BLOOD PRODUCT ADMINISTRATION AND KIDNEY FUNCTION AS A MORTALITY INDICATOR FOR VA-ECMO: A RETROSPECTIVE REVIEW OF A SINGLE INSTITUTION

by

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As members of the Master's Committee, we certify that we have read the thesis prepared by **Jesse Montoya**, titled **Blood Product Administration and Kidney Function as a Mortality Indicator for VA-ECMO: A Retrospective Review of a Single Institution** and recommend that it be accepted as fulfilling the thesis requirement for the Master's Degree.

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Final approval and acceptance of this thesis is contingent upon the candidate's submission of the final copies of the thesis to the Graduate College.

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Jesse Montoya

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Abstract

Background

Veno-arterial extracorporeal membrane oxygenation (VA ECMO) is a rapidly growing treatment for critically ill patients. The management of this life-saving therapy is extremely complicated; requiring highly trained professionals in the intensive care unit. Since the epidemic of influenza A in 2009, the usage of ECMO has increased by a 1000 fold. Unfortunately, the research and data is not able to keep up. Herein, we aim to increase this data with our own and look for markers that show an increase risk of mortality. We especially want to take note of blood product usage, kidney function, and patient platelet counts as indicators for increased mortality.

Methods

This is a retrospective analysis of patients that underwent VA ECMO treatment at Banner University Medical Center – Tucson, during the time period of January 2010 – December 2015. We disqualified patients that were on VA ECMO for less than 22 hours, as we felt this was not long enough of a time period to allow the changes we were hoping to discern. Data from the remaining 70 patients (32F/38M), median age 44 (11 – 61.5) years, was obtained by chart review. Patients were separated into two groups: those who survived until discharge (survivors, N = 25), and those who did not (nonsurvivors, N = 45).

Results

Our VA ECMO survival rates are 35.7% for our included patients. Nonsurvivors had much higher rates of receiving CRRT (64.4% vs 20.0%, $p < 0.001$) and higher initial (22 vs 18, $p = 0.030$) and average (31 vs 21, $p = .023$) BUN values than the survivors. Non survivors also received much more pRBCs (3451 vs 2080 ml, $p = 0.003$), platelets (1900 vs 556 ml, $p = 0.003$) and FFP (1123 vs 240 ml, $p = .001$) over the course of their run than survivors. There was no significant difference in any measured platelet counts between patients.

Conclusions

Patients that receive increased blood product administration and reduced kidney function during VA ECMO are at an increased risk of mortality. Further studies are required to further elucidate markers of ECMO outcomes that can guide the practice.

Introduction

Veno-arterial Extracorporeal Membrane Oxygenation (VA ECMO)

Veno-arterial extracorporeal membrane oxygenation (VA ECMO) is a critical care therapy that is utilized for acute cardiorespiratory failure. There are numerous indication for use of VA ECMO, including: accidental hypothermia, acute heart failure, fulminant pulmonary embolism, refractory shock, and need for extracorporeal cardiopulmonary resuscitation (ECPR)[1-4]. It is an invasive procedure that requires, at minimum, a percutaneous cannulation site, if not a completely opened sternum and thoracic cavity. VA ECMO drains a patient's blood from a venous (inflow, drainage) cannula, where the blood is then pulled through the tubing to

a centrifugal (rotational) pump. Once it passed through the pump, the blood is now pushed through an extracorporeal oxygenator that sweeps CO2 out of the blood and delivers O2 to the blood. The now oxygenated blood is then reinfused into the patient via an arterial (outflow, return) cannula.

