but potentially reversible respiratory or cardiac failure when conventional treatments have failed or are likely to fail. Mechanical cardiopulmonary support is most often used in the operating room to assist with cardiac surgeries. This type of support, known as cardiopulmonary bypass, is used for only a couple of hours. ECMO, which is used much less frequently, supports a patient for several days and requires hospitalization in an intensive care unit (ICU). There are two types of ECMO: venovenous (VV) and venoarterial (VA). Both types provide pulmonary support, but VA ECMO also provides cardiac support.

The following description of how ECMO is performed is from an article by Bartlett and Gattinoni.(1) Placing a patient on ECMO requires skill and experience. As with cardiopulmonary bypass, initial cannulation is usually performed by a cardiac surgeon. The patient's blood is removed from the right atrium via a large cannula, circulated through an oxygenator that saturates the hemoglobin with oxygen while removing carbon dioxide, and returned to the patient either back into the right atrium (VV ECMO) or into the aorta (VA ECMO). Therefore, VA ECMO provides both heart and lung function, whereas

VV ECMO provides just lung function, leaving hemodynamic function to the native heart. Despite the type of ECMO used, the blood flow needs to match the entire cardiac output. This requires the use of large-bore and low-resistance cannulas. These cannulas can be placed in the proper positions either through the large vessels in the neck or groin. Anticoagulation must be used to inhibit clot formation and is usually achieved by a continuous infusion of unfractionated heparin. The goal activated clotting time (ACT) is between 180 and 210 seconds. Platelet infusions are common as the platelets get activated when exposed to the foreign surface of the ECMO circuit. Adequate tissue perfusion is determined by measuring the arterial blood pressure, oxygen saturation, and serum lactate levels. Complications of ECMO include bleeding and thromboembolism. Bleeding occurs in 30-40% of patients receiving ECMO due to the anticoagulation and platelet dysfunction. Thromboembolism due to a thrombus that forms within the ECMO circuit can be life threatening, but happens infrequently due to anticoagulation and constant monitoring of connectors and pressure gradients.

One of the most difficult aspects of ECMO is patient selection. The Extracorporeal Life Support Organization (ELSO, Ann Arbor, MI) is an international consortium of health care professionals and scientists based at the University of Michigan that collects data and conducts research regarding the use of ECMO. They made guidelines in order to help clinicians with patient

selection.(2) Their criterion for ECMO initiation is acute severe pulmonary or cardiac failure that is unresponsive to conventional management and potentially reversible. Clinical scenarios that meet their guidelines for ECMO support include hypoxemic respiratory failure with a ratio of arterial oxygen tension to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) of less than 100 mmHg despite optimizing ventilation settings, hypercapnic respiratory failure with an arterial pH less than 7.20, refractory cardiogenic shock, cardiac arrest, and failure to wean from cardiopulmonary bypass after cardiac surgery. ECMO can also be used as a bridge to cardiac transplantation or the placement of a ventricular assist device (VAD). ECMO is contraindicated for patients with irreversible respiratory or cardiac failure, patients that cannot receive anticoagulation, and patients that have cardiac failure but are not candidates for transplantation or VAD placement.

Although most physicians are familiar with the use of ECMO to support neonates with respiratory failure, the first successful case of ECMO was actually in an adult, a 24-year-old man who sustained multiple injuries due to blunt trauma resulting in shock-lung syndrome (now known as acute respiratory distress syndrome or ARDS) in 1971.(3) Despite surgical repair of his injuries and maximal conventional supportive therapy, he deteriorated for four days following his trauma, but was then placed on VA ECMO for 75 hours, which

allowed his lungs to recover. This raised hope for the use of ECMO in treating adults with severe acute respiratory failure, so a large multi-center prospective randomized trial was commissioned by the National Institutes of Health (NIH) in 1975. Nine medical centers participated and a total of 90 patients with severe acute respiratory failure were treated with either conventional mechanical ventilation or mechanical ventilation supplemented with VA ECMO.(4) The survival rates were 9.5% for the ECMO group and 8.3% for the control group with no statistically significant difference. The conclusion was that ECMO did not improve long-term survival in adults, and research on ECMO use in adults stalled for a decade.(5)

Meanwhile, ECMO was proving to be successful in treating neonates with respiratory failure.(6-8) Multiple successful case reports led to two prospective randomized trials, which both showed near perfect survival rates for newborns with respiratory failure treated with ECMO.(9, 10) This led to ECMO becoming standard treatment for neonates suffering from severe respiratory failure.(5) Eighteen neonatal centers had successful ECMO teams by 1986.(11)

Despite the great success of ECMO in critical care pediatrics, all but a few centers abandoned the idea of ECMO use in adults. For the remainder of the 20th century, there were very few reported cases of adults receiving ECMO

relative to neonates. In 1997, a case series by a group in the United Kingdom reported a 66% survival rate for 50 adults with severe respiratory failure who underwent ECMO in their treatment regimens.(12) They compared this to two previously reported case series where adult patients with severe respiratory failure received positive pressure ventilation without ECMO and had survival rates of 55.6% and 42%. Although this was not a randomized trial or even a direct comparison of the two treatments, the ECMO survival rate of 66% was much better than the 9.5% in the original randomized clinical trial.(4) It must be noted that the survival rates for patients receiving only mechanical ventilation also improved dramatically over the twenty-year period. In addition, two groups published promising results of case series of adults with ARDS who underwent treatment according to predefined algorithms that used ECMO for the most severely ill.(13, 14) Patients that required ECMO had survival rates of 55% and 62%. These survival rates are extremely important because the criterion for implementing ECMO in both algorithms was deterioration or lack of response to conventional therapy, which included mechanical ventilation, permissive hypercapnia, inhaled nitric oxide, and prone positioning. Therefore these relatively high survival rates were in patients that were deteriorating despite traditional therapies.

Robert Bartlett, at the University of Michigan (who also conducted research earlier at the University of California, Irvine), is widely regarded as the founding father of ECMO. He has contributed the most research regarding ECMO and has built a huge ECMO center, which also runs ELSO and compiles the ELSO Registry. In 2004, his group published a case series of its experience using ECMO in adults with ARDS.⁽¹⁵⁾ From 1989 to 2003, they used ECMO in 255 adults with severe ARDS refractory to all other treatments and 52% survived to hospital discharge. Later in 2009, the same group released data from the ELSO Registry and reported a 50% survival to hospital discharge (including patients that were transferred to other hospitals) in 1,473 adult patients who were supported by ECMO for respiratory failure from 1986-2006.⁽¹⁶⁾

In 2009, a multi-center randomized controlled study in the United Kingdom, known as the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial, concluded that ECMO improves survival in adults with severe acute respiratory failure and is cost-effective.⁽¹⁷⁾ From 2001 to 2006, they randomly assigned 180 adults with severe but potentially reversible respiratory failure to receive continued conventional management or be considered for ECMO treatment. The primary outcomes were death or severe disability before hospital discharge and 6 months after randomization. Of 90 patients selected for consideration of ECMO, 68 (75%) received ECMO and 57

(63%) survived to six months without disability. Of the patients that received ECMO, the survival rate was 63% as well. Only 47% of the patients selected for conventional management survived to six months without disability. In addition to measuring survival, this trial also analyzed the cost-utility of ECMO and predicted the cost per quality-adjusted life-year (QALY) of ECMO to be £19,252 (~\$31,000 at the time of publication). This is regarded as cost-effective by the National Institute for Health and Care Excellence of the Department of Health in the United Kingdom.(18)

Around the same time that the results of this landmark trial were being released, the world was hit by the H1N1 influenza pandemic, resulting in many cases of ARDS with a much higher percentage of young, healthy adults affected relative to seasonal influenza.(19) An observational study of 68 patients with ARDS due to H1N1 influenza who were treated with ECMO in 15 ICUs in Australia and New Zealand in 2009 revealed a 79% survival rate.(20) This rate is slightly misleading though because at the time of article submission, 16 (24%) patients survived to ICU discharge, but remained as hospital inpatients and six (9%) remained in the ICU, two of whom were still on ECMO. Nonetheless, ECMO was proving to be effective in treating patients with H1N1-related ARDS. A retrospective cohort study from the UK came to a similar conclusion.(21) Eighty patients with ARDS, due to H1N1, were referred to one of four adult

ECMO center in the UK, where 69 (86.3%) received ECMO and 58 (72.5%) survived to hospital discharge. The study used a few different methods to match controls of patients with similar degrees of illness that were not referred to an ECMO center. These non-ECMO-referred patients had survival rates that ranged from 47.5% to 53.3%. Even with different methods of pairing and multiple sensitivity analyses, the patients that were referred to a center capable of using ECMO did significantly better.

Although most of the adult ECMO research has focused on its use in patients with respiratory failure, multiple observational studies and case series have suggested the potential benefit of ECMO in treating adults suffering from cardiac failure. Cardiac arrest results in very poor outcomes, as reported in the most recent statistics available for the United States.⁽²²⁾ The survival to hospital discharge in 2011 for adults that suffered cardiac arrest outside of a hospital and were assessed by EMS was 6.7%. This survival rate increases to 31.7% when the cardiac arrest was witnessed by a bystander and the patient was found to have a shockable rhythm, but this was a minority of the cases. When cardiac arrest occurs in the hospital, the outcomes are better, but still not great. The overall survival rate in 2011 was 22.7%. This increases to 41.5% for patients found to have a shockable rhythm. Given the poor outcomes of cardiac arrest treated with conventional cardiopulmonary resuscitation (CPR) and that defibrillators often

cannot be used because the rhythm is not determined to be shockable, some groups started exploring the use of ECMO as a possible therapy.

The use of ECMO during resuscitation is known as extracorporeal CPR (ECPR). In 1999, the ECMO center at the University of Michigan published its outcomes using ECPR.(23) Over a seven-year period, 22 adult patients underwent ECPR and nine (41%) survived to hospital discharge. The group concluded that the biggest challenge it faced was patient selection. In the moment, it can be very difficult to determine which patients would benefit from ECPR and then to implement the therapy quickly with minimal complications.

In an attempt to better compare the outcomes of ECPR versus conventional CPR in adults with cardiac arrest, a group in Taiwan did a 3-year prospective observational study.(24) The 59 patients who received ECPR did significantly better than the 113 patients who only received conventional CPR in three outcomes: survival to hospital discharge, 30-day survival, and 1-year survival. The rate of survival to hospital discharge was 29% for the ECPR group versus 12% for the conventional CPR group. Therefore, they concluded that ECPR had both short-term and long-term survival benefits compared to conventional CPR in patients with in-hospital cardiac arrest of cardiac etiology.

In 2011, a group in Korea published results that came to the same conclusion regarding the benefits of ECPR over conventional CPR in patients with in-hospital cardiac arrest.(25) In a retrospective, single-center study using propensity score matching, the survival to hospital discharge rate with minimal neurologic damage in the ECPR group was significantly higher than in the conventional CPR group. There was also a significant difference in 6-month survival. This study was very similar to the one in Taiwan, although the inclusion criteria here allowed arrests of some noncardiac origins. A striking finding in this study was that in patients with refractory arrest for greater than 30 minutes, the survival rate was only 1.3% in the conventional CPR group, whereas it was 19.2% in the ECPR group. They believed that ECMO allowed for an extension of the time window for effective resuscitation.

