



Student Name: Summer Debreuil

Date: August 4, 2016

Project Title: Long-term outcomes of survivors undergoing extracorporeal membrane oxygenation in Manitoba between 2007 and 2016

Primary Supervisor Name: Dr. Rohit K. Singal

Department: Department of Surgery, Max Rady College of Medicine, University of Manitoba

Co-Supervisor Name: Dr. Rakesh C. Arora

Department: Department of Surgery, Max Rady College of Medicine, University of Manitoba

Summary (250 words max single spaced):

Background: Extracorporeal membrane oxygenation (ECMO) to treat severe cardiorespiratory illness has seen a marked increase in the last decade. Much of the data regarding this intensive therapy is short-term in nature and focused on survival. There exists a need for assessment of long-term survival and health related quality of life (HRQoL) to improve our understanding of the benefits of this therapy.

Methods: A retrospective chart review of all 239 patients supported with ECMO in Manitoba between 2007 and 2016 was performed as well as prospective long-term HRQoL analysis of the survivors, who were invited to undergo detailed HRQoL assessments involving eight questionnaires and three clinical assessments. Fifty-one patients, 38 undergoing venoarterial-ECMO and 13 venovenous-ECMO, were interviewed.

Results: One hundred and eighty-four patients were supported with venoarterial-ECMO most commonly for cardiogenic shock (63%) where 30-day and 2 year survival were 43.5% and 36.6% respectively. Fifty-five patients supported with venovenous-ECMO most commonly had acute respiratory distress syndrome (78%) where 30 day and 2 year survival was 56.4% and 48.0% respectively. Two year survival estimates for patients surviving to hospital discharge were 85% for all patients. Twenty-nine percent of VA-ECMO and 43% of VV-ECMO patients reported having a low quality of life. Despite their younger age, VV-ECMO patients had greater deficits, including depression (23.1%), anxiety (38.5%), PTSD (38%) and low physical activity (53%).

Conclusion: Survival, particularly of patients discharged from hospital, was reasonable on long-term follow-up but persistent issues with HRQoL were identified. This study provides better understanding of patient survival and issues post ECMO therapy which may be used to counsel patients and families and identify areas for enhanced ongoing care.

Acknowledgments

a) I gratefully acknowledge the support of the following sole sponsor: _____

b) If not solely funded, I gratefully acknowledge the funding support from one or more of the following sponsors:

H.T. Thorlakson Foundation
Dean, College of Medicine
Research Manitoba

Vice-Dean, Research Rady FHS
Health Sciences Centre Research Foundation
Heart and Stroke Foundation

Student Signature

Primary Supervisor Signature

MD/PhD MD/MSc. BSc. (MED) MED II Research Program

Joe Doupe Annual Event Undergraduate Medical Student Research Symposium
Canadian National Medical Student Research Symposium

Long-term outcomes of survivors undergoing extracorporeal membrane oxygenation in Manitoba between 2007 and 2016

Authors: S. Debreuil^{1,2}, K. Barrie^{1,2}, A. Cornick¹, E. Lee¹, B.M. Hiebert¹, S. Zieroth³, R. Manji^{4,5}, O.J. Bienvenu⁶, R.C. Arora^{4,5}, R.K. Singal^{4,5}

Institutions: ¹Institute of Cardiovascular Sciences, St. Boniface Hospital Research Centre, Winnipeg, Manitoba. ²Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba. ³Section of Cardiology, Department of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba. ⁴Section of Cardiac Surgery, Department of Surgery, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba. ⁵Section of Critical Care, Department of Medicine, Max Rady College of Medicine University of Manitoba, Winnipeg, Manitoba. ⁶John Hopkins School of Medicine, Baltimore, Maryland.

Abstract

Background: Extracorporeal membrane oxygenation (ECMO) to treat severe cardiorespiratory illness has seen a marked increase in the last decade. Much of the data regarding this intensive therapy is short term in nature and focused on survival. There exists a need for assessment of long-term survival and health related quality of life (HRQoL) to improve our understanding of the benefits of this therapy.

Methods: A retrospective chart review of all 239 patients supported with ECMO in Manitoba between 2007 and 2016 was performed as well as prospective long-term HRQoL analysis of the survivors, who were invited to undergo detailed HRQoL assessments involving eight questionnaires and three clinical assessments. Fifty-one patients, 38 undergoing venoarterial-ECMO and 13 venovenous-ECMO, were interviewed.

Results: One hundred and eighty-four patients were supported with venoarterial-ECMO most commonly for cardiogenic shock (63%) where 30-day and 2-year survivals were 43.5% and 36.6% respectively. Fifty-five patients supported with venovenous-ECMO most commonly had acute respiratory distress syndrome (78%) where 30 day and 2 year survivals were 56.4% and 48.0% respectively. Two-year survival estimates for all patients surviving to hospital discharge were 85% for all patients. Twenty-nine percent of VA-ECMO and 43% of VV-ECMO patients reported having a low quality of life. Despite their younger age, VV-ECMO patients had greater deficits, including depression (23.1%), anxiety (38.5%), PTSD (38%) and low physical activity (53%).

Conclusion: Survival, particularly of patients discharged from hospital, was reasonable on long-term follow-up but persistent issues with HRQoL were identified. This study provides better understanding of patient survival and issues post ECMO therapy, which may be used to counsel patients and families and identify areas for enhanced ongoing care.

1. Introduction and Background

Mechanical circulatory support (MCS) can be utilized to support end organ perfusion in patients suffering from severe but potentially reversible respiratory or cardiac failure. This is achieved using extracorporeal membrane oxygenation (ECMO). ECMO provides isolated respiratory support using venovenous-ECMO (VV-ECMO) by oxygenating blood and removing CO₂ in the venous circulation. Venoarterial-ECMO (VA-ECMO) provides both respiratory and hemodynamic support by bypassing both the heart and the lungs^{1,2}. The use of ECMO in adults has soared in the last 10 years, increasing by 433% across the United States between 2006-2011³.

Contributing factors to this sharp increase in use were both the H1N1 influenza pandemic⁴⁻⁶, which caused rapid and severe adult respiratory distress syndrome (ARDS) in many otherwise healthy adults, as well as several studies showing the benefit of ECMO therapy in patients with refractory heart failure^{7,8}. In fact, The Extracorporeal Life Support Organization (ELSO) 2012 Registry Report indicates an increase in extracorporeal cardiac support in adults from less than 50 cases in the year 2000 to over 200 cases per year from 2008-2012⁹.

While previous observational studies have sought to describe the short-term survival rate of patients requiring ECMO support¹⁰⁻¹³, there is a scarcity of information on the long-term health related quality of life (HRQoL) outcomes of the survivors of such intensive, complicated and resource heavy treatment. Understanding long-term outcomes is of paramount importance as the efficacy and effectiveness of this therapy are being evaluated and its role in clinical care is being determined^{1,14,15,16}. Furthermore, this understanding of overall HRQoL might assist us in identifying possible strategies for optimizing post-ECMO care as surviving patient's transition from the hospital back to the community.

A total of 239 patients have received treatment with VA- or VV-ECMO since the formal initiation of an ECMO program in Manitoba in 2007. This study represents the first analysis of the complete Provincial ECMO Program with an overarching goal of understanding the long-term outcomes of patients requiring this therapy. Specifically, we sought to determine: 1. short-term survival (30 day and to hospital discharge); 2. long-term survival; and 3. long-term HRQoL of survivors at their latest follow-up time point. In order to evaluate the long-term HRQoL outcomes of survivors of ECMO therapy, we assessed patients under three broad categories; physical function, cognitive function and mental health.

2. Methods

Study Setting

The study was carried out at St Boniface General Hospital, a tertiary care center in Winnipeg, Canada. The University of Manitoba Research Ethics Board (REB) and the St Boniface Hospital Research Review Committee (RRC) approved the study. In order to fulfill the objectives there were two arms to the research study. The first was a retrospective cohort study, which generated a database consisting of all patients greater than 16 years of age who were supported with ECMO between 2007-2016 (June 2016). The second arm was the initiation of a new long-term HRQoL "survivorship" clinic wherein patients were assessed either by an in-person clinic visit or via a telephone interview.

All ECMO cannulation was performed in Winnipeg, Manitoba by the cardiac surgery service at the patient's bedside, in the cardiac catheterization lab or in the operating room under sterile conditions and with systemic heparinization. VA-ECMO patients were cannulated centrally or peripherally either percutaneously or using a side limb graft on the femoral artery for cannulation. Fifteen to 19 French arterial catheters and 24/29 to 30/33 venous drainage cannulas were used for percutaneous cannulation. VV-ECMO patients were cannulated using a dual lumen cannula (Avalon Laboratories, Rancho Dominguez, CA, USA), or multi-site cannulation with two or three sites. Cannula position was confirmed by echocardiography, and/or fluoroscopy and chest radiography. The VA-ECMO circuit was comprised of a femoral venous line connected to a BioMedicus 540 centrifugal pump (Medtronic, Minneapolis, MN, USA) that propelled blood through a Medtronic Affinity NT oxygenator/heat exchanger into the arterial cannula. All ECMO circuits were primed with 600 mL of room temperature lactated

ringers solution. Patients were cared for in Intensive Care Units at St. Boniface General Hospital and weaned from support as possible with standard assessment of disease resolution.