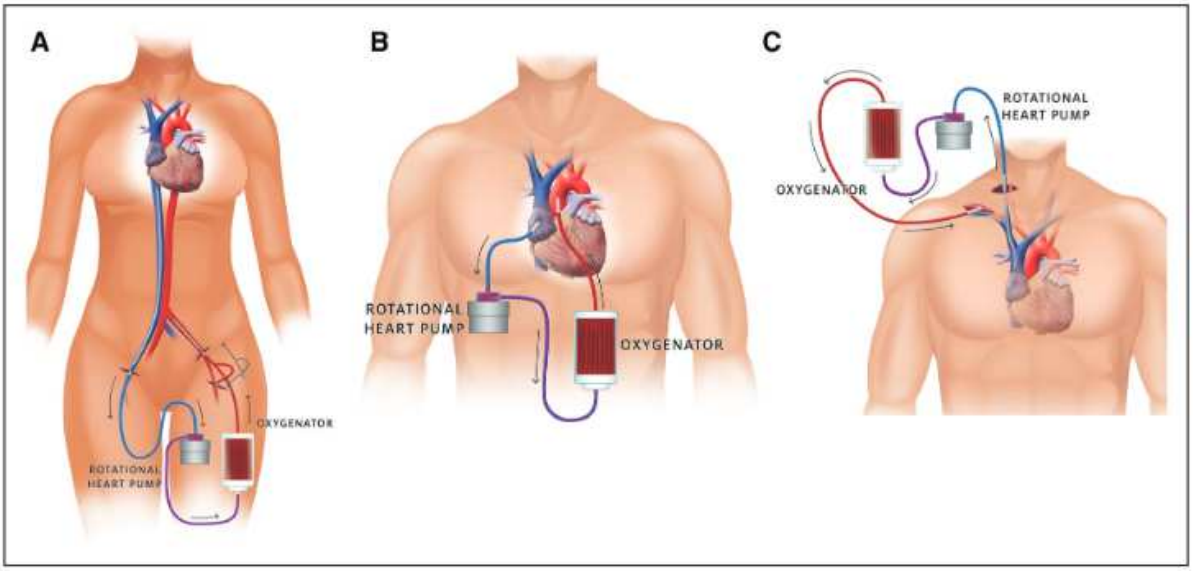

Figure 1: Central and peripheral venoarterial extracorporeal membrane oxygenation (VA-ECMO) cannulation strategies.A, Peripheral VA-ECMO (femoro-femoral configuration). B, Central VA-ECMO. C, Peripheral VA-ECMO (sport configuration). Note although one may be cannulated peripherally through a peripheral vessel, the net effect on regional perfusion may be more akin to central cannulation (cannulation of the great vessels through a sternotomy). A good example of this is axillary cannulation as in (C) [5]

There are three prevalent techniques for cannulation of a VA ECMO patient and they are seen shown and described in Figure 1. ECMO provides the ability to provide blood gas exchange and cardiac output indefinitely, provided the system remains mechanically and functionally intact.

Anticoagulation and blood product management influence the longevity of an ECMO circuit. The issue with this is that ECMO is not a long-term plan and must have an exit strategy, whether that's recovery or using ECMO as a bridge to another therapy, such as transplant or total artificial heart implantation.

Complications During VA ECMO

The current guidelines from Extracorporeal Life Support Organization (ELSO) for VA ECMO is to treat patients with unfractionated heparin [26]. An issue with chronic heparin therapy is that patients have the possibility of developing heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia thrombosis (HITT). HIT/HITT has been shown to increase patient morbidities and mortality. HIT results in antibodies strongly activating platelets and cause thrombocytopenia and massive thrombin generation which can be either arterial or venous, leading to thrombotic-related morbidities and mortality [6]. It is estimated that roughly 1-4% of the ECMO population suffer from HIT, with the highest incidence being those patients in an intensive care unit following cardiac surgery [6, 7].

There are many neurological complications that may occur during an ECMO run. Some studies have shown anywhere between 7-11% of patients suffer some degree of neurological complication during ECMO treatment [8-11]. These complications manifest most commonly as seizure, stroke, intracranial hemorrhage; these can lead to irreparable brain damage, or in some cases, even brain death [8-11]. The incidence of catastrophic neurological adverse events is greater with VA ECMO versus VV ECMO and can impact overall outcomes [12]

Patients receiving ECMO therapy experience a high rate of major and minor bleeding, incidences have been reported at approximately 30% [13-16]. Etiologies may include acquired von Willenbrand deficiency, disseminated intravascular coagulation, systemic intravascular response like syndromes, long term use of anticoagulants, and the filtering/consumption of coagulation factors. Contact with foreign surfaces of the ECMO circuit can alternately induce inflammatory and prothrombotic responses [17-19]. Anticoagulation is used to mitigate this risk, but despite these efforts, estimates of thrombotic events are close to 15% of ECMO runs [20], with some suggestion that these events are very likely underdiagnosed [21].

VA ECMO is an extremely invasive procedure and, like other invasive procedures, has a high risk of infection of the patient. Infection rates are seen in 10-30% of patients, depending on the admission diagnosis of these patients receiving treatment [13, 22, 23]. . The percutaneous nature of ECMO places these critically ill patients at a significantly higher risk of infection. These patients tend to exhibit compromised immune function which makes outcomes in infected ECMO patients worse than other critically ill patients [23]. They may also have other organ systems that are failing beyond their cardiopulmonary system that may compound the issues and make them more susceptible to infections as well. Infection increases the risk of mortality in ECMO patients by 38-63% and should be seen as a serious risk for these vulnerable patients [24, 25].