In 1999, the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial reported that early revascularization should be strongly considered for patients with acute myocardial infarction complicated by cardiogenic shock.(26) Years later, a group in Japan decided to ask the question: should we emergently revascularize occluded coronaries for cardiac arrest patients using rapid-response ECMO and intra-arrest percutaneous coronary intervention (PCI)?(27) To answer this, Kagawa et al conducted a retrospective, multi-center study. Between 2004 and 2011, 86

patients with acute coronary syndrome who were not responding to conventional CPR were put on ECMO. Intra-arrest PCI was performed in 61 (71%) patients. Out of all 86 patients put on ECMO, the rate of return of spontaneous circulation (ROSC) was 88% and 30-day survival rate was 29%. The study concluded that rapid-response ECMO followed by intra-arrest PCI is feasible and allows for better outcomes in patients who are unresponsive to conventional CPR.

Other ECMO centers also reported favorable outcomes with the use of ECMO in adults with cardiac arrest. A group in France placed 40 patients on ECMO who presented with refractory cardiac arrest and 17 (43%) patients survived ECMO with eight (20%) patients surviving to hospital discharge.(28) Six patients were weaned directly off of ECMO with five of these patients surviving to hospital discharge. Nine patients were bridged to an LVAD with three of these patients surviving to hospital discharge. Two patients were directly bridged to cardiac transplantation, but neither of these patients survived to hospital discharge. A different group in France published their outcomes of 81 patients that received ECMO for refractory cardiogenic shock with 34 (42%) patients surviving to hospital discharge.(29) These survival rates were considered by the authors to be extremely promising, as they concluded that

almost all of these patients would have died without ECMO since they were already unresponsive to conventional treatment.

The ECMO center at the University of Michigan published further results in 2001 on the use of ECMO in adults with cardiac failure.(28) Given the increasingly successful use of left ventricular assist devices (LVADs) as a bridge to transplant, the group decided to use ECMO as a bridge to LVAD calling it a "bridge to bridge." Out of 33 adult patients placed on ECMO due to cardiac arrest or severe hemodynamic instability, 10 patients survived to LVAD implantation, one was bridged directly to a heart transplant, five were weaned from ECMO, and 16 died on ECMO. Overall, 12 (36%) patients survived to hospital discharge and were still alive one year after discharge. For patients that received LVADs, the survival rate was 80%. This showed that ECMO may be useful even in patients with cardiac disease that is so severe that recovery is unlikely. Here it would be used as a bridge directly to transplant or to a longer-term bridge to transplant such as an LVAD.

In summary, the utilization of ECMO has slowly increased as different centers research its use in various clinical scenarios; the survival rates have improved for both pulmonary and cardiac etiologies; and it is considered cost-effective in the UK. In addition, interest in ECMO has increased in recent years.

Statement of Purpose

Hypothesis: The utilization of ECMO in adults within the United States has increased in recent years, and for these patients, the survival rates and costs have both increased.

Specific Aims:

- Given the increase in research articles over the past decade regarding the use of ECMO in adults, analyze the utilization of ECMO in adults within the United States to identify recent temporal trends
- Analyze the survival rates of ECMO and look for causes of variation
 - If there has been an increase in utilization, has there been a change in the survival rates?
 - Are there differences in the survival rates among hospitals with different characteristics, specifically with regards to size, type, or volume of adult ECMO cases?
 - Given the difficulties of patient selection, are there specific comorbidities that increase a patient's likelihood of survival?
- Analyze the costs of ECMO and identify if it has become more expensive over time

Methods

All of the analyses presented in this dissertation were conducted by the author.

Data Source

Data was obtained from the Nationwide Inpatient Sample (NIS), a part of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ), from the years 1999 to 2011.(30) The NIS is the largest publicly available all-payer hospital inpatient care database in the United States and contains clinical and resource use information. Its large sample size makes it suitable to study ECMO, which is an uncommon procedure with relatively few cases. A unique feature of this database is that it includes all patients despite the payer. Many large databases that are used for this type of research consist of only patients on Medicare and/or Medicaid, whereas this database includes those patients, but also patients with private insurance and patients without any insurance. Each year contains data for approximately 8 million inpatient hospital stays from about 1,000 hospitals sampled to approximate a 20% stratified sample of all US nonfederal hospitals. All discharges from sampled hospitals are included in the dataset. The hospitals are divided into strata by five characteristics: ownership/control, bed size, teaching status, urban/rural location, and geographical region. Although there are some

states that do not contribute data to the NIS, weighting the discharge-level observations using the complex sampling format provides estimates for all US hospitalized patients in a given year. For 2011, over 97 percent of the US population is represented with only Alabama, Idaho, and New Hampshire not contributing data. Since all data in the NIS is de-identified, this study was granted exemption from Institutional Review Board approval.

Calculating Utilization Rates, Survival Rates, and Costs per Day

Although all cases from 1999 to 2011 were initially looked at, the focus of this dissertation is on the most recent six years available, 2006 to 2011. The focus is on recent trends in utilization because there was an increase in the amount of publications regarding the use of ECMO in adults, signaling a growing interest. Another reason for limiting the years to six has to do with the database. The NIS makes slight alterations every year, sometimes adding or removing variables and sometimes altering variable definitions. In 1998 and 2002, there were major changes to the NIS, and in 2005, the AHA altered the definition of community hospitals, which affected the sampling frame of the NIS. Therefore, going back to 2006 gives enough data to identify trends, while not compromising the consistency of the data. To be clear, the NIS is designed for analysis of trends over years, so every effort is made to be consistent.

The NIS uses procedure codes from the International Classification of Diseases, 9th edition, Clinical Modification (ICD-9-CM), Volume 3. Patients who received ECMO were identified using the code 39.65. All patients greater than or equal to 18 years of age were included. Utilization rates were calculated as the number of cases of adult patients who received ECMO per one million adult inpatient stays. The survival rates were defined as the percentage of adult patients who received ECMO during hospitalization and survived to hospital discharge, which includes transfer to another acute care hospital.

To analyze the survival rates, hospitals were categorized by bed size, type, and volume of adult ECMO cases. The NIS categorizes hospitals into three sizes (small, medium, and large) based on bed size with the definitions dependent on the type (defined below) and geographic region. For example, in the Northeast Region, a rural hospital is characterized as small if it has less than 50 beds and as large if it has more than 100 beds, whereas an urban teaching hospital is characterized as small if it has less than 250 beds and as large if it has more than 425 beds. For more details on the categories, please see the NIS documentation.⁽³¹⁾ The NIS splits the hospitals into three categories based on type: rural, urban non-teaching, and urban teaching. Hospitals are designated as rural if they are located in a county with a Core Based Statistical Area (CBSA) type of micropolitan or non-core and as urban if they are located in a county with

a CBSA type of metropolitan. A hospital is designated as a teaching hospital if it has an American Medical Association-approved residency program, is a member of the Council of Teaching Hospitals, or has a ratio of full-time equivalent residents to beds of 25% or higher. The NIS does not divide the rural category by teaching status. Hospitals were also divided into two categories depending on their volume of adult ECMO cases with high-volume hospitals performing at least six cases annually and low-volume hospitals performing less than six cases annually. This categorization was designed based on the ELSO recommendation that centers perform at least six ECMO cases annually.(2)

Hospitalization costs were estimated using the total hospital charges for each patient adjusted using the HCUP Cost-to-Charge ratios for each hospital, which are based on information obtained from the Centers for Medicare and Medicaid Services.(32) The total cost for each patient was divided by the length of stay to find the cost per day. Medians for each year were used to compare costs over time instead of means because medians are less influenced by outliers and health care cost distributions are skewed.

All costs were adjusted for inflation using the Consumer Price Index (CPI) Inpatient Hospital Services inflation multiplier.(33) Inflation can be significant over just a few years, which is why all costs were adjusted even though the time

period only spans six years. Also, in the United States, health care inflation has outpaced the inflation of the national economy over the last decade. The growth rate of the US gross domestic product (GDP) averaged 5.5% per year during 1999-2007, whereas the growth rate of health care spending averaged 7.2% per year.⁽³⁴⁾ The CPI is often presented in the media as one rate representing inflation for the entire national economy, but it can be broken down to represent specific industries and even specific industry segments. Since ECMO is a therapy only provided in an ICU, it is more accurate to use an inflation rate that represents all inpatient hospital services, which is higher than the national inflation rate. In order to verify that this assumption is correct, the annual growth rates for hospitalization costs for all of the patients in the NIS for the years 2006 to 2011 were compared to the inflation rates for the entire economy, the inflation rates for all health care spending, and the inflation rates for health care spending specific to inpatient hospital services (data not shown). The result was that the CPI Inpatient Hospital Services inflation rate most closely matched the actual growth rate for all hospitalization costs in the United States.

Validation of NIS Data

The Extracorporeal Life Support Organization (ELSO, Ann Arbor, MI) Registry ⁽³⁵⁾, which collects data from over 100 centers worldwide on the use,

complications, and outcomes of patients who received ECMO was used to validate the trends found using the NIS. The data is voluntarily self-reported from ECMO centers. Only data regarding adults from centers in the United States was used for comparison. As with the NIS, all data was de-identified and cleaned prior to use.

Statistical Analyses

Simple linear regression analyses were conducted to compare ECMO utilization rates, survival rates, costs per day, and total costs per patient from 2006 to 2011 using summary datasets for each year, weighted using the NIS discharge weights in order to produce national estimates. Patient characteristics in the years 2006 and 2011 were compared using a t-test for mean age comparison and chi-square tests for comparisons of categorical variables. When analyzing the difference of two survival rates, which are population estimates compiled from the survey data provided in the NIS, a Wald test was used.

A multivariable binomial logistic regression incorporating all adult patients, unweighted, who underwent ECMO from 2006 to 2011 (n=1335) was performed to identify comorbidities that significantly increase mortality, adjusted for gender, age, and the patient's pre-treatment risk of mortality, which is a categorical variable with four levels of disease severity provided in the NIS

using software developed by 3M Health Information Systems and is based on patient characteristics and stage of disease. Comorbidities were included if they were clinically relevant and present in at least 10% of the sample to ensure an adequate sample size. To confirm the findings, a forward stepwise logistic regression with a significance level of 0.05 using the same independent variables was conducted. For all statistical tests, two-tailed *p*-values less than 5% were considered a priori to be statistically significant. Quantitative analyses were performed using Stata 12 (StataCorp LP, College Station, Texas).

Results

Patient Characteristics

When comparing adult patients who received ECMO in 2006 to those in 2011 (Table 1), there were no significant differences in age, gender, payer mix, the proportion of patients living in ZIP codes with the lowest 25% median household income, or major diagnostic category. There were significantly more patients in 2011 compared to 2006 categorized as having an extreme risk of mortality (78% vs. 44%, $p < 0.001$). Regarding comorbidities, there were more patients in 2011 compared to 2006 with coagulopathies, fluid/electrolyte disorders, pulmonary circulation disorders, and weight loss (Table 2).