Study Design for ECMO Database

Phase 1: We completed a retrospective cohort review of all ECMO patients from St Boniface Hospital since November 2007. Our patient list was generated using detailed perfusionist records. We included all patients who were on ECMO at any point during their hospital stay regardless of other mechanical circulatory support devices used.

The database was created using a secure online electronic data collection program (REDCap). Data was collected from St. Boniface Hospitals electronic patient charts (EPR) and supplemental paper chart review between June 2015-July 2016.

The data abstraction forms were developed internally as an adjunct to existing databases and previous interdisciplinary focus groups meetings in 2013 based on results of published ECMO literature and consensus of biologic plausibility¹⁷. Patient demographics, comorbidities, indication for ECMO, procedural data (including cannulation strategy, location of cannulation, surgeon, time on support), patient outcomes, complications, transition to other support, medication and laboratory data were collected. Medications and laboratory data were collected at hour 0, 6, 12, 18, 24, and then daily until three days post ECMO decannulation.

Summary statistics including demographic data (age, gender, diagnosis, past medical history, APACHE II score, ICU transfusions, etc.) were collected for each patient using a linkage to the WRHA Critical Care Database. The acute physiologic and chronic health evaluation (APACHE II) is a tool used to measure severity of disease and predict patients course in ICU¹⁸. All patients were screened for the following comorbidities: Asthma, Chronic Obstructive Pulmonary Disease, Renal Failure, Renal Insufficiency, Cerebrovascular Accident, Alcohol Abuse, Drug Abuse, Stable Angina, Unstable Angina, Congestive Heart Failure, Diabetes, Hyperlipidemia, Hypertension, Previous Myocardial Infarction, Peripheral Vascular Disease, GI Bleed, Tachyarrhythmia.

Statistical Analysis of Database

Several demographic and perioperative characteristics were compared between VA- and VV-ECMO patients. Categorical variables were compared using a Chi-Square or Fisher's Exact Test; continuous variables were compared using a Mann-Whitney Test where appropriate. Additional ECMO characteristics and parameters collected at follow-up were described for both populations, but not statistically compared between VA and VV ECMO patients. Long term survival for both patient groups was visualized via Kaplan Meier curves. These survival curves were developed for the entire study population and only those who survived their hospital stay. All analysis was performed using SAS version 9.3.

Data Collection for Long-term Follow-up

Phase 2: The second arm of the study was a HRQoL analysis of the surviving ECMO patients. The study period for this portion of the study was June 2016-July 2016. Median follow-up time for VA-ECMO patients was 2.0 years (0.8-3.0) post ECMO cannulation and 1.5 years (0.5-2.0) for VV-ECMO patients. We used St Boniface hospital's electronic patient record to exclude patients that were deceased. All patients greater than 18 years of age who survived >30 days post hospital discharge were eligible to participate in either a postoperative follow-up clinic or

telephone survey during the study period. Exclusion Criteria were severe mental disability and non-English speaking.

Long Term QOL Testing

We collected data on HRQoL using several tests to analyze physical function, cognitive function, and mental health. The core questionnaires for our HRQoL analysis were administered in both the telephone interview and follow up clinic (see Table 1). The eight questionnaires were as follows: (1) Euroqol 5 Dimension (EQ-5D) (2) Hospital Anxiety and Depression Score (HADS), (3) Paffenbarger Physical Activity Index, (4) Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs), (5) Post Traumatic Stress Disorder Checklist Civilian Version PCL-C, (6) Decision Regret Scale (DRS), (7) Weight loss (self-reported weight loss), and (8) Modified Center for Epidemiologic Studies Depression (CES-D).

EQ-5D is a two part questionnaire and an effective tool used to measure HRQoL^{19,20}. The first part, EQ-5D-3L, asks about general health status^{21,22}. The five dimensions of health evaluated are mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Patients are asked if they have “no problems”, “some problems”, or “extreme problems” with each dimension. The EQ-5D-3L user guide reported the age matched general population having problems with mobility, self care, usual activities, pain/discomfort and anxiety/depression are 21.9%, 5.2%, 21.8%, 43.7%, and 27.2% respectively²³. The second component, the EQ-VAS instrument, is a scale from 0 (worst imaginable health state) to 100 (best imaginable health state) where patients record their self-rated health. We chose an EQ-VAS below 60 to represent poor HRQoL. This is the mean score for individuals with advanced heart failure, malignancy and kidney failure, all of which are well accepted states of poor HRQoL^{24,25}.

The Hospital Anxiety and Depression Scale (HADS)²⁶ is used to determine levels of depression and anxiety in patients. Patients are read seven statements relating to depression and seven statements relating to anxiety. They then choose between four responses that best describe the severity of their symptom. A score between 0-3 is given with a higher number correlating to a more severe symptom of anxiety or depression. The responses are added up to give a total score out of 21. A patient's score determined if they were in the “normal” (0-7), “borderline” depression/ anxiety (8-10), or “depressed”/“anxious” (11-21) range. In a large non-clinical study the percentage of patients normal, borderline depressed and depressed were 88.6%, 7.8%, and 3.6% respectively and normal, borderline anxious and anxious were 66.8%, 20.6%, and 12.6% respectively²⁷.

The Paffenbarger Physical Activity Index²⁸ was used to assess the patients physical activity. It is a validated tool to measure the fitness of a population based on calories burned doing physical activity per week. The cut off value for low physical activity is <383 kcal/week for men and <270 kcal/week for women.

Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs)²⁹ were assessed using the “Activity” and “Functional status” questionnaires. These were utilized to determine the level of assistance a patient required with ADLs (feeding, bathing, dressing, toileting) and IADLs (cooking, cleaning, shopping, taking medication, driving, banking). Patients were either deemed independent, requiring assistance, or unable/dependent. We considered the latter two to be a positive score indicating a functional defect.

Post Traumatic Stress Disorder (PTSD) was assessed using the PTSD Check List (PCL-C)^{30,31}. Patients were asked if they any of the 17 key symptoms of PTSD. They were given points based on the severity of their symptoms for each question. The higher the severity the higher the points

received and therefore a higher total severity. Up to 20% of ICU survivors have been estimated to have clinically significant symptoms of PTSD³². The national center for PTSD recommends a cut off of between 36-44 for patients in a population of estimated PTSD of 16-39%³³. We chose to use a cut off of 40 for our population. In comparison, the estimated prevalence of PTSD in the general population is 15% the suggested cut off for this population is a PCL-C score of 30-35³³.

We administered the Decision Regret Scale (DRS) to determine if patients had distress or remorse about the decision to undergo ECMO. The patient was scored on their level of agreement or disagreement with the following five statements: (1) "It was the right decision", (2) "I regret the choice that was made", (3) "I would go for the same choice if I had to do it over again", (4) "The choice did me a lot of harm", and (5) "The decision was a wise one". The patient chooses between the following: "strongly agree", "agree", "neither agree nor disagree", "disagree" and "strongly disagree". Items (2) and (4) were reverse coded. A total score was calculated out of 100 to determine the level of regret regarding the decision. A score of 0 means no regret and a score of 100 indicates a high level of regret. A previous systematic review demonstrated that the average regret patients had regarding medical decisions generated a mean DRS score of 16.5 across studies³⁴. Finally, satisfaction with care post hospital stay was evaluated with the particular question, "Upon discharge from hospital, did you have an adequate plan of care and health services available to look after you at home?"³⁶.

Additional Tests

There were three additional cognitive and physical tests done for the patients who attended our in hospital clinic (see Table 2). They allowed us to investigate the Modified Fried Frailty parameters. The three additional tests were as follows: (1) 5-m gait speed measurement, (2) Handgrip strength measurement, (3) Montreal Cognitive Assessment (MoCA).

Under the Modified Fried definition, a patient was deemed "frail" if he/she met ≥ 3 of the following 7 criteria: slowness (as determined by the 5-m gait speed measurement)³⁷, weakness (handgrip strength measurement)^{38,39}, weight loss (self-reported weight loss), exhaustion (the modified 2-item CES-D Scale), depression (the 5-GDS), low physical activity (the Paffenbarger Physical Activity Index), and cognitive impairment (the MoCA).

Montreal Cognitive Assessment (MoCA) was used to assess cognitive function of patients who attended the clinic. It is a validated tool, which provides assessment of several cognitive domains including the following: visual spatial abilities, recognition, recall, attention, language, abstraction and orientation⁴⁰. A maximum score of 30 can be achieved with this test. A score < 25 is a marker of cognitive impairment.