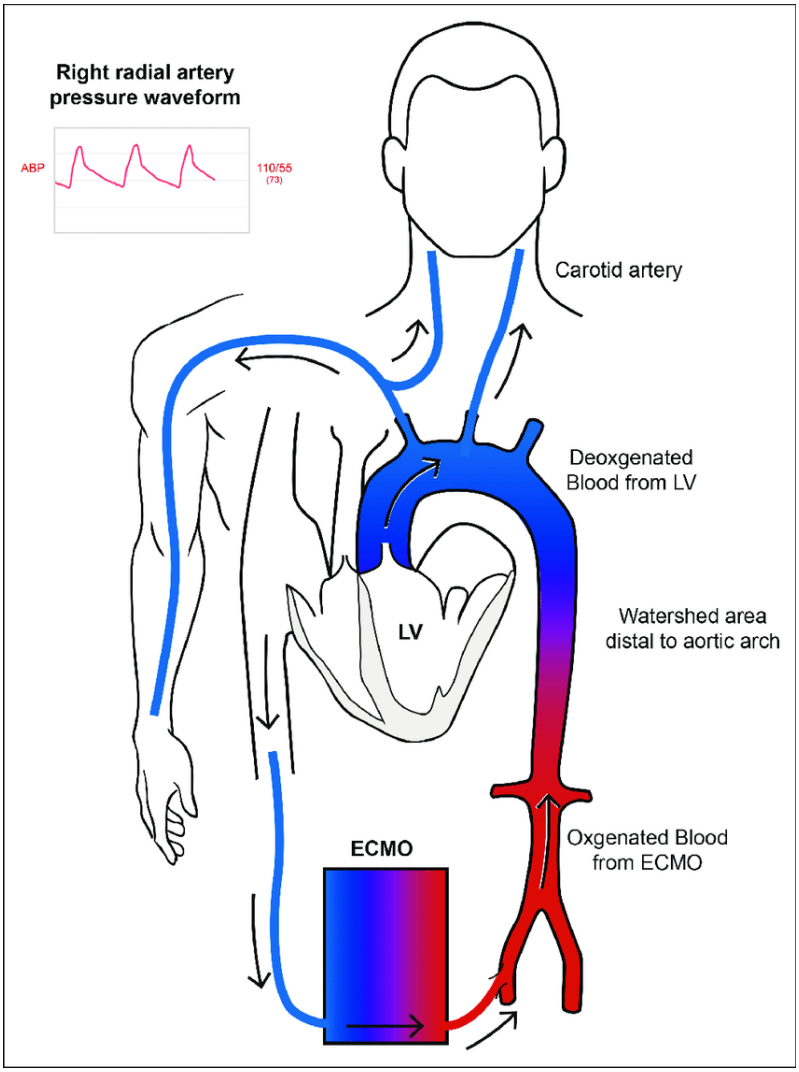

Figure 2: North-south (Harlequin) syndrome: a common consideration with femoral artery cannulation and when the lungs are not adequately oxygenating blood [5].

VA ECMO is generally started when cardiac output is poor. As the heart recovers, it can compete with the ECMO pump and cause issues since the blood it is pumping is not well oxygenated. This deoxygenated blood is delivered to the coronaries and upper body. This complication has two commonly used names: North-South Syndrome and Harlequin Syndrome. This is most commonly an issue with femoral cannulation for VA ECMO.

The Need For Research

The popularity of ECMO therapy is growing at an accelerated rate, however, rigorous study of protocols and procedure are lacking. The number of adult VA ECMO cases across the country has increased from 259 cases in 2008, to 3433 cases in 2018 [27]. This is an increase of over 1300% in just a decade of time. As for VV ECMO, the number of adult cases jumped from 200 cases in 2008, to 2923 cases in 2018. This is over a 1400% increase in the same amount of time [27]. Much of the investigation in this field stems from case reports and small cohorts of patients. There is little guidance available for blood and blood product transfusion thresholds. Most of the studies showing an increased risk of any type for these patients, usually is in a patient population that is nowhere near the size that our cardiopulmonary bypass studies will have. The data that does come out isn't strong enough in most cases have 200 or less patients in the study. This is barely more than 5% of the total patients that receive just adult VA ECMO, let alone all the different types of ECMO utilized in the field.

Hypothesis and Specific Aims

Hypothesis

Our central hypothesis is to retrospectively review the VA ECMO population of our center in hopes of elucidating that: 1) low platelet count is an increased risk or predictor of mortality. We suspect that giving patients platelets at low platelet counts may not always be the best decision, especially if the patient is not having any issues with bleeding. 2) There is a correlation between markers of coagulation and higher rates of blood product administration and the mortality rate of patients. Finally, 3) Decreased function of the kidneys will lead to higher rates of mortality. The goal of this is to test our hypotheses, but to also see if there are

other demographics or markers that are not well known with association of mortality with ECMO.