Table 1. Patient characteristics for adults who received extracorporeal membrane oxygenation (ECMO) in the United States in 2006 and 2011^A

| | 2006 | 2011 | <i>p</i> -value |
|--|---------------|-----------------|-----------------|
| Number of Cases - no. [95% CI] | 375 [200-549] | 2004 [889-3119] | |
| Age - yr ^B | 50 ± 17 | 50 ± 18 | 0.88 |
| Female - % | 49 | 38 | 0.12 |
| Primary Payer - % | | | |
| Medicare | 32 | 29 | 0.25 |
| Medicaid | 13 | 14 | |
| Private | 44 | 46 | |
| Uninsured | 3 | 7 | |
| Other ^C | 9 | 4 | |
| Median Household Income - % ^D | | | |
| Low | 31 | 26 | 0.46 |
| Not Low | 69 | 74 | |
| Risk of Mortality - % ^E | | | |
| Minor | 8 | 1 | <0.001 |
| Moderate | 13 | 3 | |
| Major | 35 | 18 | |
| Extreme | 44 | 78 | |
| Major Diagnostic Category - % | | | |
| Cardiac | 57 | 50 | 0.58 |
| Respiratory | 26 | 28 | |
| Other | 17 | 22 | |

^A Characteristics were compared using chi-square tests, unless otherwise specified. All values and proportions are national estimates calculated using the NIS discharge weights. Percentages may not sum to 100 due to rounding.

^B Values are means ± SD. Means were compared using a *t*-test.

^C Includes Worker's Compensation, CHAMPUS, CHAMPVA, Title V, and other government programs.

^D Patients living in ZIP codes with the lowest 25% median household income are classified as "Low."

^E Four categories developed by 3M Health Information Systems to predict mortality risk using severity of illness and other patient characteristics.

Table 2. Comorbidities of adults who received extracorporeal membrane oxygenation (ECMO) in the United States in 2006 and 2011

| | 2006 | 2011 | <i>p</i> -value |
|--------------------------------|------|------|-----------------|
| Comorbidities - % | | | |
| Anemia | 10 | 18 | 0.15 |
| Congestive Heart Failure | 29 | 33 | 0.47 |
| Chronic Pulmonary Disease | 12 | 17 | 0.27 |
| Coagulopathy | 25 | 56 | <0.001 |
| Diabetes (uncomplicated) | 11 | 21 | 0.13 |
| Hypertension | 26 | 39 | 0.09 |
| Fluid/Electrolyte Disorder | 37 | 66 | <0.001 |
| Obesity | 10 | 17 | 0.20 |
| Peripheral Vascular Disease | 7 | 11 | 0.29 |
| Pulmonary Circulation Disorder | 9 | 22 | 0.01 |
| Renal Failure | 17 | 16 | 0.84 |
| Valvular Disease | 16 | 14 | 0.75 |
| Weight Loss | 8 | 22 | 0.003 |

Utilization

The rates of ECMO cases per million adult discharges from 1999 to 2011 are shown in Figure 1. There was no significant difference from 1999 to 2007 (p for trend = 0.14), but the rate increased 433% from 11.4 (95% CI, 6.1-16.8) in 2006 to 60.9 (95% CI, 28.1-93.7) in 2011. A simple linear regression run from 2006 to 2011 (Table 3) indicates that there was a significant increase in the rate of ECMO cases per million adult discharges throughout the years (p for trend = 0.001).

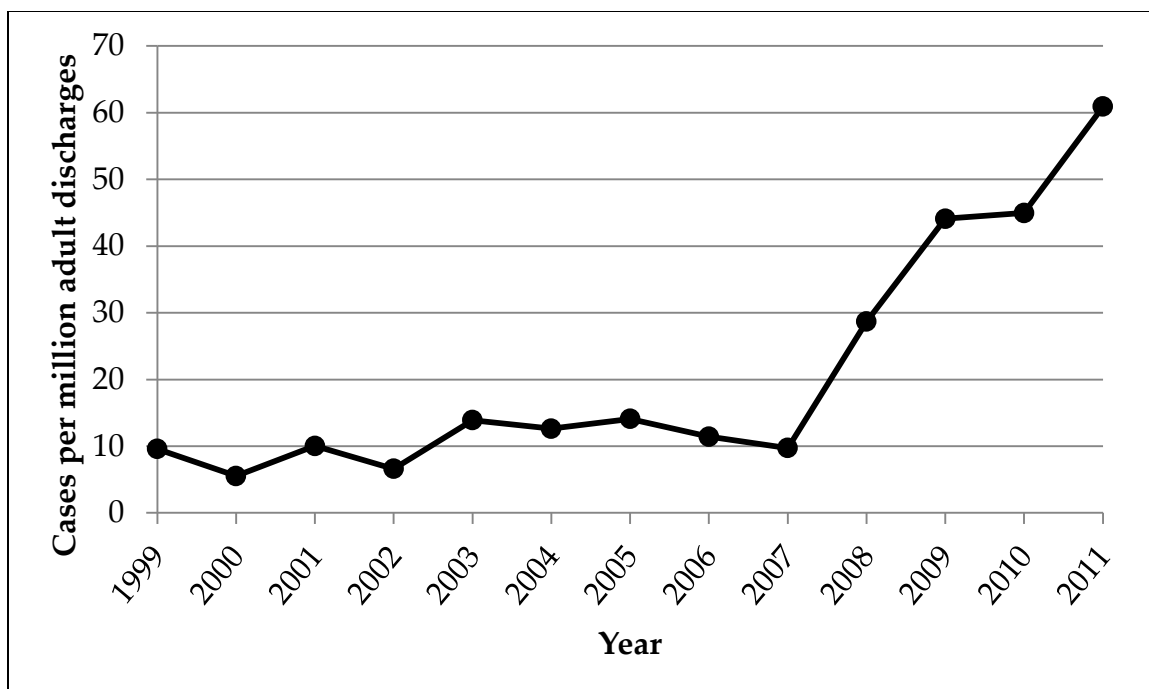


Figure 1. Utilization rates of extracorporeal membrane oxygenation (ECMO) in adults in the United States from 1999 to 2011.

Table 3. Average yearly changes for adults who received extracorporeal membrane oxygenation (ECMO) in the United States from 2006 to 2011

| | Univariable (95%CI) | <i>p</i> -value |
|---|------------------------------------|-----------------|
| ECMO cases per million adult discharges - no. | 10.5 (7.1 to 14.0) | 0.001 |
| Survival rate - % ^A | 1.7 (-0.9 to 4.2) | 0.14 |
| Cost per day - 2011 US dollars ^B | -990.7 (-2,114.5 to 133.1) | 0.07 |
| Cost per patient - 2011 US dollars ^B | 1,073.1 (-16,624.3 to 18,770.4) | 0.87 |

^A Values are presented as percentage points.

^B All costs were adjusted to 2011 US dollars using the Consumer Price Index Inpatient Hospital Services inflation multiplier.

In Figure 2, the utilization rates are broken down by quarter-year. The first quarter represents January through March; the second quarter represents April through June; the third quarter represents July through September; and the fourth quarter represents October through December. There was a steady increase throughout the six years with little seasonal variation, except in 2009 when there was a large jump in the fourth quarter relative to the other quarters of the year.

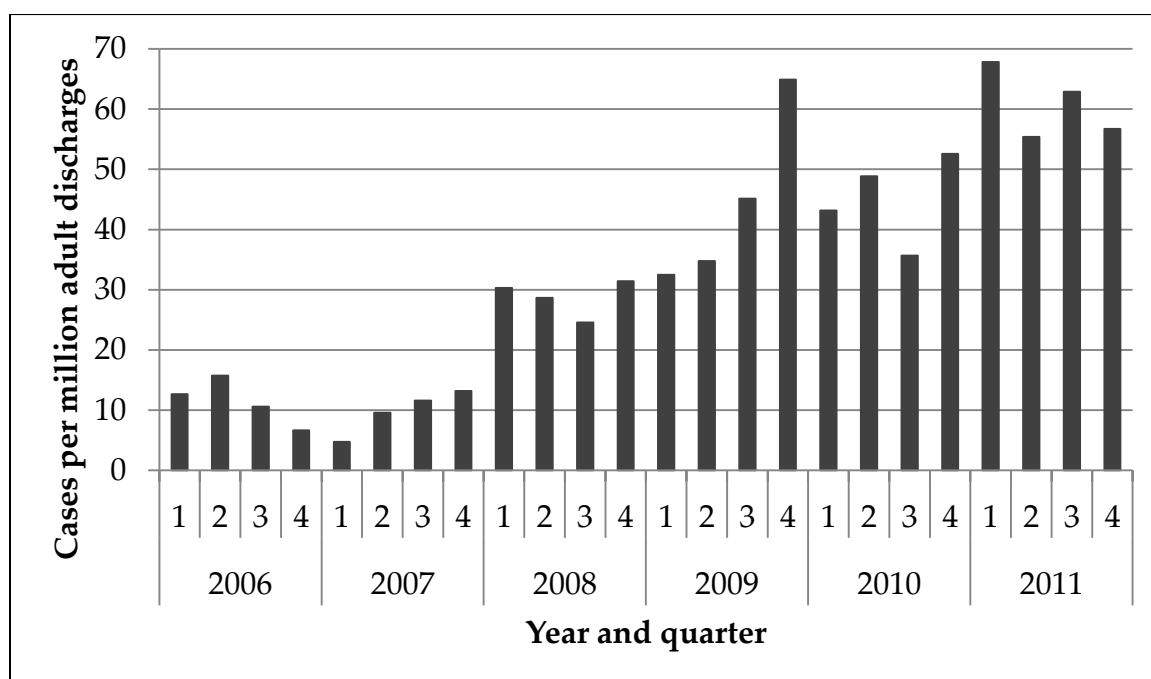


Figure 2. Utilization rates of extracorporeal membrane oxygenation (ECMO) in adults in the United States by quarter from 2006 to 2011.

Survival

The survival rates, defined as the percentage of adults who received ECMO and survived to hospital discharge, for 2006 to 2011 are shown in Figure 3. In 2006, the survival rate was 30% (95% CI, 21-39%), and in 2011, it was 42% (95% CI, 32-52%), representing a 12% increase, although this increase is not statistically significant. A simple linear regression run from 2006 through 2011, shown in Table 3 (p. 23), indicates that although there was a trend towards an improvement in the survival rate, it is not statistically significant (p for trend = 0.14). In addition, the difference between 2006 and 2011 is not statistically significant ($p = 0.09$).