3. Results

Patient Demographic and Therapy Indications

The demographic characteristics of ECMO patients were described (see Table 3). For patients in the VA-ECMO cohort the median age was 58 years old (50-65). A greater proportion of men were supported on this therapy (68%). The majority of patients, 152 (83%) had one or more comorbidities. The most prevalent were hypertension, hyperlipidemia, and diabetes. The patients were very sick in the ICU with a median APACHE II score was 27 (20-32). One hundred and sixty-seven patients (91%) needed one or more transfusions in the ICU.

Patients in the VV-ECMO cohort were younger with a median age of 43 years old (26-56). There were only slightly more men than women who received the therapy (53% vs. 47%). Thirty-nine

patients (71%) had one or more comorbidities. The most prevalent were hypertension, diabetes, and alcohol abuse. Twenty-two percent of patients had a history of alcohol abuse. The median APACHE II score was similar to VA-ECMO patients with a score of 26 (20-32). A large percentage of VV-ECMO patients (93%) needed one or more transfusions in the ICU.

The indications for ECMO, laboratory parameters, and complications were described (see Table 4). The most common indication leading to use of VA-ECMO was cardiogenic shock in 116 (63%) patients, specifically ischemic heart disease (46.7%). Other common indications for therapy were postcardiotomy (19.6%), hypothermia (8.7%) and toxic overdose (3.3%). Thirty-two patients used an additional MCS device before or after ECMO. Three patients had a prior left ventricular assist device (LVAD) and 29 transitioned to the following devices: 12 to left ventricular assist device (LVAD), 8 to VV-ECMO, 6 to biventricular assist devices (BIVAD), and 3 to right ventricular assist device (RVAD). The most common indication for VV-ECMO was acute respiratory distress syndrome (ARDS) consisting of 43 patients (78.2%). The top three causes of ARDS in these patients were pneumonia (30.9%), H1N1 influenza (18.2%) and blastomycosis (9.1%).

The median pH at time of cannulation for VA-ECMO patients was 7.22 (7.08-7.37). There was a spike in median serum lactate values measured at time of cannulation, which then dropped at 6 hours and 12 hours post cannulation. The values were 11.1 mmol/L, 8.0 mmol/L, and 4.5 mmol/L respectively. The median peak and lowest haemoglobin were 103g/L and 73g/L for all VA-ECMO patients. The most common complications in this cohort were pneumonia (21%), GI bleed (17%), cannula revision (16.3%), and neurologic injury (16%).

In the VV-ECMO cohort median pH at cannulation was 7.33 (7.26-7.41). The median lactate values measured at cannulation, 6 hours, and 12 hours post cannulation did not spike in these patients. The values were 3.5 mmol/L, 2.9 mmol/L, and 2.4 mmol/L respectively. The median peak and lowest haemoglobin were 101g/L and 73g/L. The most common complications were sepsis (71%), pneumonia (38%), GI bleed (18%), and neurologic injury (11%).

Course in Hospital

A timeline of in-hospital events are presented (see Figure 1), comparing ECMO duration, intensive care unit length of stay (ICU LOS), and hospital length of stay (hospital LOS) between the following four groups: VA-ECMO total (entire cohort), VA-ECMO follow-up (patients surviving to the long-term follow-up study), VV-ECMO total, VA-ECMO follow-up. The VV-ECMO patients, in general, required a longer duration of ECMO support, ICU LOS and hospital LOS than the VA-ECMO cohort.

Survival

Kaplan Meier Curves were generated to estimate survival based on our available data. We analyzed survival following ECMO initiation for all patients (see Figure 2) as well as survival of patients surviving to hospital discharge (see Figure 3). Of the total 184 VA-ECMO patients, 43.5% survived their hospital stay, 46.2% survived to 30 days, 40.5% survived to 6 months and 39.1% were alive at one year. For our 55 VV-ECMO patients, 56.4% survived their hospital stay, 58.2% survived to 30 days, 52.4% survived to 6 months and 48.0% were alive at one year. One and two-year survival estimates for patients discharged from hospital were 89.1% and 84.8% for VA-ECMO patients and 85.1% and 85.1% for VV-ECMO patients respectively.

Long term HRQoL

There were 89 patients eligible to participate by our definition (66 VA-ECMO and 23 VV-ECMO patients). We interviewed 51 of these patients (see Figure 4). Twenty patients attended our in hospital follow-up clinic and 31 patients were interviewed over the telephone. A total of 38 VA-ECMO patients participated in our long-term follow-up interviews at a median of 2.0 years (0.8-3.0) post initiation. This cohort demonstrated a median age of 58 years with 66% males and a median APACHE II score of 23 (17-29). There were 13 VV-ECMO patients interviewed at a median follow-up time of 1.5 years (0.5-2.6). This cohort had a median age of 49 years, 62% males and a median APACHE II score of 22 (20-26). The long-term follow-up patient demographics were described (see Table 5) as well as their interview parameters (see Table 6).

Overall quality of life was assessed using EQ-VAS for the 51 patients who were interviewed. There were 11 VA-ECMO patients (29%) and 6 VV-ECMO patients (46%) identifying themselves as having a low quality of life. Based on results of EQ-5D-3L, there were 9 VA-ECMO patients (23.7%) who reported at least some issues with mobility, 3 (7.9%) with self-care, 14 (36.8%) performing their usual activities, 17 (44.7%) reported pain or discomfort, and 8 patients (21.1%) reported anxiety/depression. In the VV-ECMO cohort there were more issues reported. There were 9 patients (69.2%) who reported issues with mobility, 3 (23.1%) with self-care, 8 (61.5%) performing usual activities, and 9 patients (69.2%) reported anxiety or depression. All 13 (100%) of VV-ECMO patients reported at least some ongoing issues with pain or discomfort.

There were 13 VA-ECMO patients (34.2%) and 7 VV-ECMO patients (53.9%) with a low physical activity score based on results of the Paffenbarger Physical Activity Index. There were 6 VA-ECMO patients (15.8%) who reported problems with ADLs and 14 (36.8%) with IADLs. There were more problems with daily activities in the VV-ECMO cohort. There were 3 patients (23.1%) who reported problems with ADLs and 6 (46.2%) with IADLs.

There were lower rates of depression and anxiety reported using HADS than EQ-5D as it is a more specific test. Five percent of VA-ECMO patients had significant symptoms of depression and 7.9% had significant symptoms for anxiety. In the VV-ECMO cohort 23.1% patients had significant symptoms of depression and 38.5% with significant symptoms of anxiety. There were 4 VA-ECMO patients (13%) and 5 VV-ECMO patients (38%) who had a positive screen for PTSD.

Both cohorts of patients had little regret regarding their decision to be put on ECMO. VA-ECMO survivors had a median of 5 (0-13) distress or remorse regarding the decision while VV-ECMO survivors had a median of 0 (0 - 10). All patients in both cohorts reported less regret than the average patient has regarding a medical decision. Both cohorts were also satisfied with the care they had following hospital discharge.

Of the 20 patients who attended the follow-up clinic (see Table 7), the Modified Fried Frailty parameters revealed four VA-ECMO patients (26.7%) and 3 VV-ECMO patients (75%) met the criteria for frailty. Seventy-three percent of VA-ECMO survivors in clinic and 75% of VV-ECMO survivors had MoCA scores <25 indicating at least mild cognitive impairment at time of follow-up.

4. Discussion

This study was a retrospective chart review of all ECMO patients in Manitoba between 2007-2016 with prospective long-term follow-up and HRQoL analysis of survivors of this therapy. ECMO is an intensive and invasive intervention used to resuscitate and treat the most critically

ill patient population in the health care system. Our patients certainly fit this description with high APACHE II scores in both cohorts and markedly elevated serum lactate levels in the VA-ECMO cohort. Not surprisingly, a significant proportion of patients treated with either VA-ECMO or VV-ECMO did not survive to hospital discharge. Approximately 55% and 44% of VA- and VV-ECMO patients respectively died in hospital. The survivors had longer ICU LOS and hospital LOS due to the large number of patients who died on ECMO support, cutting short both their hospital and ICU duration.

ECMO patients have high in-hospital mortality due to the severe illness requiring support, along with comorbidities and complications. Certain significant complications, such as pneumonia, GI bleeding, sepsis and neurologic injury, which all had an incidence of greater than 10%, were likely the result of multifactorial issues. However, complications specifically related to VA-ECMO such as ischemic leg, haemorrhage, compartment syndrome, fasciotomy, as well as rate of cannula revision of 11% in VV-ECMO and 16% in VA-ECMO patients, demonstrate the complexity and potential harms specifically related to this therapy that contribute to poor outcomes.

Despite significant critical illness, rate of complication and in-hospital mortality, the subsequent course of patients who survived to hospital discharge was quite remarkable, with an 85% survival at 2 years. This is clearly evident in the Kaplan Meier survival curves for these patients, which markedly level out somewhere between 1 and 9 months and suggests that even longer-term survival should be very stable. This verification of long-term success is an important addition to our understanding of the genuine benefit of this therapy.