Specific Aims

I. To find if there is a significant difference between low platelet counts and the survival rate of the patients.
    a. We will compare the initial, the total average, and the final platelet counts between the two groups to see if lower platelet counts result in higher mortality rates.

II. To evaluate if kidney function is indicative of increased risk of mortality for a patient.
    a. We will compare the initial, total average, and final BUN tests between the two groups to see if higher test reading result in higher mortality rates.
    b. We will compare the occurrence of utilization of continuous renal replacement therapy (CRRT) for a correlation of higher mortality rates between the two groups.

III. To show if there is a correlation between higher rates of blood product administration and an increased mortality of patients between the two groups.
    a. We will compare the amount of cryoprecipitate (Cryo), fresh frozen plasma (FFP), platelets, and packed red blood cells (pRBCs) given between the two groups to show that increased administration of products results in higher mortality of the patient.

b. We will try to show that even though patients may have low platelet counts, that administration of platelets and other blood products may not be required if they're not bleeding.

IV. To mine all other bio-markers and patient's demographic in elucidate any correlations leading to increased mortality between survivors and nonsurvivors VA-ECMO.

Materials and Methods

Study Design

This is a retrospective observational chart review performed on patients at a 487 bed, acute-care academic medical center who received ECMO support from January 2010 to December 2015. Patients that required VA-ECMO were eligible for inclusion. Patients who were supported for less than 22 hours were excluded.

We looked at 55 different variables in these patients. These include many demographics such as: age, weight, sex, height, medical histories, reason for hospital admission and reason for VA ECMO. Laboratory values extracted include: platelet count, partial thromboplastin time (PTT), fibrinogen, D-dimer (DD), prothrombin time (PT), international normalized ratio (INR), activated clotting time (ACT), antithrombin III level, native thromboelastogram (n-TEG) with heparinase parameters (R and coagulation index). Our standard practice is to monitor ACT hourly (immediately upon cannulation with decreasing frequencies after 24 to 48 hours), PTT every 4-6 hours, PT/INR and fibrinogen every 12 hours, platelet count at least twice daily unless transfusion is required, and antithrombin III level and TEGs daily. All laboratory values during ECMO support were recorded and averaged per day. ECMO circuit flow rate, sweep, and MO

arterial-venous pressure gradients were recorded at the highest and lowest point per 24 hour time period. Morning arterial blood gases (pH, pCO_2, pO_2) were recorded. Anticoagulant dosing was collected by hour and averaged for the day. Daily transfusions of packed red blood cells (pRBC), platelets, fresh frozen plasma (FFP), and cryoprecipitate (cryo) were recorded in milliliters (mL). The average daily values of each lab were recorded for the entirety of the run. This study was approved by the University's Investigational Review Board.

VA ECMO Equipment and Hemostasis

Patients were treated with venoarterial VA ECMO using a heparin-coated circuit (Bioline; Maquet Cardopulmonary AG, Hirrlingen, Germany) consisting of a Quadrox oxygenator and a Rotaflow centrifugal blood pump (both Maquet Cardiopulmonary). Systemic anticoagulation was administered starting with a goal target ACT of 160-220 seconds depending on baseline bleeding and assessed risk of bleeding. In general, our anticoagulation was initiated with the target of an ACT of 180-220 seconds. Anticoagulation targets were tailored to the individual throughout the ECMO course using ACT, PTT, and n-TEG. Antithrombin III was administered at provider discretion, but goal antithrombin level of at least 85% was the usual target. Standing orders for transfusion of cryoprecipitate, platelets, and pRBCs were standard of care and products were given to maintain fibrinogen levels >150 mg/dL, PLT >80-100 1000/µL, and HCT of 25%, respectively.

Data Analysis

Data collected was compiled into a Microsoft Excel file which was then imported into International Business Machines Corporation's (IBM) SPSS software. The data was first split into

two different groups: those that survived until discharge from the hospital (survivors [n = 25]), and those that died during their stay (non-survivors [n = 45]). There was a small sample size for the survivors group that we could not assume normal distribution under the central limit theorem, therefore, each data point was tested for normality. Shapiro-Wilk and the Kolmogorov-Smirnov tests were used alongside a visual inspection to analyze the data distributions and they indicated the data to be non-normal, so we used strictly nonparametric tests for our analyses. For ordinal data, we utilized the Pearson's Chi Squared test, while the Mann-Whitney U test were used for continuous data. Our results were recorded as either percentages for ordinal data, or a median with corresponding interquartile ranges (IQR) for continuous data.