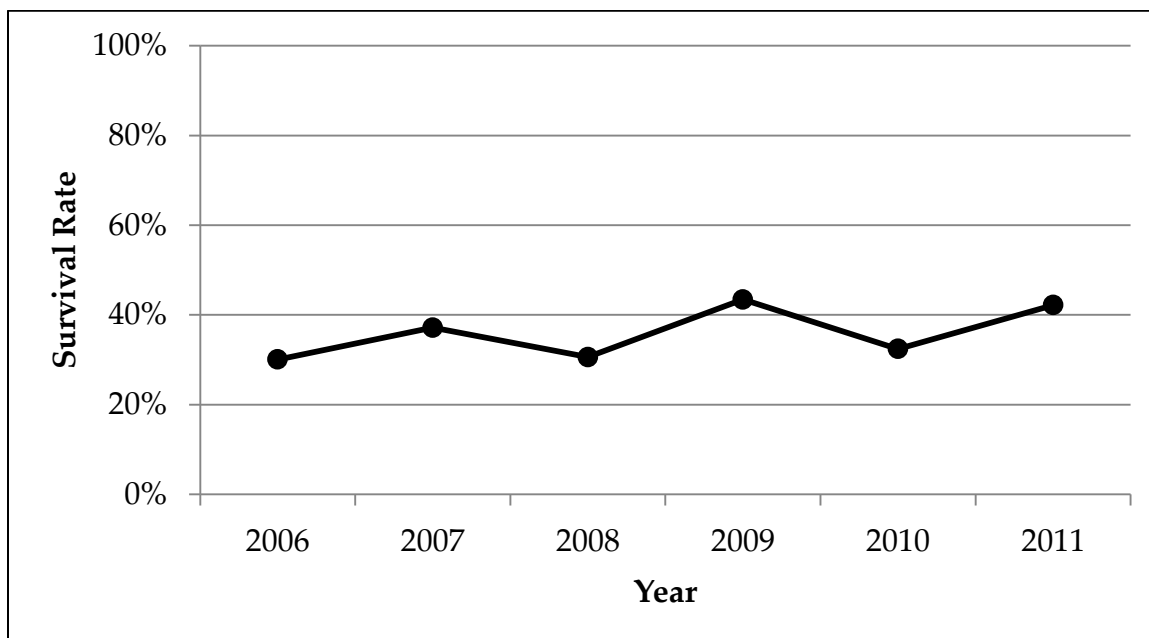


Figure 3. The percentage of adults that underwent extracorporeal membrane oxygenation (ECMO) during hospitalization in the United States from 2006 to 2011 and survived to hospital discharge.

The definition of survival in the NIS can be misleading because it defines overall survival as the survival to hospital discharge, which includes transfers to other hospitals. Consider the hypothetical case where a hospital that has a very complicated and sick patient on ECMO transfers the patient to another hospital where he/she then dies. For the original discharge at the first hospital, the NIS would classify the patient as a survivor because he/she survived to discharge even though he/she was transferred to another hospital. Unfortunately, the NIS does not provide a way to track patients as they are transferred to other hospitals. In order to clarify the issue, the dispositions of all the survivors of ECMO from 2006 to 2011 were looked at (Figure 4). Approximately 16% were transferred to other acute care hospitals and 84% were discharged home or transferred to long-term care facilities.

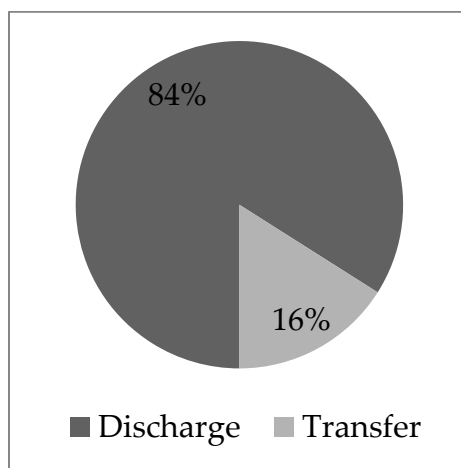


Figure 4. Disposition, by percentage, of all adult survivors who received extracorporeal membrane oxygenation (ECMO) from 2006 to 2011 (n=6588). Discharge: discharged home or to a long-term care facility. Transfer: transferred to another acute care hospital.

Since the NIS does not allow the tracking of individual patients, the outcomes of the patients after transfer are unknown. To estimate the outcomes, the survival rates of patients that were received as transfers and then underwent ECMO were identified (Figure 5). For this analysis, data is only available from 2008 to 2011. Approximately 36% of the patients were received as transfers from other acute care hospitals and had an overall survival rate of 37% (95% CI, 29-45%). Patients that were not transfers had a survival rate of 39% (95% CI, 34-44%). These two survival rates do not significantly differ ($p = 0.54$).

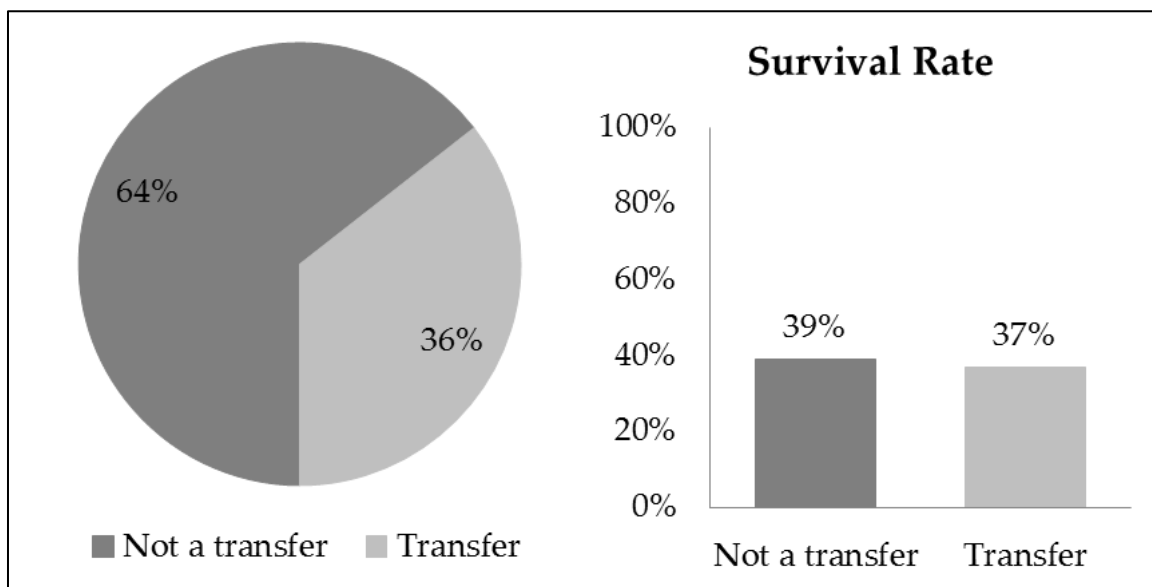


Figure 5. Sample consists of all adults who received extracorporeal membrane oxygenation (ECMO) in the United States from 2008 to 2011 (n=5895). Left: Proportion of patients who were received as transfers from other acute care hospitals. Right: Percentage of patients from each group who survived to discharge.

When grouping all adult ECMO cases from 2006 to 2011 by hospital size (Figure 6), the large majority of the cases (90%) took place in large hospitals with an overall survival rate of 37% (95% CI, 31-42%). Only 2% of the cases took place in small hospitals with an overall survival rate of 25% (95% CI, 9-41%). The remaining 8% of cases took place in medium-sized hospitals with an overall survival rate of 51% (95% CI, 42-61%). The survival rate for medium-sized hospitals is significantly better than for large ($p = 0.01$) and small hospitals ($p = 0.006$). There is no statistically significant difference in survival rates for large and small hospitals ($p = 0.17$). Survivors from medium-sized hospitals were much more likely to have been transferred to another hospital (49%), while survivors from large hospitals were much less likely (11%).

When grouping all adult ECMO cases from 2006 to 2011 by hospital type (Figure 7), the large majority of cases (93%) were conducted at urban teaching hospitals with an overall survival rate of 36% (95% CI, 31-42%). Urban non-teaching hospitals, which conducted 6% of the cases, had a survival rate of 55% (95% CI, 44-66%). The difference in survival rates between urban teaching and non-teaching hospitals is statistically significant ($p = 0.004$). Rural hospitals had very few cases (0.3%) with a survival rate of 41% (95% CI, 0-84%, the large standard error because of the small sample size limits the ability to compare this to the other two survival rates). Survivors from rural and urban non-teaching

hospitals were much more likely to have been transferred to another hospital (50% and 56%) compared to survivors from urban teaching hospitals (12%).

When grouping all adult ECMO cases from 2006 to 2011 by hospital volume of adult ECMO cases (Figure 8), the percentage of adult ECMO cases that were performed at low-volume centers (less than six cases annually) was 27% from 2006 to 2011 with an overall survival rate of 40% (95% CI, 34-45%), and the percentage of cases performed at high-volume centers (at least six cases annually) was 73% with an overall survival rate of 37% (95% CI, 30-44%). These survival rates are not significantly different ($p = 0.53$). Survivors from low-volume centers were much more likely to have been transferred to another hospital (44%) compared to survivors from high-volume centers (5%). From 2006 to 2011, the percentage of cases that were performed in high-volume centers increased from 37% to 78%.

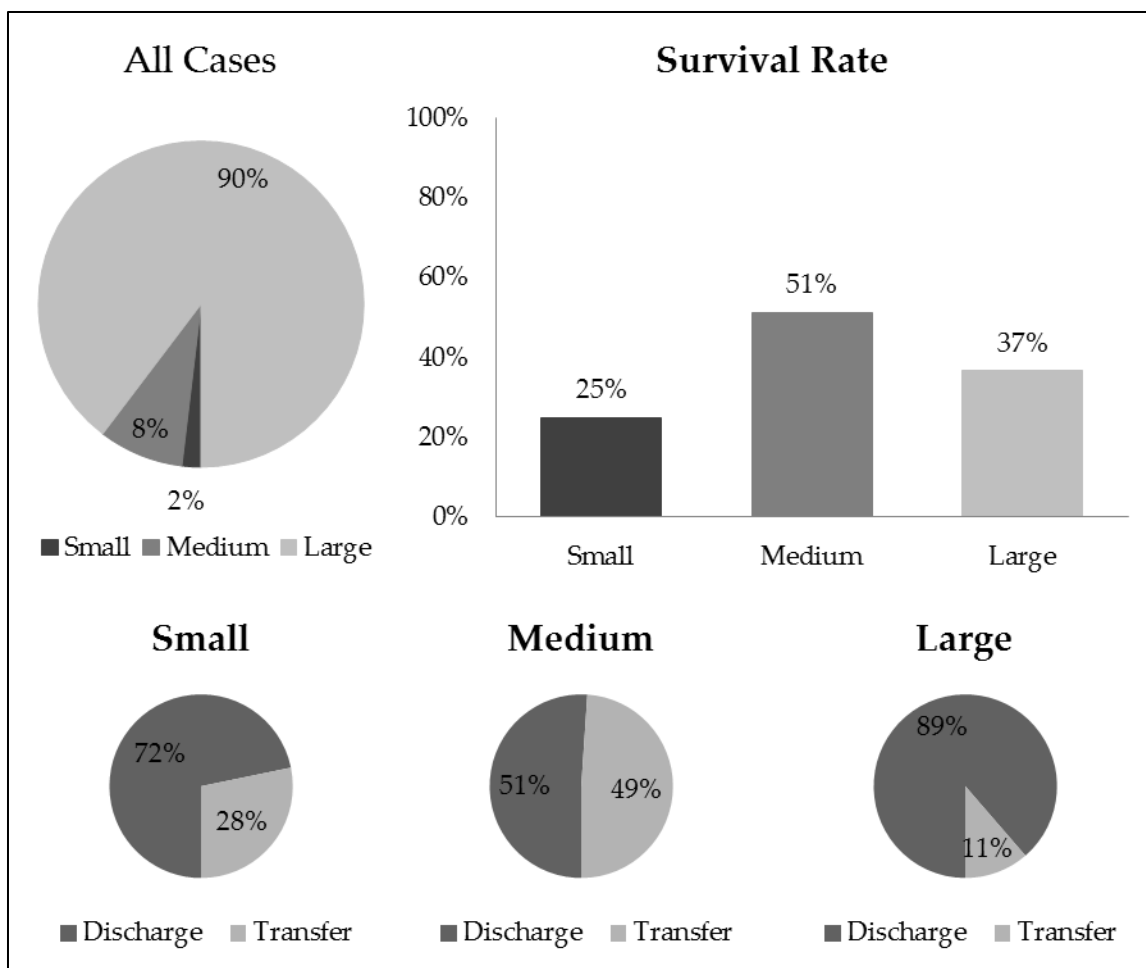


Figure 6. Sample consists of all adults who received extracorporeal membrane oxygenation (ECMO) from 2006 to 2011 grouped by hospital size (n=6588). Top Left: Proportion of cases performed. Top Right: Percentage of patients who survived to discharge. Bottom: Disposition of survivors. Transfer refers to a patient being transferred to another acute care hospital.