A 2016 cross sectional study of 100 VA and VV-ECMO patients demonstrated that HRQoL in these patients is higher than patients with other serious illnesses, but lower than the general population using the Short Form-36⁴¹. Two studies examined VA-ECMO patients alone. A study of 28 cardiogenic shock patients in 2008, with a median follow-up of 11 months, reported satisfactory mental health and vitality of VA-ECMO patients but persistent problems with work or other daily activities using the Short Form-36 questionnaire⁷. A smaller study of 7 VA-ECMO surviving refractory circulatory collapse found that patients at 46 (36-54) months post hospital discharge had acceptable long-term HRQoL and return to work⁴².

Although our VA-ECMO patients have equally encouraging results, the long lasting effects of the severe critical illness were still demonstrable at the median follow-up time of 2 years. Seventy-five percent of patients reported no issues with mobility and 65% were able to perform their usual activities. There were greater than two-thirds of survivors who reported having a good quality of life, despite their history of severe critical illness. Seventy five percent of patients tested for frailty during the follow-up clinic visit were not frail. Twenty-one percent of patients reported issues with anxiety or depression. This is lower than what has been reported for patients with similar severity of illness. There was a 25% reported depression rate at one year in a study of 448 survivors of severe sepsis using the same screening test (EQ-5D-3L)⁴³. A 37.7% rate of depression was reported in a six-month follow-up of 374 cardiac surgery patients screened with the Patient Health Questionnaire-9⁴⁴. The latter population has a greater resemblance to our patients, but the follow-up time was much shorter which may account for the greater rate of depression. Overall, these results suggest our patients have very reasonable functionality and independence at their latest follow-up. That is not to say they do not struggle post discharge as almost 50% had pain or discomfort and 11 out of 13 (73%) seen in clinic had cognitive impairment. Importantly, as a measure of their experience from treatment to follow-up, patients reported very low regret or remorse regarding the decision to undergo ECMO.

Despite younger age and less comorbidity, VV-ECMO patients appeared to demonstrate greater deficits in HRQoL. This may be a simple reflection of shorter median duration of follow-up (1.5 years) but the findings are impressive. Sixty-nine percent of patients reported issues with mobility and 61% with their usual activities. Compared to 7.9% in the VA-ECMO group, 23% of VV-ECMO patients reported issues with self-care. Forty-six percent of patients reported low quality of life and difficulty with IADLs. Seventy-five percent of patients seen in clinic met the criteria for frailty. In the whole follow-up cohort, significant symptoms of depression (23.1%), anxiety (38.5%), and PTSD (38%) were present. All of the VV-ECMO patients seen in follow-up reported pain or discomfort.

Thus, despite the shorter median follow-up time, there is still a real concern that patients requiring VV-ECMO had significantly more disability, discomfort and psychological issues. These findings are most likely related to the underlying disease process (predominately ARDS) and are consistent with studies specifically looking at ARDS outcomes. A 2013 study analyzing HRQoL in 67 adult ARDS patients supported with ECMO in three French ICUs⁴⁵ used HADS to identify that 25% patients had significant symptoms of depression and 34% anxiety. In the same study 16% of patients screened positive for PTSD using the Impact Event scale. A smaller study done in Australia in 2012 looked at 15 ARDS patients⁴⁶. Using EQ5D they reported patients having issues with mobility, usual activities, and self-care at 53%, 42% and 20% respectively consistent with our study where we found an incidence of 69%, 61%, and 23.1% respectively. Pulmonary sequelae following ARDS have been shown to cause a reduction in HRQoL regardless of ECMO initiation⁴⁶. Many ARDS survivors also suffer from permanent neurocognitive impairments and emotional morbidity following hospital discharge⁴⁷, also as seen in our study.

Advancements in life sustaining technology such as ECMO introduces numerous ethical issues^{48,49}. Due to the severity and urgency of illnesses where ECMO may be utilized, therapy often has to be implemented expeditiously with little opportunity to involve the patient in decision making. This leaves clinicians and substitute decision makers in a difficult position. They have to decide whether or not subjecting these patients to this invasive therapy, with a high likelihood of complications and mortality, is warranted. Furthermore, ECMO is resource intensive from an equipment, critical care and personnel standpoint, which can often create strain at a programmatic and institutional level. Ultimately, the question as to what benefit ECMO provides is critical for everyone involved from the system level to clinicians, families and ultimately patients. Our study adds important data verifying that the effects of this lifesaving therapy are long lasting beyond hospital discharge.

This long-term data may be utilized by clinicians in counselling family members and patients on the probability of survival with this therapy. Two-year survival post ECMO initiation is 37% with VA-ECMO and 48% with VV-ECMO but, importantly, if patients survive to hospital discharge they appear to have excellent predicted two-year survival of 85% at that time point. This provides reassurance at the time of hospital discharge. Although survival is better in the VV-ECMO cohort, somewhat counter intuitively, HRQoL outcomes appear to be poorer with this group. This fits with the ARDS literature in general, but is novel when the outcomes are referenced to survivors of VA-ECMO who demonstrate very reasonable outcomes. In fact, when compared to age-matched reference scores of EQ-5D-3L (Table 6) we see that VA-ECMO survivors were relatively similar to the reference score of the general population whereas the VV-ECMO survivors reported a much higher proportion of disability in the relevant domains. In both cohorts this alerts the need for specialized post discharge care focused on physical and cognitive rehabilitation, but also in the domains of pain and psychological management. Patients and families can be provided more accurate and reasonable expectations for recovery. Furthermore, even though VV support has not been traditionally considered as 'ultimately

critical' as VA support, this data reveals that the VV cohort may actually be the higher risk cohort at the time of hospital discharge. This is an unexpected and important finding. Finally, the significant finding from the DRS administration indicated that there was very little regret from the patient's perspective regarding the decision to be placed on ECMO, in particular none in the VV-ECMO cohort. These findings serve not only to inform and reassure recipients, providers and administrators of health care, but also identify areas for optimization of post ECMO care. In our own center, this data is helping to develop a specialized, team-based health care delivery model, as a solution to care of such complex patients and other patients with a prolonged ICU stay. We are currently hosting focus groups designed for researchers to gain a better understanding of the effectiveness of current health care processes from a patient perspective and determine where potential gaps in health care exist.

To our knowledge, this is the most comprehensive long-term HRQoL follow-up study on VA- and VV-ECMO patients. The focus of most previous studies were on mortality outcomes and predictors of mortality rather than HRQoL¹⁰⁻¹³. Five studies that analyzed long-term HRQoL in ECMO patients were described in the discussion above. Two analyzed outcomes in ARDS patients alone^{46,45}, three analyzed patients with cardiogenic shock^{7,42}, and one analyzed the VA- and VV-ECMO cohorts combined⁴¹. Some of these studies had larger sample sizes than ours, but none had as detailed of assessments or a clinical component.

Limitations

In order to complete a comprehensive review of HRQoL in all survivors of ECMO we had many limitations. To capture all patients who received ECMO in Manitoba we had very broad inclusion criteria, including a large duration between therapy and follow-up interview. We did not complete all interviews in the same setting. We chose questionnaires that could be completed both over the telephone and in clinic in order to maximize the sample size. Studies have shown that phone surveys are just as effective as face-to-face for the administration of certain questionnaires⁵⁰⁻⁵². Our study lacks both a control group and randomization. It is susceptible to center-specific selection bias in terms of clinical implementation of ECMO, which may limit generalizability. While our follow-up was of fair median duration, it was not complete as only 57% of surviving patients were reachable and willing to participate. This introduces the possibility of volunteer bias as well, although it is impossible to interpret the meaning of this as some of the patients refusing to participate did so because they were too busy in their daily lives suggesting high functionality. We do not have baseline HRQoL data for our patients. Finally with the high rates of comorbidities including drug and alcohol abuse there is a possibility that some patients had HRQoL impairments prior to their need for ECMO support.

Conclusions

In our long-term follow-up study of patients treated with ECMO in Manitoba, 2 year survival was 37% post VA-ECMO and 48% with VV-ECMO. Patients who survived to hospital discharge had an excellent estimated two-year survival of 85% that appeared stable at that time point. HRQoL outcomes were very reasonable considering the severity of illness at the time of treatment, especially in the patients receiving VA-ECMO. Their EQ-5D-3L results were very similar to age-matched controls in the general population. However, difficulties in physical, mental and psychological health as well as issues with pain and overall quality of life were still present in VA-ECMO patients and even more so in VV-ECMO patients, with a median time of follow-up of 2 years and 1.5 years respectively. Both cohorts of patients had very low regret or remorse regarding the decision to implement ECMO. These findings may be utilized by clinicians to provide family members and patients with their probability of survival as well as providing

reassurance and preparation for what to expect at the time of hospital discharge. Additionally, these important findings will serve to identify areas where we can improve and optimize care post ECMO, especially for VV-ECMO patients who may be at higher risk for poor subsequent HRQoL. It represents the first step in understanding long-term outcomes of ECMO and will help clinicians in their ongoing effort to ensure that patients not only survive, but also thrive following hospital discharge.

Conflict of Interest

The authors have no financial or other conflicts of interest to disclose.