Results

Patient Demographics

	All Patients (n = 70)	Nonsurvivors (n = 45)	Survivors (n = 25)	p-value
Age (years)	**44.0 [11.0, 61.5]**	**50 [18.5, 65.0]**	**35.0 [.62, 47.5]**	**0.028**
Sex: Male	54.3%	57.8%	48%	0.431
Sex: Female	45.7%	42.2%	52%	0.431
Weight (kg)	72.0 [45.4, 92.1]	75.0 [56.5, 91.9]	65.0 [5.45, 92.1]	0.391
Height (cm)	166.0 [152.4, 177.8]	167.6 [158.1, 177.8]	161.3 [57.6, 176.5]	0.264
BMI	26.6 [21.7, 31.6]	26.3 [22.5, 31.1]	28.0 [19.5, 31.8]	0.718
BSA (m^2)	1.83 [.74, 2.09]	1.88 [1.57, 2.11]	1.73 [.28, 2.11]	0.443
Diabetes Mellitus	18.6%	24.4%	8.0%	0.090
Hypertension	22.9%	20.0%	28.0%	0.445
Atrial Fibrillation	**21.4%**	**28.9%**	**8.0%**	**0.041**
COPD	2.9%	4.4%	0%	0.285
Previous MI	21.4%	24.4%	16.0%	0.409
Peripheral Vascular Disease	21.4%	22.2%	20.0%	0.828
Chronic Heart Failure	20.0%	26.7%	8.0%	0.061

Figure 3: Table comparing patient demographics between all patients, survivors and nonsurvivors**.**

A total of 70 patients (median age 44 years, with IQR 11 to 61.5) were included in the study. In our patient population, we had a survival until discharge rate of 35.7%. The first portion we decided to analyze was patient demographics and history. These are the measures and values that we as clinicians can examine before further deciding treatment for the patient. First, we found that nonsurvivors were significantly older on average than survivors (median ages 50 vs 35, p = 0.028). We found there to be no significant difference between sex, weight, height, BMI, or BSA between the two groups. As for medical histories of the patients, we were surprised to find that nonsurvivors had a significantly higher prevalence of atrial fibrillation (28.9% vs 8.0%, p = 0.041). We found no significant difference between the two groups with medical histories that included: diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), previous myocardial infarction (MI), peripheral vascular disease, or chronic heart failure (CHF).

Pre ECMO

	All Patients (n = 70)	Nonsurvivors (n = 45)	Survivors (n = 25)	p-value
Admission Diagnosis:				**0.039**
1) Surgery	24.3%	31.1%	12.0%	
2) Heart Failure	15.7%	20.0%	8.0%	
3) Cardiac Arrest	7.1%	4.4%	12.0%	
4) Transplant	5.7%	8.9%	0%	
5) Septic Shock	10.0%	11.1%	8.0%	
6) Respiratory	11.4%	4.4%	24.0%	
7) Congenital Defects	14.3%	8.9%	24.0%	
8) Other	10.0%	8.9%	12.0%	

Reason for ECMO:				0.257
1) Cardiac Failure	10.0%	15.6%	0%	
2) Cardiopulmonary Arrest	12.9%	15.6%	8.0%	
3) Cardiogenic Shock	40.0%	33.3%	52.0%	
4) Respiratory Related	12.9%	11.1%	16.0%	
5) Cardiopulmonary Collapse	18.6%	17.8%	20.0%	
6) Other	5.7%	6.7%	4.0%	
Surgery Prior to ECMO?	51.4%	53.3%	48.0%	0.669
Surgery Type:				**0.024**
0) No Surgery	48.6%	46.7%	52.0%	
1) Elective Adult Cardiac	25.7%	35.6%	8.0%	
2) Emergent Adult Cardiac	2.9%	0%	8.0%	
3) Congenital	8.6%	2.2%	20.0%	
4) Transplant	5.7%	6.7%	4.0%	
5) Cath Procedure	4.3%	4.4%	4.0%	
6) Other	4.3%	4.4%	4.0%	
IABP	31.4%	33.3%	28.0%	0.645
Cath lab prior to ECMO	18.8%	15.9%	24.0%	0.409
Infection Prior to ECMO	22.9%	22.2%	24.0%	0.865
Infection Type:				0.817
0) None	77.1%	77.8%	76.0%	
1) Bacterial	14.3%	13.3%	16.0%	
2) Viral	2.9%	2.2%	4.0%	
3) Bacterial and Viral	2.9%	4.4%	0%	
4) Fungal and Bacterial	2.9%	2.2%	4.0%	

Figure 4: Table comparing diagnosis and interventions prior to ECMO initiation between all patients, survivors and nonsurvivors.