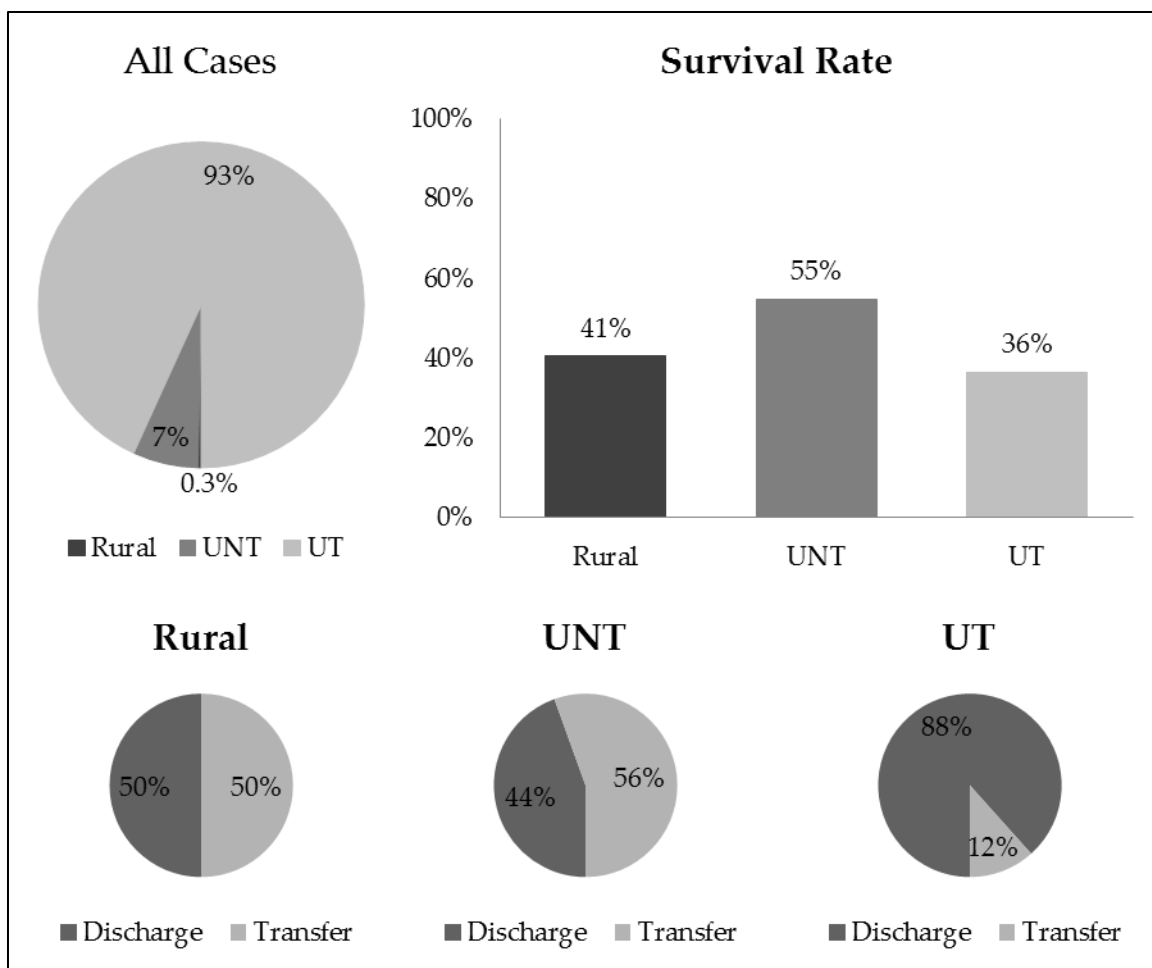


Figure 7. Sample consists of all adults who received extracorporeal membrane oxygenation (ECMO) from 2006 to 2011 grouped by hospital type (n=6588). Top Left: Proportion of cases performed. Top Right: Percentage of patients who survived to discharge. Bottom: Disposition of survivors. Transfer refers to a patient being transferred to another acute care hospital. Abbreviations: UNT – Urban non-teaching, UT – Urban teaching.

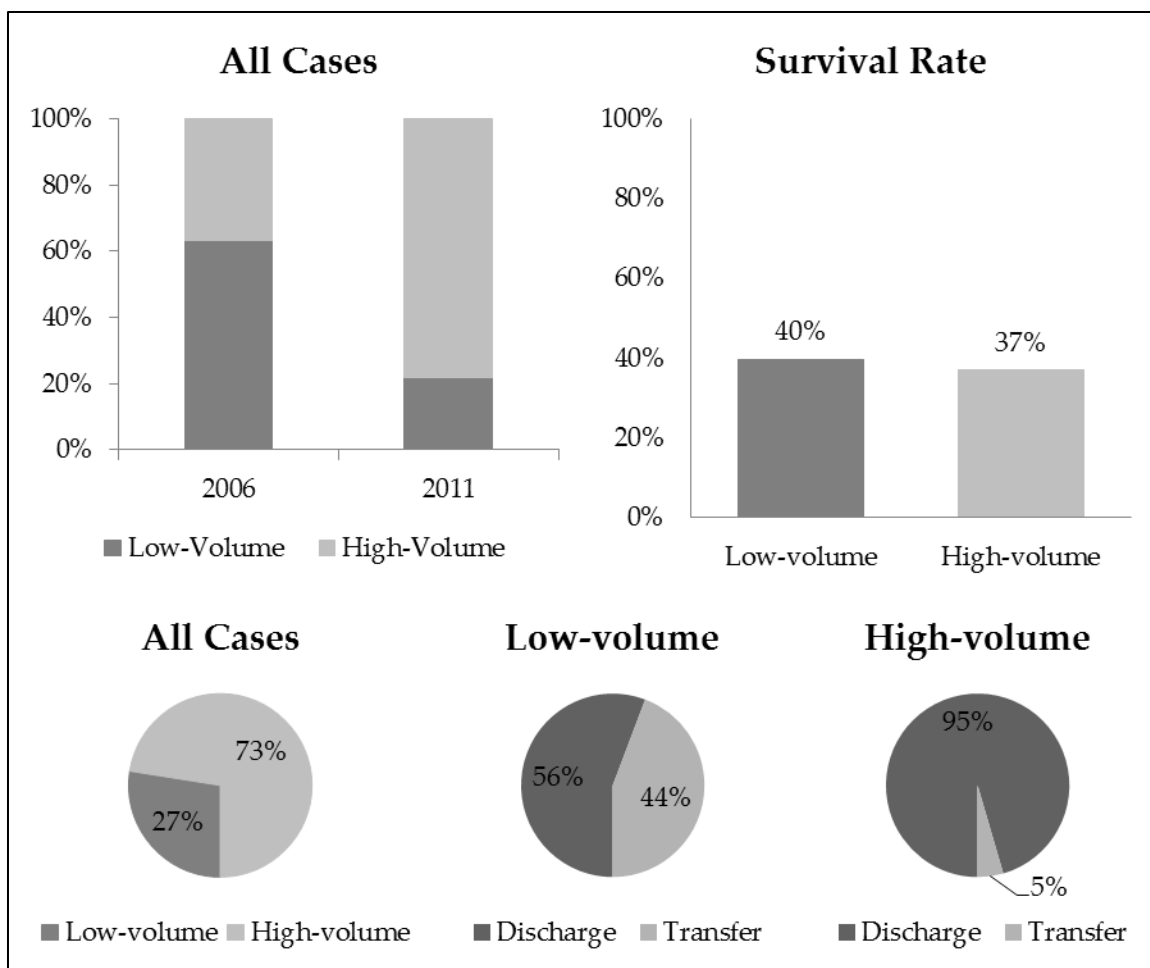


Figure 8. Sample consists of all adults who received extracorporeal membrane oxygenation (ECMO) from 2006 to 2011 grouped by hospital volume of adult ECMO cases (n=6588). Top Left: Proportion of cases performed in 2006 and 2011. Top Right: Percentage of patients who survived to discharge. Bottom Left: Proportion of all cases performed in the six-year period. Bottom Right: Disposition of survivors. Transfer refers to a patient being transferred to another acute care hospital. Categorizations: Low-volume – less than six cases annually, High-volume – at least six cases annually.

Since patient selection is one of the most difficult decisions for clinicians who use ECMO, a multivariable binomial logistic regression was conducted to determine the comorbidities that significantly increased the likelihood of mortality (Table 4). They were coagulopathy (OR, 1.35; 95% CI, 1.06-1.73; $p = 0.02$), renal failure (OR, 1.63; 95% CI, 1.10-2.40; $p = 0.01$), and valvular disease (OR, 1.60; 95% CI, 1.11-2.30; $p = 0.01$). A comorbidity that significantly decreased the likelihood of mortality was weight loss (OR, 0.38; 95% CI, 0.28-0.51; $p < 0.001$), defined as abnormal weight loss or protein-calorie malnutrition. When the analysis was conducted using a forward stepwise regression, the same comorbidities were again found to be significant, although the odds ratios change slightly (Table 5).