References:

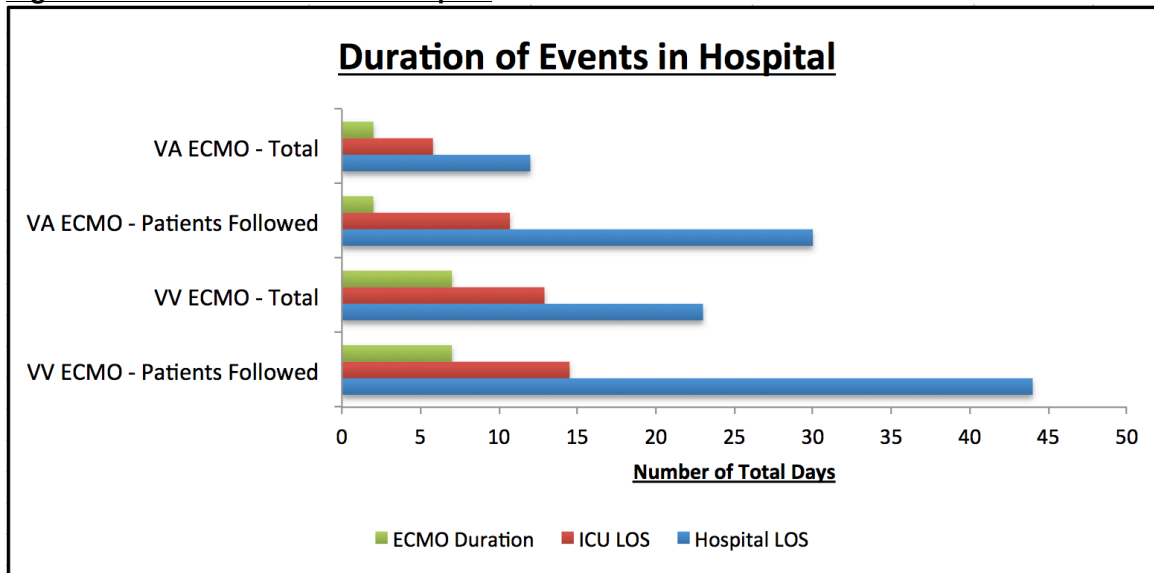
1. Abrams D, Combes A, Brodie D. Extracorporeal membrane oxygenation in cardiopulmonary disease in adults. *J Am Coll Cardiol*. 2014;63(25 PART A):2769-2778. doi:10.1016/j.jacc.2014.03.046.
2. Lafçi G, Budak AB, Yener AÜ, Cicek OF. Use of extracorporeal membrane oxygenation in adults. *Heart Lung Circ*. 2014;23(1):10-23. doi:10.1016/j.hlc.2013.08.009.
3. Sauer CM, Yuh DD BP. Extracorporeal membrane oxygenation use has increased by 433% in adults in the United States from 2006 to 2011. *ASAIO J*. 2015;61(1):31-36. doi:10.1097/MAT.0000000000000160.
4. The ANZIC Influenza Investigators. Critical Care Services and 2009 H1N1 Influenza in Australia and New Zealand. *N Engl J Med*. 2009;NEJMoa0908481. doi:10.1056/NEJMoa0908481.
5. Zangrillo A, Biondi-Zoccai G, Landoni G, et al. Extracorporeal membrane oxygenation (ECMO) in patients with H1N1 influenza infection: a systematic review and meta-analysis including 8 studies and 266 patients receiving ECMO. *Crit Care*. 2013;17(1):R30. doi:10.1186/cc12512.
6. Freed DH, Henzler D, White CW, et al. Extracorporeal lung support for patients who had severe respiratory failure secondary to influenza A (H1N1) 2009 infection in Canada. *Can J Anesth*. 2010;57(3):240-247. doi:10.1007/s12630-009-9253-0.
7. Combes A, Leprince P, Luyt C-E, et al. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. *Crit Care Med*. 2008;36(5):1404-1411. doi:10.1097/CCM.0b013e31816f7cf7.
8. Chen YS, Lin JW, Yu HY, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet*. 2008;372(9638):554-561. doi:10.1016/S0140-6736(08)60958-7.
9. Paden ML, Conrad S a, Rycus PT, Thiagarajan RR, ELSO Registry. Extracorporeal Life Support Organization Registry Report 2012. *ASAIO J*. 2013;59(3):202-210. doi:10.1097/MAT.0b013e3182904a52.
10. Schmidt M, Bailey M, Sheldrake J, et al. Predicting Survival after ECMO for Severe Acute Respiratory Failure: the Respiratory ECMO Survival Prediction (RESP)-Score. *Am J Respir Crit Care Med*. 2014;189(11):1374-1382. doi:10.1164/rccm.201311-2023OC.
11. Schmidt M, Burrell A, Roberts L, et al. Predicting survival after ECMO for refractory cardiogenic shock: The survival after veno-arterial-ECMO (SAVE)-score. *Eur Heart J*. 2015;36(33):2246-2256. doi:10.1093/eurheartj/ehv194.
12. Narotsky DL, Mosca MS, Mochari-Greenberger H, et al. Short-term and longer-term survival after veno-arterial extracorporeal membrane oxygenation in an adult patient population: does older age matter? *Perfusion*. 2015. doi:10.1177/0267659115609092.
13. Lee SH, Chung CH, Lee JW, Jung SH, Choo SJ. Factors predicting early- and long-term survival in patients undergoing extracorporeal membrane oxygenation (ECMO). *J Card Surg*. 2012;27(2):255-263. doi:10.1111/j.1540-8191.2011.01400.x.
14. Singal RK, Arora RC. Use of extracorporeal membrane oxygenation in cardiac arrest: Developing a new frontier. *J Thorac Cardiovasc Surg*. 2015;150(5):1350-1351. doi:10.1016/j.jtcvs.2015.08.021.
15. Bednarczyk JM, Singal RK. Functional outcomes after resuscitative extracorporeal membrane oxygenation for cardiac arrest: The patients speak for themselves. *J Thorac Cardiovasc Surg*. 2015;150(4):955-956. doi:10.1016/j.jtcvs.2015.06.035.

16. Riggs KR, Becker LB, Sugarman J. Ethics in the use of extracorporeal cardiopulmonary resuscitation in adults. *Resuscitation*. 2015;91:73-75. doi:10.1016/j.resuscitation.2015.03.021.
17. Bednarczyk JM, White CW, Ducas RA, et al. Resuscitative extracorporeal membrane oxygenation for in hospital cardiac arrest: A Canadian observational experience. *Resuscitation*. 2014;85(12):1713-1719. doi:10.1016/j.resuscitation.2014.09.026.
18. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-829. doi:10.1097/00003465-198603000-00013.
19. P.K. *The EuroQoL Instrument: An Index of Health Related Quality of Life.*; 1996.
20. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37(1):53-72. doi:10.1016/0168-8510(96)00822-6.
21. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: A multi-country study. *Qual Life Res*. 2013;22(7):1717-1727. doi:10.1007/s11136-012-0322-4.
22. Kim SH, Kim HJ, Lee S II, Jo MW. Comparing the psychometric properties of the EQ-5D-3L and EQ-5D-5L in cancer patients in Korea. *Qual Life Res*. 2012;21(6):1065-1073. doi:10.1007/s11136-011-0018-1.
23. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ*. 1998;316(7133):736-741. doi:10.1136/bmj.316.7133.731.
24. Calvert MJ, Freemantle N, Cleland JG. The impact of chronic heart failure on health-related quality of life data acquired in the baseline phase of the CARE-HF study. *Eur J Hear Fail*. 2005;7(2):243-251. doi:S1388-9842(05)00016-4 [pii]r10.1016/j.ejheart.2005.01.012.
25. Møller AH, Erntoft S, Vinding GR, Jemec GB. A systematic literature review to compare quality of life in psoriasis with other chronic diseases using EQ-5D-derived utility values. *Patient Relat Outcome Meas*. 2015;6:167-177. doi:10.2147/PROM.S81428.
26. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370. doi:10.1111/j.1600-0447.1983.tb09716.x.
27. Crawford JR, Henry JD, Crombie C, Taylor EP. Normative data for the HADS from a large non-clinical sample. *Br J Clin Psychol*. 2001;40(Pt 4):429-434. doi:10.1348/014466501163904.
28. Paffenbarger RS, Blair SN, Lee IM, Hyde RT. Measurement of physical activity to assess health effects in free-living populations. In: *Medicine and Science in Sports and Exercise*. Vol 25.; 1993:60-70. doi:10.1249/00005768-199301000-00010.
29. Spector WD, Fleishman J a. Combining activities of daily living with instrumental activities of daily living to measure functional disability. *J Gerontol B Psychol Sci Soc Sci*. 1998;53(1):S46-S57. doi:10.1093/geronb/53B.1.S46.
30. Weathers FW, Litz BT, Herman DS, Huska J a., Keane TM. The PTSD Checklist (PCL): Reliability, Validity, and Diagnostic Utility. *Pap Present Annu Meet Int Soc Trauma Stress Stud San Antonio, TX, October, 1993* . 1993;2:90-92.
31. Veterans Affairs UD. PTSD Checklist – Civilian Version (PCL-C). 1994:16-17.
32. Jackson JC, Jutte JE, Hunter CH, et al. Posttraumatic stress disorder (PTSD) after critical illness: A conceptual review of distinct clinical issues and their implications. *Rehabil Psychol*. 2016;61(2):132-140. doi:10.1037/rep0000085.
33. U.S. Department of Veterans Affairs. Using the PTSD Checklist for DSM-IV (PCL) Handbook. 2014;5(January):10-12.
34. Becerra Pérez MM, Menear M, Brehaut JC, Légaré F. Extent and Predictors of Decision Regret about Health Care Decisions: A Systematic Review. *Med Decis Making*. 2016;0272989X16636113 - . doi:10.1177/0272989X16636113.
35. Sinuff T, Dodek P, You JJ, et al. Improving end-of-life communication and decision making: The development of a conceptual framework and quality indicators. *J Pain Symptom Manage*. 2015;49(6):1070-1080. doi:10.1016/j.jpainsymman.2014.12.007.
36. Heyland DK, Dodek P, Rocker G, et al. What matters most in end-of-life care: perceptions of seriously ill patients and their family members. *CMAJ*. 2006;174(5):627-633. doi:10.1503/cmaj.050626.
37. Afilalo J, Eisenberg MJ, Morin J-F, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. *J Am Coll Cardiol*.