Next, we examined the patient's status prior to ECMO initiation. We found that there was a significant difference in admission diagnosis between the two groups ($p = 0.039$). Nonsurvivors were most commonly admitted for either surgery or heart failure (31.1% and 20.0% respectively), while survivors were most commonly admitted for respiratory issues and congenital defects (24.0% for both). We see no significance between the two groups with

whether or not the patient had surgery prior to ECMO initiation (p = 0.669), but if they did have surgery, then the type of surgery they had was of significance between the two groups (p = 0.024). The most common surgery for the nonsurvivors was elective adult cardiac cases (35.6%) while survivors most common surgery was for congenital defects (20.0%). Between both groups, we found no significant difference in: why the patient was put on ECMO, if they had an infection prior to ECMO, if they had been to the cath lab prior to ECMO, or if there had been an intra-aortic balloon pump (IABP) placed at any time before or during ECMO.

During ECMO

	All Patients (n = 70)	Nonsurvivors (n = 45)	Survivors (n = 25)	p-value
ECMO Cannulation Site				0.716
1) Central	31.4%	26.7%	40.0%	
2) Peripheral, Fem	44.3%	48.9%	36.0%	
3) Peripheral, Neck	15.7%	15.6%	16.0%	
4) Peripheral, Other	7.1%	6.7%	8.0%	
Duration of ECMO (Hr)	**130.0 [81.8, 167.8]**	**143.0 [93.0, 170.5]**	**87.0 [63.25, 152.0]**	**0.044**
CRRT During ECMO	**48.6%**	**64.4%**	**20.0%**	**< 0.001**
Severity of Bleeding:				0.393
0) No Bleed	60.0%	60.0%	60.0%	
1) Minor	17.1%	13.3%	24.0%	
2) Major	22.9%	26.7%	16.0%	

Figure 5: Table comparing events that occurred during ECMO between all patients, survivors and nonsurvivors.

ECMO cannulation site was found to have no significance between the two groups. There was seen to be no difference in occurrence and severity of bleeding between survivors and nonsurvivors (p = 0.393). There was a significant difference in utilization of CRRT, where nonsurvivors had a drastically higher percentage of patients require this treatment during

ECMO (64.4% vs 20.0%, p < 0.001). The survivor group had significantly shorter ECMO runs than the nonsurvivor groups (median duration of 87.0 hours vs 143 hours).

ECMO Coagulation and Chemistry

	Nonsurvivors (n = 45)	Survivors (n = 25)	p-value
Flow Rate	3.46 [2.89, 4.14]	3.03 [.65, 4.00]	0.140
Flow Rate/kg (ml/kg)	50.3 [39.9, 65.5]	59.3 [38.6, 98.5]	0.436
CI of Flow	1.99 [1.72, 2.26]	1.94 [1.57, [2.30]	0.352
pH	7.39 [7.36, 7.42]	7.40 [7.38, 7.42]	0.607
ACT	185 [174, 201]	186 [176, 192]	0.641
Heparin Dose (u/kg/hr)	**7.0 [2.9, 9.9]**	**14.6 [6.4, 20.7]**	**0.002**
PTT	62 [48, 75]	69 [50, 78]	0.444
INR	1.6 [1.3, 1.8]	1.4 [1.3, 1.6]	0.103
D-Dimer	9.7 [3.3, 15.7]	8.2 [2.3, 13.4]	0.404
TEG R (w/ Heparinase)	23.3 [21.8, 29.3]	23.8 [19.4, 27.3]	0.444
TEG CI (w/ Heparinase)	.33 [-0.58, .93]	.33 [-0.35, 1.26]	0.466
Initial BUN	**22 [17, 42]**	**18 [12, 30]**	**0.030**
Average BUN	**31 [23, 38]**	**21 [16, 35]**	**0.023**
Final BUN	30 [19, 48]	26 [18, 37]	0.425

Figure 6: Table comparing kidney and coagulation markers between both groups.

Flow rate, flow rate/kg, cardiac index of flow were all found to have no significance between the two groups. While ACT, PTT, INR, D-Dimer, n-TEG R and CI were all found to have no significant difference between the survivor and nonsurvivor groups, the heparin dosing was seen to have a significant difference; survivors received, on average, more than twice the dose of nonsurvivors (14.6 vs 7.0, p = 0.002).