Table 4. Comorbidities predicting mortality for all patients (n=1335, unweighted sample), a multivariable binomial logistic regression

| Variable | Patients - no. (%) | Odds Ratio (95% CI) | p-value |
|--|-----------------------|------------------------|---------|
| Female | 499 (37) | 0.84 (0.66 to 1.06) | 0.14 |
| Age ≥ 65 | 292 (22) | 1.16 (0.86 to 1.55) | 0.34 |
| Extreme Risk of Mortality ^A | 1004 (75) | 1.99 (1.51 to 2.63) | <0.001 |
| Comorbidities | | | |
| Anemia | 206 (15) | 0.83 (0.59 to 1.15) | 0.26 |
| Congestive Heart Failure | 452 (34) | 1.16 (0.89 to 1.50) | 0.28 |
| Chronic Pulmonary Disease | 172 (13) | 1.03 (0.72 to 1.46) | 0.88 |
| Coagulopathy | 592 (44) | 1.35 (1.06 to 1.73) | 0.02 |
| Diabetes (uncomplicated) | 205 (15) | 0.92 (0.65 to 1.29) | 0.63 |
| Hypertension | 459 (34) | 0.93 (0.71 to 1.23) | 0.62 |
| Fluid/Electrolyte Disorder | 769 (58) | 1.17 (0.92 to 1.50) | 0.20 |
| Obesity | 149 (11) | 1.03 (0.70 to 1.51) | 0.88 |
| Peripheral Vascular Disease | 132 (10) | 1.37 (0.90 to 2.08) | 0.15 |
| Pulmonary Circulation Disorder | 220 (16) | 1.15 (0.84 to 1.59) | 0.39 |
| Renal Failure | 172 (13) | 1.63 (1.10 to 2.40) | 0.01 |
| Valvular Disease | 191 (14) | 1.60 (1.11 to 2.30) | 0.01 |
| Weight Loss | 246 (18) | 0.38 (0.28 to 0.51) | <0.001 |

^A Extreme risk is the highest risk out of four categories developed by 3M Health Information Systems to predict mortality risk using severity of illness and other patient characteristics.

Table 5. Comorbidities predicting mortality for all patients (n=1335, unweighted sample), a multivariable forward stepwise binomial logistic regression^A

| Variable | Patients - % | Odds Ratio (95% CI) | <i>p</i> -value |
|--|--------------|---------------------|-----------------|
| Extreme Risk of Mortality ^B | 1004 (75) | 2.20 (1.69 to 2.87) | <0.001 |
| Comorbidities | | | |
| Coagulopathy | 592 (44) | 1.35 (1.06 to 1.72) | 0.01 |
| Renal Failure | 172 (13) | 1.69 (1.16 to 2.44) | 0.006 |
| Valvular Disease | 191 (14) | 1.69 (1.19 to 2.40) | 0.004 |
| Weight Loss | 246 (18) | 0.39 (0.29 to 0.52) | <0.001 |

^A A significance level of 0.05 was used and the independent variables were the same as in Table 4.

^B Extreme risk is the highest risk out of four categories developed by 3M Health Information Systems to predict mortality risk using severity of illness and other patient characteristics.

Cost

The costs per day of hospitalization for adults who received ECMO, as well as the costs per patient were compared from 2006 to 2011 with the medians shown in Figure 9. All costs were adjusted to 2011 US dollars using the CPI Inpatient Hospital Services inflation multiplier. In 2006, the median cost per day was \$12,773 (interquartile range, IQR, \$7,376-23,290), and the median total cost per patient was \$97,305 (IQR, \$59,645-203,449). In 2011, the median cost per day was \$8,089 (IQR, \$5,778-14,962), and the median total cost per patient was \$117,336 (IQR, \$68,106-202,356). Two separate simple linear regressions run from 2006 to 2011, shown in Table 3 (p. 23), indicate that there were no significant

differences in the median costs per day (p for trend = 0.07) or in the median costs per patient (p for trend = 0.87).

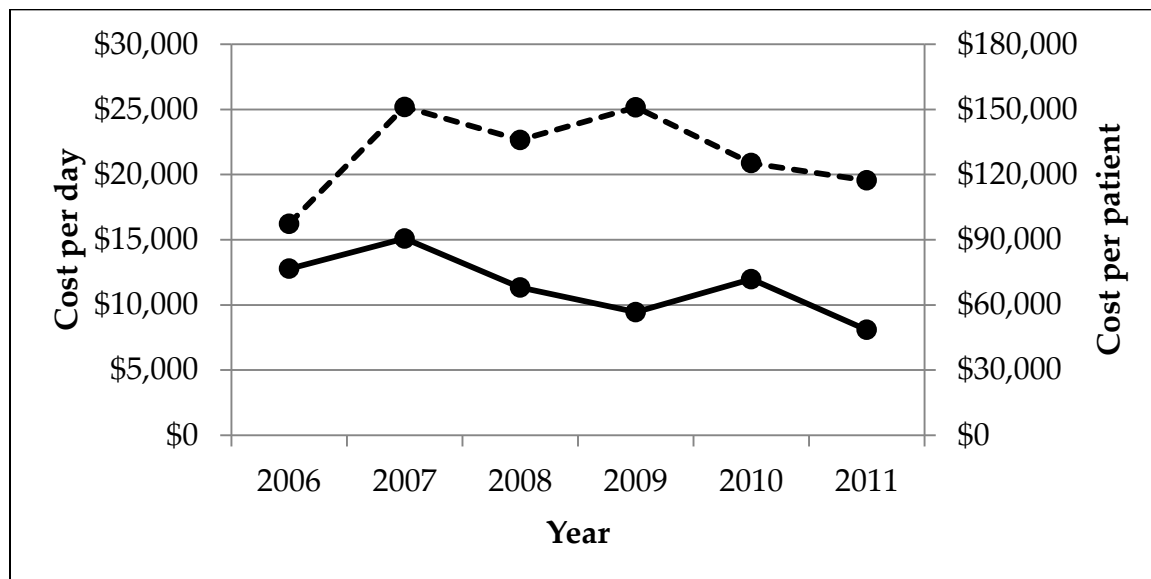


Figure 9. Median costs per day of hospitalization (solid line) and median total hospitalization costs per patient (dotted line) for adults who received extracorporeal membrane oxygenation (ECMO) from 2006 to 2011. All amounts adjusted to 2011 US dollars using the Consumer Price Index Inpatient Hospital Services inflation multiplier.

Validation of NIS Estimates

The ELSO Registry recorded a gradual increase from 82 adult ECMO cases in 1999 to 155 cases in 2007 (Figure 10). The number of cases then increased rapidly to 591 in 2011. The survival rate recorded by the ELSO Registry remained mostly constant from 2006 to 2011 (Figure 11), averaging 42% overall for the six year period. This is higher than the average survival rate over that time period in the NIS (38%), but a paired t-test shows that there is no significant

difference in survival rates between the ELSO Registry and the NIS from 2006 to 2011 ($p = 0.13$). Since the ELSO Registry receives its information from the clinicians directly, it is able to give a clear indication for ECMO. It splits the indications into two broad categories: respiratory and cardiac. As shown in Figure 12, the cases are split evenly between the two categories, but the survival rates differ. The respiratory cases have a higher survival rate (46%) than the cardiac cases (38%).

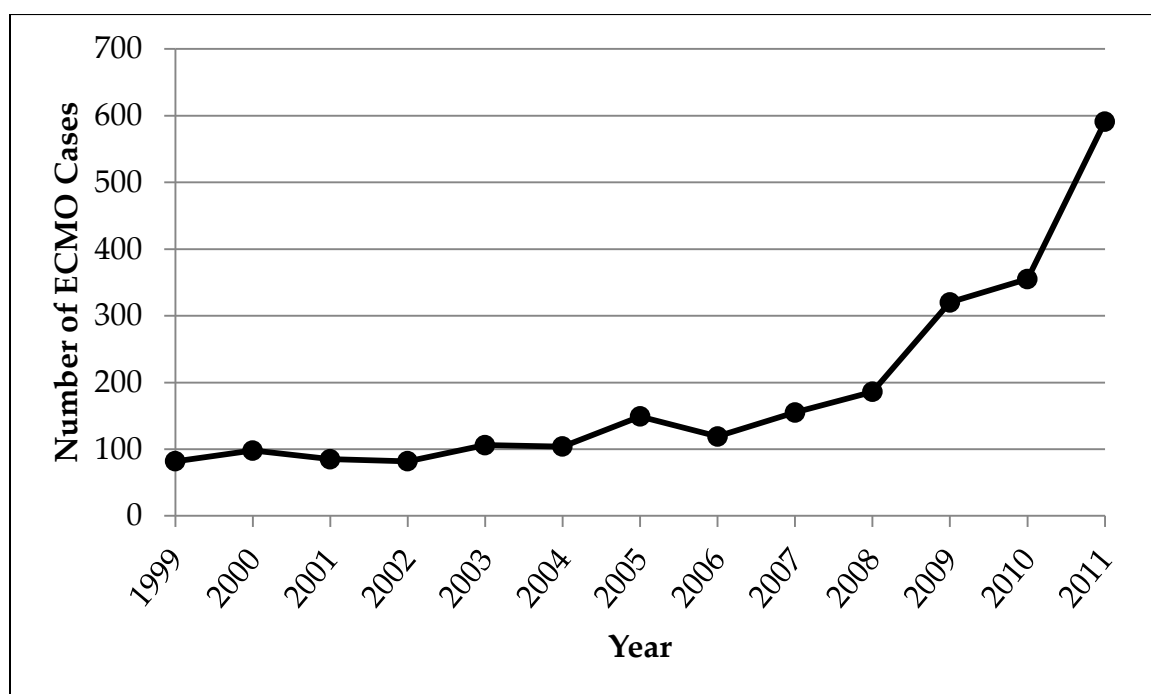


Figure 10. Total number of adult extracorporeal membrane oxygenation (ECMO) cases in the United States recorded by the Extracorporeal Life Support Organization (ELSO) Registry annually from 1999 – 2011.

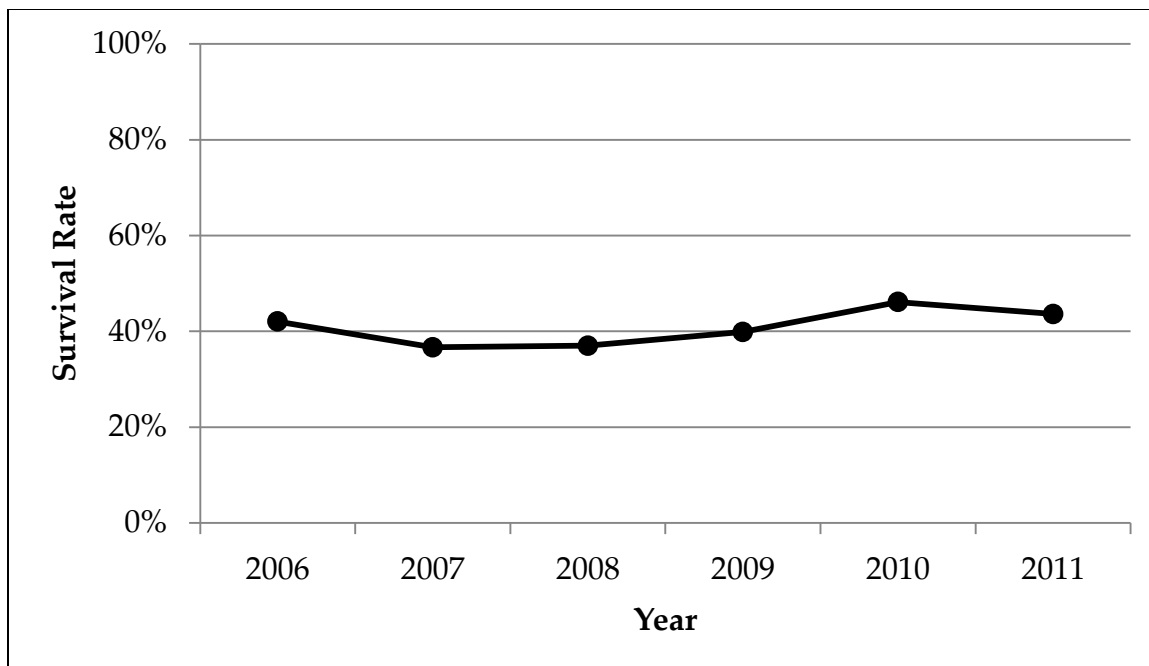


Figure 11. Percentage of adult extracorporeal membrane oxygenation (ECMO) cases that survived to discharge in the United States from 2006-2011 recorded by the Extracorporeal Life Support Organization (ELSO) Registry.