- 2010;56(20):1668-1676. doi:10.1016/j.jacc.2010.06.039.
38. Newman DG, Pearn J, Barnes a, Young CM, Kehoe M, Newman J. Norms for hand grip strength. *Arch Dis Child*. 1984;59(5):453-459. doi:10.1136/ad.59.5.453.
39. Fried LP, Tangen CM, Walston J, et al. Frailty in Older Adults: Evidence for a Phenotype. *Journals Gerontol Ser A Biol Sci Med Sci*. 2001;56(3):M146-M157. doi:10.1093/gerona/56.3.M146.
40. Nasreddine ZS, Phillips NA, B??dirian V, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x.
41. Hsieh FT, Huang GS, Ko WJ, Lou MF. Health status and quality of life of survivors of extra corporeal membrane oxygenation: A cross-sectional study. *J Adv Nurs*. 2016. doi:10.1111/jan.12943.
42. Mojoli F, Venti A, Pellegrini C, et al. Hospital survival and long term quality of life after emergency institution of venoarterial ECMO for refractory circulatory collapse. *Minerva Anesthesiol*. 2013;79(10):1147-1155.
43. Yende S, Austin S, Rhodes A, et al. Long-Term Quality of Life Among Survivors of Severe Sepsis. *Crit Care Med*. 2016;1. doi:10.1097/CCM.0000000000001658.
44. Horne D, Kehler S, Kaoukis G, et al. Depression before and after cardiac surgery: Do all patients respond the same? *J Thorac Cardiovasc Surg*. 2013;145(5):1400-1406. doi:10.1016/j.jtcvs.2012.11.011.
45. Schmidt M, Zogheib E, Rozé H, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome SEVEN-DAY PROFILE PUBLICATION. *Intensive Care Med*. 2013;39:1704-1713. doi:10.1007/s00134-013-3037-2.
46. Hodgson CL, Hayes K, Everard T, et al. Long-term quality of life in patients with acute respiratory distress syndrome requiring extracorporeal membrane oxygenation for refractory hypoxaemia. *Crit Care*. 2012;16(5):R202. doi:10.1186/cc11811.
47. Biehl M, Kashyap R, Ahmed AH, et al. Six-month quality-of-life and functional status of acute respiratory distress syndrome survivors compared to patients at risk: a population-based study. *Crit Care*. 2015;19(1):356. doi:10.1186/s13054-015-1062-y.
48. Abrams DC, Prager K, Blinderman CD, Burkart KM, Brodie D. Ethical dilemmas encountered with the use of extracorporeal membrane oxygenation in adults. *Chest*. 2014;145(4):876-882. doi:10.1378/chest.13-1138.
49. Consent I, Asch A, Wasserman D. The appropriate use of increasingly sophisticated life-sustaining technology. *Am Med Assoc J Ethics*. 2009;11(9):721-724.
50. van Wijck EE, Bosch JL, Hunink MG. Time-tradeoff values and standard-gamble utilities assessed during telephone interviews versus face-to-face interviews. *Med Decis Making*. 1998;18(4):400-405. doi:10.1177/0272989X9801800407.
51. McPhail S, Lane P, Russell T, et al. Telephone reliability of the Frenchay Activity Index and EQ-5D amongst older adults. *Health Qual Life Outcomes*. 2009;7(1):48+. doi:10.1186/1477-7525-7-48.
52. Wu AW, Jacobson DL, Berzon RA, et al. The effect of mode of administration on medical outcomes study health ratings and EuroQol scores in AIDS. *Qual life Res an Int J Qual life Asp Treat care Rehabil*. 1997;6(1):3-10. <http://www.ncbi.nlm.nih.gov/pubmed/9062436>.

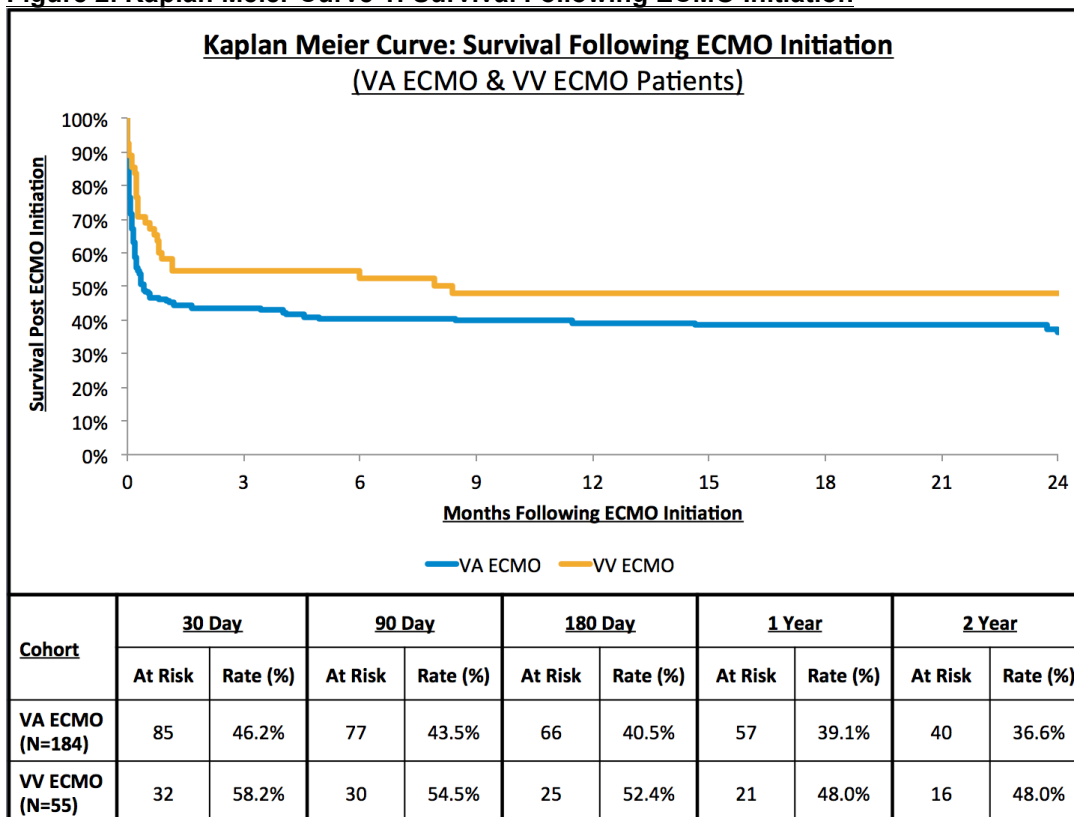
Figures and Tables:

Figure 1: Duration of Events in Hospital



Hospital LOS hospital length of stay, ICU LOS intensive care unit length of stay, VA ECMO venoarterial-extracorporeal membrane oxygenation, VV ECMO venovenous-extracorporeal membrane oxygenation

Figure 2. Kaplan Meier Curve 1: Survival Following ECMO Initiation



Cohort	30 Day		90 Day		180 Day		1 Year		2 Year	
	At Risk	Rate (%)	At Risk	Rate (%)	At Risk	Rate (%)	At Risk	Rate (%)	At Risk	Rate (%)
VA ECMO (N=184)	85	46.2%	77	43.5%	66	40.5%	57	39.1%	40	36.6%
VV ECMO (N=55)	32	58.2%	30	54.5%	25	52.4%	21	48.0%	16	48.0%