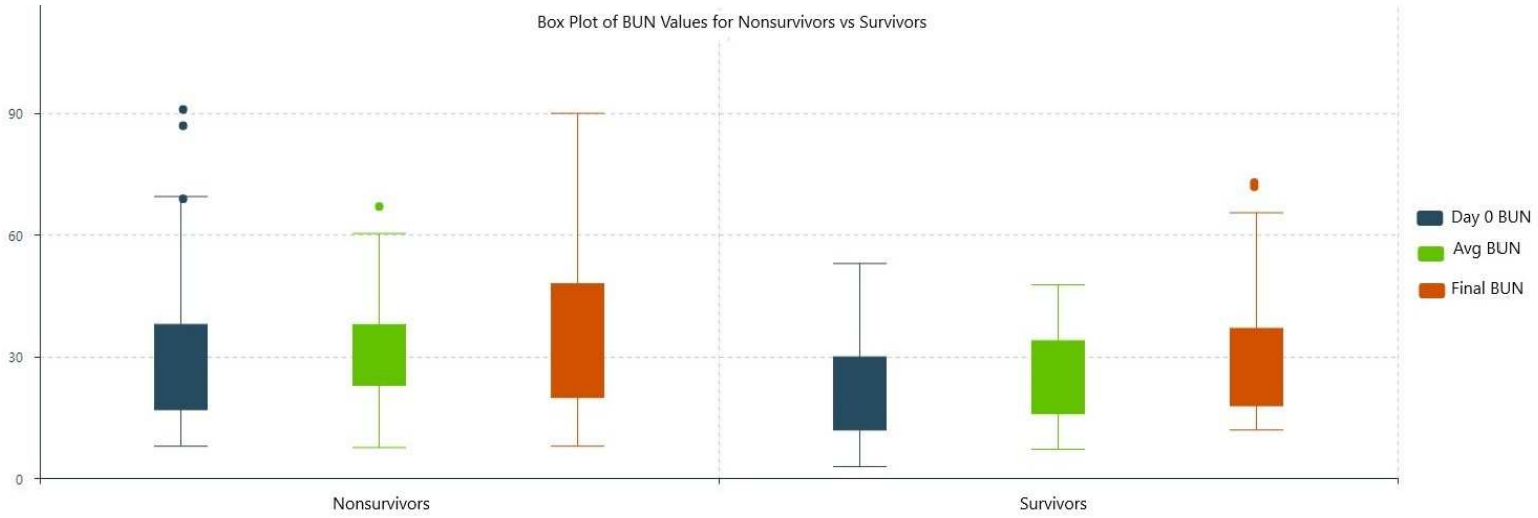

Figure 7: Both initial BUN (blue) and average BUN (orange) are significantly lower in survivors, while final BUN (orange) was seen to have no difference.

In the figure above, we see that the initial BUN was lower in survivors and they had a much smaller IQR as well (18 [12,30] vs 22 [17, 42], p = 0.030). We also can see that the average BUN for survivors was lower as well (21 [16, 35] vs 31 [23, 38], p = 0.023). There was no difference in the final BUN between both groups though.

ECMO Blood Products

	Nonsurvivors (n = 45)	Survivors (n = 25)	p-value
Total pRBCs given	**3451 [1754, 8007]**	**2080 [600, 3173]**	**0.003**
pRBCs/day	781 [368, 1293]	373 [157, 888]	0.085
Initial Platelet Count	120 [61, 190]	140 [74, 204]	0.394
Average Platelet Count	98 [89, 107]	106 [84, 119]	0.099

Final Platelet Count	91 [73, 105]	88 [75, 111]	0.731
Total Platelets Given	**1900 [552, 3765]**	**556 [195, 1168]**	**0.003**
Platelets/day	**337 [141, 492]**	**147 [37, 272]**	**0.011**
Average AT III Level	70 [58, 83]	66 [62, 74]	0.408
AT III Given	4336 [413, 9151]	3681 [449, 5807]	0.576
Average Fibrinogen	365 [242, 482]	327 [276, 458]	0.681
Total Cryoprecipitate Given	95 [0, 477]	0 [0, 170]	0.244
Total FFP Given	**1123 [223, 1894]**	**240 [0, 638]**	**0.001**
FFP/day	**195 [36, 313]**	**48 [0, 153]**	**0.006**

Figure 8: Table comparing blood markers and blood product administration between groups.

There was no statistically significant difference in initial, average, or final platelet counts. However, non-survivors tended to receive greater amounts of platelet transfusions (337 ml/day vs 147 ml/day, p = 0.003) and FFP per day (195 ml/day vs 48 ml/day, p = 0.006) than survivors, but there was seen to be no significant difference in pRBCs given per day. There was no significant difference in fibrinogen levels, average AT III levels, or AT III replacement between groups.