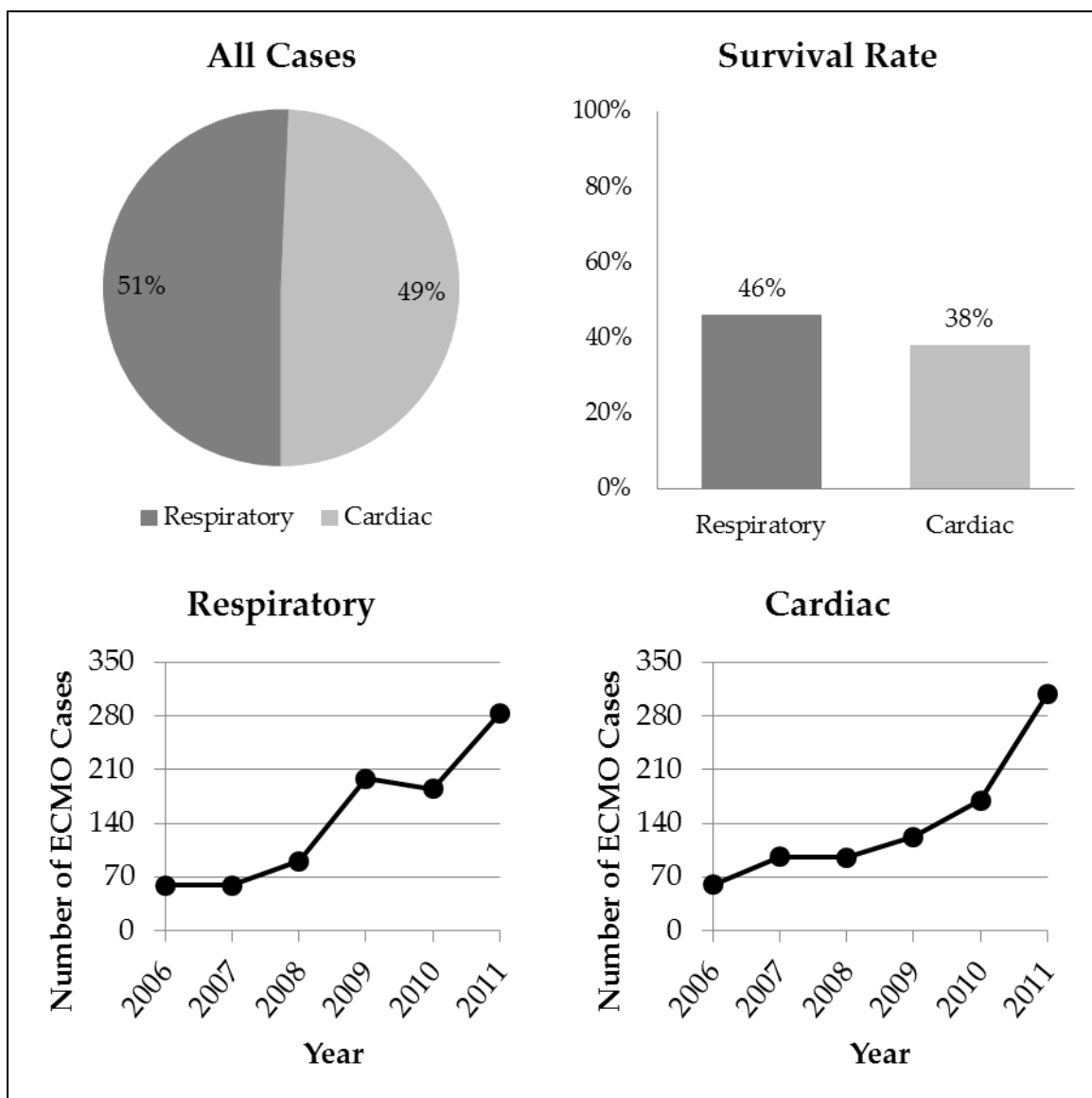


Figure 12. Sample consists of all adult extracorporeal membrane oxygenation (ECMO) cases in the United States from 2006 to 2011 in the Extracorporeal Life Support Organization (ELSO) Registry grouped by etiology (n=1726). Top Left: Proportion of all cases. Top Right: Percentage that survived to discharge. Bottom: Annual number of cases by etiology.

Discussion

Utilization

Although the use of ECMO in adults has been consistently low for many years, there has been a sharp increase since 2007. This is the first time that such a huge jump in the number of ECMO cases has been reported. There are likely many contributing factors to this increase, but two possible explanations are important to mention.

First, the H1N1 pandemic hit the United States in the spring of 2009, resulting in many cases of ARDS with a much higher percentage of young, healthy adults affected compared to seasonal influenza.(19) A study from Australia and New Zealand was published in October 2009 showing a large increase in the number of patients receiving ECMO for ARDS over July and August of 2009 with high survival rates.(20) In addition, two large studies, both published in September 2009, showed favorable survival rates for adults with severe respiratory failure treated with ECMO.(16, 17) The timing of these publications showing the potential benefit of ECMO therapy combined with the increase in the amount of previously healthy adults suffering from severe respiratory failure due to the H1N1 pandemic likely resulted in an increase in utilization. There is evidence to support this hypothesis in Figure 2 (p. 24),

which shows an uncharacteristically large increase in cases in the fourth quarter of 2009, representing October to December, compared to the first three quarters. It is reasonable to expect some seasonal variation, but this substantial difference between quarters is not seen during the other years.

Second, recent studies have shown success in using ECMO as a bridge to therapy for cardiac failure. A study from Taiwan published in 2008 showed survival benefits for patients with in-hospital cardiac arrest that received extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation,(24) and another study published in 2008 from France showed that ECMO support rescued 40% of patients who would have otherwise died from refractory cardiogenic shock.(29) In addition to the hypothesis that the increase in ECMO utilization for adults was largely due to respiratory failure from H1N1 influenza, it is likely that the increase was also due to adults with cardiac failure. This hypothesis is supported by the ELSO Registry, which groups its data by etiology: respiratory or cardiac. As shown in Figure 12 (p. 39), the increase in ECMO cases from 2006 to 2011 is similar for both etiologies. The only noticeable difference is that the number of respiratory cases took a larger jump in 2009 compared to cardiac cases, lending further evidence to the hypothesis above regarding the H1N1 influenza pandemic.

Survival

Although it is disappointing to not see a statistically significant increase in survival rates with the tremendous increase in utilization, there is evidence suggesting improvement when the rates are analyzed in depth. Patients in 2011 were almost twice as likely as in 2006 to be categorized as having an “extreme” risk of mortality, the highest risk signifying the most serious level of disease (shown in Table 1 on p. 21). Therefore, the patients who received ECMO in more recent years were characterized as sicker than in previous years, yet the survival rates did not decline. In addition, six years is a relatively short period to see a statistically significant increase in the survival rates given that there have not been any major breakthroughs in the technology. Since ECMO use in adults is uncommon, the lack of statistical significance may be due to small sample sizes.

There have been consistent improvements in survival rates dating back to its use in the 1970s. In the first randomized clinical trial in 1979, the survival rate of adults treated with ECMO for severe acute respiratory failure was 9.5%.⁽⁴⁾ The CESAR trial in 2009 had a survival rate of 63% for patients who received ECMO for severe adult respiratory failure.⁽¹⁷⁾ Similarly, there has been a tremendous improvement in survival rates for patients receiving ECMO for cardiac failure. A meta-analysis analyzed the use of ECMO for adults in cardiac

arrest from 1990 to 2007 and found an increase in survival rates from 30% to 59% over time.(36) A recently published study concluded that although ECMO for cardiac arrest in elderly patients has a lower survival rate than in younger adult patients (29% to 40%), there are benefits since it is still higher than the survival rate of conventional CPR (17%).(37) Regardless of the etiology, the survival rates will likely continue to improve due to advancements in technology, a decrease in the frequency of complications such as clotting or oxygenator failure, an improved ability to support critically ill patients, and most importantly, an improved ability to treat the underlying conditions affecting these patients.

The survival rates shown here are lower than in most other studies. This is no surprise, since those studies were conducted in large hospitals with more experience using ECMO and well-established protocols, whereas the NIS captures all of the ECMO cases that were done everywhere in the United States, including hospitals with little experience. This is likely also the reason for higher survival rates in the ELSO Registry, although this difference is not statistically significant. The ELSO Registry receives data from a stable group of large centers that use ECMO frequently. In fact, the ELSO guidelines recommend that centers only provide ECMO if they are able to do at least six cases per year.(2) When looking at individual cases in the NIS, there are many examples of ECMO being used as a heroic final effort in patients that were not likely to survive with or

without ECMO. One patient had significant third degree burns in over 50% of his body, another had metastatic cancer, and a few had significant trauma with multiple organ failure. This category of patients (represented in Table 1 in the “Other” category for “Major Diagnostic Category”) had much lower survival rates than patients that primarily suffered from cardiac or respiratory disease.

A problem with using a clinical database like the NIS is that it can be very difficult to get an accurate clinical picture of a patient. The data is derived from administrative data, which is compiled mostly for billing purposes and can oversimplify the actual clinical situation. Therefore, although it is tempting to look at patient scenarios in hindsight and say that something should or should not have been done, it is impossible to see the exact clinical scenario that the health care provider team saw when deciding to put a patient on ECMO.

Before diving into a detailed analysis of the survival rates, it is important to discuss the definition of survival in the NIS. A patient is considered a survivor if he/she survives to hospital discharge, which includes a transfer to another acute care hospital. This definition of survival is standard in many databases, including the ELSO Registry, and rarely causes problems because patient transfers are usually rare. However, with patients requiring ECMO, transfers are more common because the level of care is so high. Sometimes

patients are transferred because the current hospital does not offer ECMO, but the attending physician feels that the patient could benefit from ECMO. Another situation that arises is a patient is started on ECMO at one hospital, but the provider team runs into complications that they are not comfortable with and then try to transfer the patient to a center with more experience.

Given this potential issue, further analysis of the survivors, as defined by the NIS, is required. Of all the adult ECMO cases from 2006 to 2011, approximately 16% of the survivors were transferred to another acute care hospital for further treatment (as shown in Figure 4 on p. 26). This is a significant amount, which could greatly affect the overall survival rate depending on how these patients did after transfer. Imagine the worst scenario where every one of these transferred patients died at the subsequent hospital. This would lower the average survival rate over the six years from 38% to 32%. However, if every transfer survives, the average survival rate remains at 38%. Therefore, the survival rates reported here are inflated because the definition of survival in the NIS includes transfers, the transfer rate is relatively high for adult ECMO cases, and it can be assumed that not all of the transfers survived to discharge at the subsequent hospital. Given that the NIS does not allow the tracking of patients for privacy reasons, the exact survival to discharge rate

(excluding hospital transfers) cannot be determined, although it ranges from 32% to 38%. Nonetheless, with further analysis, an estimate can be found.