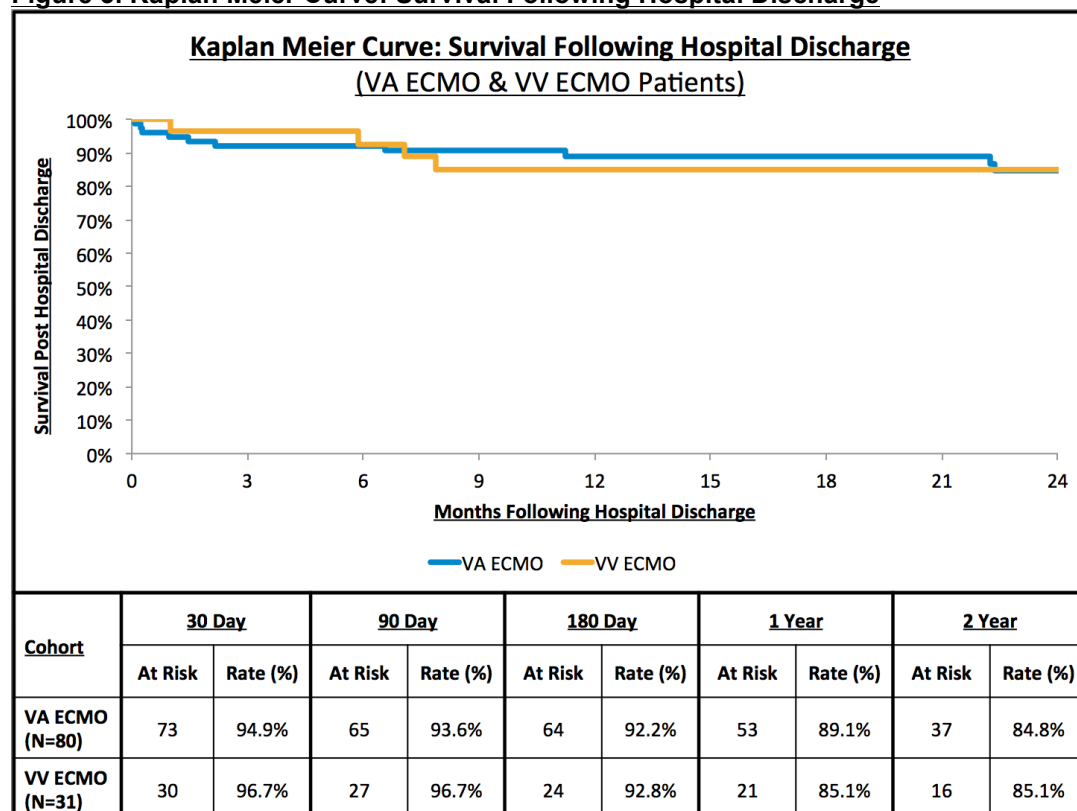
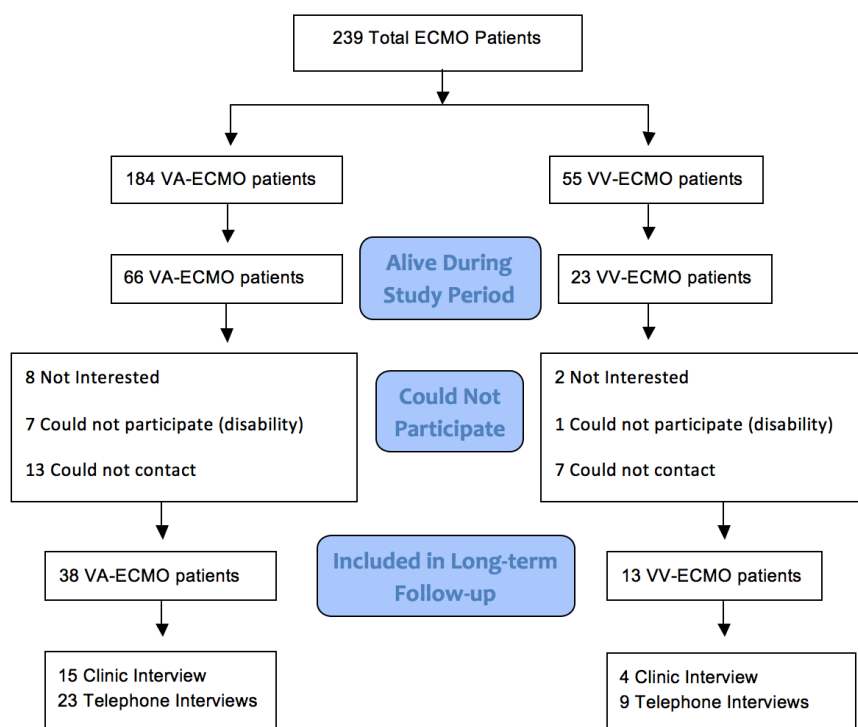
Figure 3. Kaplan Meier Curve: Survival Following Hospital Discharge**Figure 4. Summary of patient flow among adults treated with extracorporeal membrane oxygenation (ECMO).**

Table 1: Patient Questionnaires for Phone and Clinic

Questionnaires	Outcome Measure
1. ADLs & IADLs	Independence with ADLs and IADLs/Functional Status
2. Hospital Anxiety and Depression Score (HADS)	Anxiety and Depression Screen
3. PTSD Check List (PCL-C)	Post Traumatic Stress Disorder Screen
4. Decision Regret Scale	Degree of regret about having cardiac surgery
5. Paffenbarger Physical Activity Index	Part of the Modified Fried definition in order to assess frailty
6. EQ-5D/EQ-VAS	Overall HRQoL
7. Self-reported weight loss and Nutrition	Part of the Modified Fried definition in order to assess frailty
8. The Modified 2-item CES-D Scale	Part of the Modified Fried definition in order to assess frailty

ADL activities of daily living, CES-D Center for Epidemiologic Studies Depression, IADL instrumental activity of daily living, EQ-5D EuroQol five dimension, EQ-VAS Euroqol visual analog scale, ICU intensive care unit, PCL-C post traumatic stress disorder checklist-civilian, PTSD post traumatic stress disorder

Table 2: Patient Assessments for Clinic Only

Assessments	Outcome Measure
1. 5-meter gait speed measurement	Part of the Modified Fried/ Short Physical Performance Battery (SPPB) definition in order to assess frailty
2. Handgrip strength measurement	Part of the Modified Fried definition in order to assess frailty
3. Montreal Cognitive Assessment (MoCA)	Part of the Modified Fried definition in order to assess frailty

Table 3. Demographic Characteristics of ECMO Patients - November 2007 to June 2016

Variable	VA ECMO Patients (N=184)	VV ECMO Patients (N=55)	P-Value
Age	58 (50 - 65)	43 (26 - 56)	<0.01
Gender (Female)	58 (32%)	26 (47%)	0.03
Asthma	8 (4%)	9 (16%)	<0.01
COPD	11 (6%)	1 (2%)	0.31
Renal Failure	7 (4%)	1 (2%)	0.69
Renal Insufficiency	3 (2%)	3 (5%)	0.14
Cerebrovascular Accident	15 (8%)	0 (0%)	0.03
Alcohol Abuse	16 (9%)	12 (22%)	<0.01
Drug Abuse	6 (3%)	5 (9%)	0.13
Stable Angina	44 (24%)	1 (2%)	<0.01
Unstable Angina	6 (3%)	0 (0%)	0.34
Congestive Heart Failure	26 (14%)	2 (4%)	0.03
Diabetes	56 (30%)	15 (27%)	0.65
Hyperlipidemia	60 (33%)	10 (18%)	0.04
Hypertension	91 (49%)	19 (35%)	0.05
Previous Myocardial Infarction	25 (14%)	1 (2%)	0.01
Peripheral Vascular Disease	27 (15%)	2 (4%)	0.03
Tachyarrhythmia	30 (16%)	4 (7%)	0.09
GI Bleed	4 (2%)	0 (0%)	0.58
One or more comorbidity	152 (83%)	39 (71%)	0.06
APACHE II Score	27 (20 - 32)	26 (20 - 32)	0.99
Red Blood Cell Transfusions (ICU)	10 (4 - 18)	4 (3 - 9)	<0.01
FFP Transfusions (ICU)	6 (0 - 12)	0 (0 - 0)	<0.01
Platelet Transfusions (ICU)	5 (0 - 14)	0 (0 - 10)	0.02
Albumin 25% Transfusions (ICU)	4 (0 - 10)	4 (1 - 8)	0.97
Albumin 5% Transfusions (ICU)	6 (2 - 12)	2 (0 - 8)	0.01
One or more transfusion	167 (91%)	51 (93%)	0.79
ICU Length of Stay (Days)	5.8 (2.1 - 12.7)	12.9 (7.2 - 22.1)	<0.01
Hospital Length of Stay (Days)	12 (2 - 33)	23 (8 - 49)	0.02

Continuous variables expressed as median (interquartile range) compared using Mann-Whitney Test

Categorical variables expressed as N(%) compared using Fisher's Exact Test or Chi-Square Test.