The question of what the survival rate is for the patients who were transferred to another acute care hospital cannot be answered, but the question of what the overall survival rate is for adult ECMO patients who arrived to the hospital via transfer from another hospital is answered in Figure 5 (p. 27). Approximately 37% survived and this does not significantly differ from the survival rate for non-transfers. To clarify, the transfer rate in Figure 5 (36%) is higher than in Figure 4 (16%) because these transfer rates represent different things. The higher rate represents patients that were transferred in from another hospital and then received ECMO, which includes patients that were previously at hospitals that do not provide ECMO, whereas the lower rate represents patients that received ECMO and were then transferred to another hospital.

Now to estimate the overall survival rate (excluding hospital transfers) for adult ECMO patients from 2006 to 2011, take the overall survival rate of 38% and assume that 16% of these patients were actually transferred to another hospital and their survival rate after transfer was 37%. Ignore the possibility of a patient being transferred more than once because this would be extremely rare. The overall survival to discharge rate becomes approximately 34%. Understanding

the effect of transferring a patient to another hospital on the survival rate is important when analyzing the survival rates of subpopulations.

With regards to common surgical procedures, differences in mortality rates are more related to differences in the “failure to rescue” (meaning death after a complication) rates than differences in complication rates,(38) and failure to rescue rates are more associated with hospital characteristics than patient characteristics.(39) One study found that with pancreatectomies, teaching hospitals and large hospitals were associated with lower failure to rescue rates.(40) How do the survival rates for ECMO differ with regards to these particular hospital characteristics?

As shown in Figure 6 (p. 30), small hospitals had a lower survival rate than large hospitals from 2006 to 2011, but this difference was not statistically significant. However, only 2% of the total ECMO cases took place at small hospitals and this small sample size limits the statistical power of this particular analysis. In addition, the patients that survived at small hospitals were much more likely to have been transferred to another hospital compared to the survivors at large hospitals (28% vs. 11%). Using the estimation method above, the overall survival rate (excluding hospital transfers) drops to approximately 21% for patients at small hospitals and 34% for patients at large hospitals.

Although medium-sized hospitals have a significantly better overall survival rate compared to large and small hospitals, this is likely due to their high rate of transferring patients to other hospitals (49%). When taking this into account, their overall survival rate (excluding hospital transfers) drops to approximately 35%. Therefore, although at first glance the average survival rate looks much better for medium-sized hospitals, it is likely about the same as the average survival rate for large hospitals when you exclude the hospital transfers.

When it comes to the teaching status of the hospital, there is a statistically significant difference in the survival rates, but it differs from the results of the study above regarding pancreatectomies, although in that study rural hospitals were included in the non-teaching hospital category, whereas here they are separate categories. As shown in Figure 7 (p. 31), urban non-teaching hospitals had a higher survival rate than urban teaching hospitals (55% vs. 36%). However, this is misleading because the urban non-teaching hospitals had much higher transfer rates. When corrected for the transfer rates, the estimated survival rate becomes 36% for urban non-teaching hospitals and 33% for urban teaching hospitals. Similar to the results regarding hospital sizes, it seems that the urban non-teaching hospitals have the best results when looking at overall survival rates, but this is likely due to their high transfer rates.

Another hospital characteristic that has been shown to be associated with failure to rescue is the hospital's volume of a particular type of case. In a study on ovarian cancer, it was found that although low-volume hospitals had slightly lower complication rates compared to high-volume hospitals, the failure to rescue rates were significantly higher resulting in worse overall mortality rates.⁽⁴¹⁾ The ELSO guidelines recommend that centers perform at least six ECMO cases annually,⁽²⁾ so this seemed like a good threshold for low- versus high-volume hospitals. As seen in Figure 8 (p. 32), the patients who received ECMO at low-volume hospitals had a slightly higher survival rate compared to patients at high-volume hospitals (40% vs. 37%), but their percentage of transferring patients to another hospital was much higher (44% vs. 5%). Using the estimation method above correcting for transfer rates, the low-volume hospitals really had a survival rate closer to 29%, whereas the high-volume hospitals had a rate closer to 36%. Therefore, it seems that the low- and high-volume hospitals are achieving the same results when looking at overall survival rates, but this is due to the high transfer rate of low-volume hospitals masking their true outcomes. When taking into account the transfer rates, it is likely that the high-volume hospitals are achieving better results. This analysis supports the ELSO guideline of six ECMO cases annually, although a sensitivity analysis was not conducted to look at other thresholds to separate low- and high-volume

centers. A promising trend is that a larger proportion of cases were done in high-volume hospitals in 2011 compared to 2006.

It is easy to become entrenched in the numbers when conducting statistical analyses and wonder about the differences a few assumptions can make. Nonetheless, as important as it is to look at various hospital characteristics, appropriate patient selection is the key to good outcomes with ECMO. Using a multivariable logistic regression, significant independent predictors of mortality in adult patients who received ECMO were identified. Not surprisingly, patients categorized as having a higher risk of mortality did indeed have a higher likelihood of dying, thereby validating the categorization in the NIS. In addition, the comorbidities of coagulopathy, renal failure, and valvular disease increased the risk of mortality. This makes sense since all three of these comorbidities carry serious consequences and can make it extremely difficult to maintain a patient on ECMO and especially to wean them off ECMO. The more interesting findings may be some of the comorbidities that did not significantly increase the risk of mortality, such as congestive heart failure, chronic pulmonary disease, fluid/electrolyte disorders, obesity, and pulmonary circulation disorders. Another unexpected result was that the comorbidity of weight loss showed a significant survival benefit. A major limitation of this analysis regarding comorbidities and their effects on mortality is that this data is

derived from administrative data. Although this is a recurring limitation throughout all of the analyses presented in this thesis, it is most problematic here. A comorbidity, by definition, is a preexisting condition, one that exists independently of the primary disease. However, given the way that data was reported to and presented in the NIS, it is difficult to confirm that these are actual comorbidities and not complications. Many of the comorbidities listed could easily be complications from ECMO or from the underlying disease that led to the use of ECMO. Nonetheless, despite this major shortcoming in this particular analysis, it still serves as an important step in analyzing the survival rates of ECMO. Further research is needed to better determine which patients are more likely to benefit from the use of ECMO.

Cost

There were no significant differences in the median costs per day of hospitalization or the median total costs of hospitalization per patient for adults receiving ECMO from 2006 to 2011. Using the total hospitalization cost as a proxy for the cost of ECMO, it has not gotten more expensive for hospitals to provide this therapy. For this analysis, the trend is more important than the values of the numbers presented, since for each patient, the number represents the costs of all services and procedures received during hospitalization, not all of

which pertain to ECMO. Medians were used instead of means to compare costs over time because medians are less influenced by outliers and health care cost distributions are skewed. The CPI Inpatient Hospital Services inflation multipliers for each given year were used to adjust all costs to 2011 US Dollars. These inflation rates are higher than the overall CPI inflation rates because healthcare inflation has outpaced the inflation of most other goods in our economy during this time period.

It is important to note that these numbers should not be used to draw any conclusions regarding the cost-effectiveness of ECMO. First, these numbers represent the total cost of hospitalization for the patients, incorporating costs for services other than ECMO. Second, there is no data in the NIS on the length of survival or quality of life after treatment. In order to perform a cost-effective analysis, one needs to look at long-term survival and the effects on quality of life, in addition to the costs. The best cost-effectiveness study to date was conducted in the UK as part of the CESAR trial, which found ECMO to be cost-effective with a predicted cost per quality-adjusted-life-year (QALY) of £19,252 (~\$31,000 at time of publication).(17)

Limitations

Although the NIS has been used many times in estimating national trends and is well validated, it is possible that the sample over- or under-represented patients receiving ECMO. The hospitals sampled change every year (repeats are allowed), so a large center that does a lot of ECMO cases and is included in one year, but not others, could bias estimates since there are few cases relative to the total number of inpatient visits. Another limitation is that the NIS is derived from administrative data, which is largely collected for billing purposes. This can result in misleading data. A hospital might list one diagnosis over another as the primary diagnosis because it captures a larger reimbursement. Although the large majority of the data offered in the NIS is likely accurate, it is possible that there are cases where the data was manipulated to receive better reimbursements. Nonetheless, the overall NIS survey design is very complex in order to take all of these limitations into account, requiring powerful statistical software to conduct the statistical analyses. The trends found here using the NIS match those seen in the ELSO Registry, which is a relatively stable sample of centers from 2006 to 2011 and is based on data collected directly from the clinicians utilizing ECMO.

Conclusion

When you look at absolute survivors, there were approximately 732 more adult patients who survived hospitalization with ECMO therapy in 2011 compared to 2006. Yes, this surge of survivors is due to the increase in utilization, not an increase in the survival rate, but since the indication to initiate ECMO is severe disease unresponsive to other therapies, one can assume that the survival rate in these patients would likely have been close to zero if ECMO was not utilized. More patients are surviving today who likely would have perished twenty years ago, presumably due to the advances in ECMO.

Cardiac surgeons have an important role to play in patient selection, provision of care and subsequent post-procedure care, which is best accomplished in a Cardiothoracic Intensive Care Unit (CTICU). This is particularly true when one considers that the most frequently reported causes of complications are bleeding, cannula related issues, and device malfunction,(42) all of which can be expertly dealt with by the cardiac surgical team consisting of CTICU intensivists, cardiac surgeons, perfusionists, and nursing staff. This has implications for the provision of care and future training of the cardiac surgical residents. As the case volume of coronary artery bypass surgery decreases, there needs to be an initiative to lead and support active ECMO programs in academic

cardiac centers as they become more ubiquitous. New programs that adopt ECMO and strive to improve outcomes must be enthusiastically welcomed.

This research provides stepping stones for further research. Although it is clear that the utilization has increased in recent years and will likely continue to increase, it is not clear why there are so many variations in the survival rates. Patient selection is likely the most important factor in the likelihood of success with ECMO, and it is important that future studies try to determine which patients are better candidates than others, although this will be a difficult task. In a healthcare environment where providers strive to make clinical decisions based on evidence-based medicine, there must be an attempt to formulate more definitive and specific guidelines on the best patient selection criteria. In addition, further research into the cost-effectiveness of ECMO is needed. Although this dissertation shows that it does not appear to be getting more expensive, it offers little insight into whether the current cost of therapy is acceptable. It is encouraging that it is deemed cost-effective in the United Kingdom, but this needs to be found in the United States, as well. Currently, reimbursement in the United States does not depend on the cost-effectiveness of a therapy, as it does in some other countries such as the United Kingdom, but this could change in the future, especially as the government focuses on decreasing healthcare costs.

In conclusion, there has been an increase in ECMO utilization in adult patients within the United States in recent years with no significant changes in the survival rates or costs. The increase in utilization is likely to continue with improvements in survival rates as the technology advances and our ability to support critically ill patients and cure their underlying conditions improves.

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