APACHE acute physiologic and chronic health evaluation COPD chronic obstructive pulmonary disease, GI gastrointestinal, ICU intensive care unit, VA ECMO venoarterial-extracorporeal membrane oxygenation, VV ECMO venovenous-extracorporeal membrane oxygenation

Table 4. Primary Diagnosis, Secondary Diagnosis and Additional MCS Device, ECMO parameters

Variable	VA ECMO Patients (N=184)	VV ECMO Patients (N=55)
Duration of ECMO (Days)	2 (1 - 4)	7 (3 - 13)
Primary Diagnosis		
Cardiogenic Shock	116 (63.0%)*	1 (1.8%)
ADHF	3 (1.6%)	0 (0.0%)
Ischemic Heart Disease	86 (46.7%)	1 (1.8%)
Primary Arrhythmia	2 (1.1%)	0 (0.0%)
Valvular	10 (5.4%)	0 (0.0%)
Other	15 (8.2%)	0 (0.0%)
Postcardiotomy	36 (19.6%)	4 (7.3%)
Hypothermia	16 (8.7%)	0 (0.0%)
Pneumonia	0 (0.0%)	1 (1.8%)
Pulmonary Embolism	2 (1.1%)	0 (0.0%)
Toxic OD	6 (3.3%)	0 (0.0%)
Calcium Channel Blocker	3 (1.6%)	0 (0.0%)
TCA	1 (0.5%)	0 (0.0%)
Other	2 (1.1%)	0 (0.0%)
ARDS	4 (2.2%)	43 (78.2%)
H1N1 Influenza	1 (0.5%)	10 (18.2%)
Blastomycosis	0 (0.0%)	5 (9.1%)
Aspiration	0 (0.0%)	1 (1.8%)
Non H1N1 Influenza	0 (0.0%)	4 (7.3%)
Pneumonia	2 (1.1%)	17 (30.9%)
Other	1 (0.5%)	6 (10.9%)
Other	4 (2.2%)	6 (10.9%)
Labs		
pH at Cannulation	7.22 (7.08 - 7.37)	7.33 (7.26 - 7.41)
Lactate at Cannulation (mmol/L)	11.1 (7.4 - 14.5)	3.5 (2.1 - 6.4)
Lactate at 6h (mmol/L)	8.0 (5.0 - 11.4)	2.9 (2.1 - 6.1)
Lactate at 12h (mmol/L)	4.5 (2.9 - 8.3)	2.4 (1.8 - 5.0)
Peak Hemoglobin (g/L)	103 (95 - 114)	101 (95 - 110)
Lowest Hemoglobin (g/L)	73 (66 - 80)	73 (69 - 77)
Complications		
Compartment Syndrome	12 (6.5%)	0 (0.0%)
Cannula Revision	30 (16.3%)	6 (10.9%)
Device Failure	1 (0.5%)	0 (0.0%)
Hemolysis	0 (0.0%)	0 (0.0%)
Fasciotomy	6 (3.3%)	0 (0.0%)
Hemorrhage - Cannulation	9 (4.9%)	0 (0.0%)
Hemorrhage - Other	9 (4.9%)	2 (3.6%)
Ischemic Leg	5 (2.7%)	1 (1.8%)
Neurologic Injury (Stroke)	29 (16%)	6 (11%)
DVT	16 (9%)	1 (2%)
Pulmonary Embolism	4 (2%)	3 (5%)
Sepsis / Septic Shock	24 (13%)	39 (71%)
Pneumonia	39 (21%)	21 (38%)
GI Bleeding	32 (17%)	10 (18%)

*Continuous variables expressed as median (interquartile range); Categorical variables expressed as N(%)

ADHF acute decompensated heart failure, ARDS acute respiratory distress syndrome, DVT deep vein thrombosis, GI gastrointestinal, OD overdose, TCA tricyclic antidepressant

Table 5. Demographic Characteristics of ECMO Follow up Patients

Variable	VA ECMO Patients (N=38)	VV ECMO Patients (N=13)
Age	58 (46 - 64)	49 (40 - 52)
Gender (Female)	13 (34%)	5 (38%)
Obesity (BMI 30 to 39.9)	6 (16%)	3 (23%)
Alcohol Abuse	3 (8%)	5 (38%)
Drug Abuse	1 (3%)	1 (8%)
Congestive Heart Failure	6 (16%)	0 (0%)
Diabetes	4 (11%)	3 (23%)
Hyperlipidemia	8 (21%)	4 (31%)
Hypertension	18 (47%)	4 (31%)
Previous Myocardial Infarction	3 (8%)	0 (0%)
Peripheral Vascular Disease	3 (8%)	0 (0%)
Tachyarrhythmia	7 (18%)	1 (8%)
APACHE II Score	23 (17 - 29)	22 (20 - 26)
ICU Length of Stay (Days)	10.7 (5.7 - 19.7)	14.5 (11.8 - 43.7)
Hospital Length of Stay (Days)	30 (18 - 44)	44 (20 - 67)
Follow-up Time (Years Post ECMO Initiation)	2.0 (0.8 - 3.0)	1.5 (0.5 - 2.6)
Primary Diagnosis		
Cardiogenic Shock	25 (65.8%)	0 (0.0%)
Postcardiotomy	6 (15.8%)	2 (15.4%)
Hypothermia	1 (2.6%)	0 (0.0%)
Pneumonia	0 (0.0%)	1 (7.7%)
Pulmonary Embolism	1 (2.6%)	0 (0.0%)
Toxic OD	2 (5.3%)	0 (0.0%)
ARDS	1 (2.6%)	10 (76.9%)
Other	2 (5.3%)	0 (0.0%)

*Continuous variables expressed as median (interquartile range); Categorical variables expressed as N(%)
 APACHE acute physiologic and chronic health evaluation, BMI body mass index, ICU intensive care unit, OD overdose

Table 6. Demographic Characteristics of ECMO Follow up Patients

Variable	VA ECMO Patients (N=38)	VV ECMO Patients (N=13)	Reference Scores**
EQ-VAS Score	70 (60 - 80)	70 (50 - 75)	≤ 60 = low
Patients with EQ-VAS ≤ 60	11 (29%)	6 (46%)	-
EQ-5D-3L (Patients with Any Issue)			
Mobility	9 (23.7%)	9 (69.2%)	21.9%
Self Care	3 (7.9%)	3 (23.1%)	5.2%
Usual Activities	14 (36.8%)	8 (61.5%)	21.8%
Pain or Discomfort	17 (44.7%)	13 (100.0%)	43.7%
Anxiety or Depression	8 (21.1%)	9 (69.2%)	27.2%
Patients with Depression (HADS)			
No Depression	34 (89.5%)	7 (53.9%)	88.6%
Borderline	2 (5.3%)	3 (23.1%)	7.8%
Yes	2 (5.3%)	3 (23.1%)	3.6%
Patients with Anxiety (HADS)			
No Anxiety 0-7	28 (73.7%)	6 (46.2%)	66.8%
Borderline 8-10	7 (18.4%)	2 (15.4%)	20.6%
Yes 11-21	3 (7.9%)	5 (38.5%)	12.6%
Paffenbarger Score	584 (252 - 1036)	336 (168 - 1624)	≤ 326.5 = low
Patients with Low Physical Activity	13 (34.2%)	7 (53.9%)	-
ADLs & IADLs			
Patient difficulty with Any ADL	6 (15.8%)	3 (23.1%)	-
Patient difficulty with Any IADL	14 (36.8%)	6 (46.2%)	-
PTSD Severity Score (/85)	26 (21 - 35)	30 (22 - 50)	30-35
Patients with PTSD (≥ 40)	4 (13%)	5 (38%)	<15%
DRS Score Total (/100)	5 (0 - 13)	0 (0 - 10)	16.5

*Continuous variables expressed as median (interquartile range); Categorical variables expressed as N (%)

** References found in methods section

ADL activities of daily living, ARDS acute respiratory distress syndrome, DRS decision regret scale, EQ-5D-3L EuroQol five dimension 3L, EQ-VAS EuroQol visual analog scale, HADS hospital anxiety and depression score, IADL instrumental activity of daily living, PTSD post traumatic stress disorder

Table 7. Follow-up of ECMO Patients (Clinic Only)

Variable	VA ECMO Patients (N=15)	VV ECMO Patients (N=4)
Modified Fried Frailty Parameters		
Cognitive Impairment (MoCA < 25)	11 (73.3%)	3 (75.0%)
GDS Depression	5 (33.3%)	2 (50.0%)
Slow Gait Speed	3 (20.0%)	2 (50.0%)
Poor Grip Strength	3 (20.0%)	2 (50.0%)
Weight Loss	1 (6.7%)	2 (50.0%)
Exhaustion	3 (20.0%)	1 (25.0%)
Low Physical Activity	4 (26.7%)	3 (75.0%)
Modified Fried Frail (≥ 3)	4 (26.7%)	3 (75.0%)
Modified Fried Score	2 (1 - 3)	4 (2 - 6)
Clinical Frailty Scale	2 (2 - 4)	3 (3 - 4)

***Continuous variables expressed as median (interquartile range) ; Categorical variables expressed as N(%)**
GDS geriatric depression scale, HADS hospital anxiety and depression scale, MoCA Montreal cognitive assessment