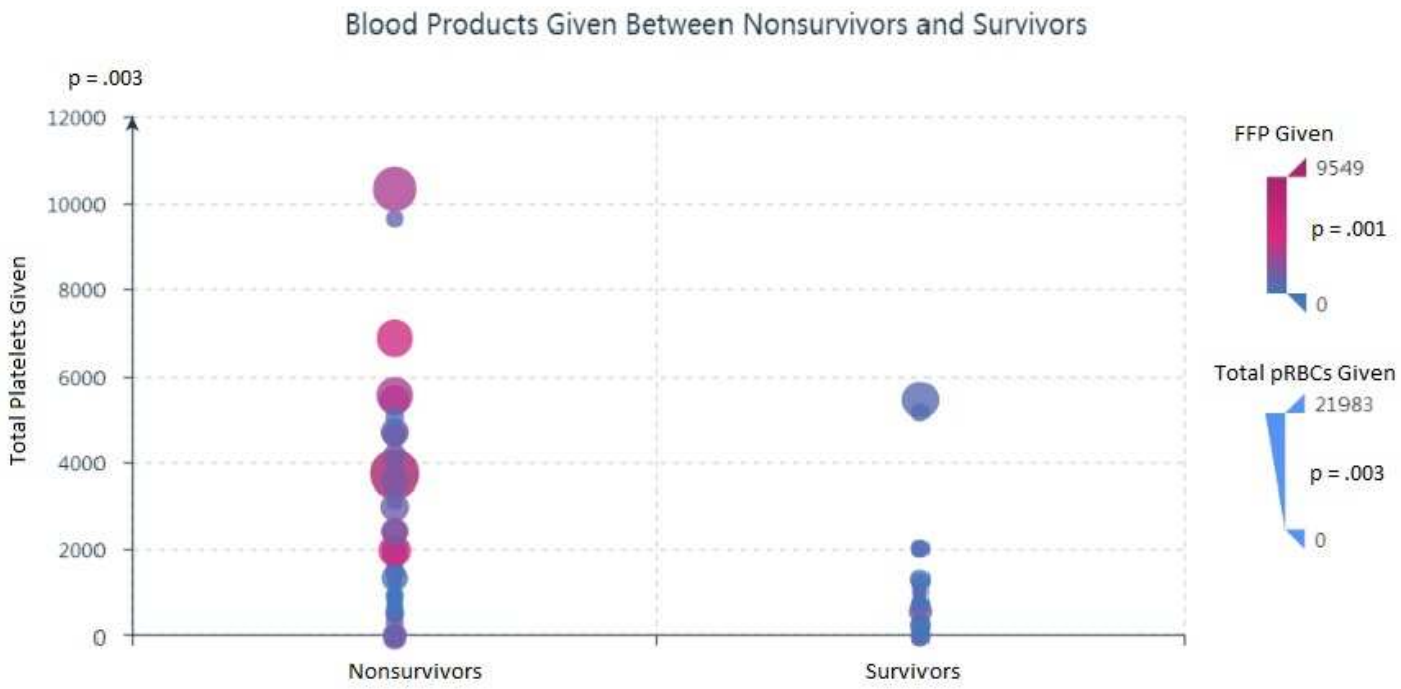

Figure 9: The higher on the Y-axis, the more platelets received. The larger the circle, the more pRBCs received. The redder the circle, the more FFP given. Survivors have significantly smaller, lower and more blue circles than nonsurvivors.

There was seen to be a significant difference for all blood products given, except for cryoprecipitate. Across the board, survivors received less platelets (556 ml vs 1900 ml, p = 0.003), less pRBCs (2080 ml vs 3451 ml, p = 0.003), and less FFP (240 ml vs 1123 ml, p = 0.001) than those in the nonsurvivor group.

Discussion

VA ECMO is rapidly growing field in the cardiac world and is usually a last resort treatment for patients in dire situations. According to the ELSO registry, the survival rates for adult VA ECMO between the years of 2010-2015 ranged between 36-43%. Our survival rate of

35.7% during that same time period was a bit lower than the average, but this may be due to the exclusion of some patients from our study, as well as the fact that we as a university hospital will treat patients that are turned away from other hospitals. During that same 2010-2015 time period, the number of adult VA ECMO cases across the country increased over 600%, from 416 patients in 2010 to 2497 patients in 2015 [27]. The growth in this field is much faster than the data and research can keep up with and there needs to be as much interest in furthering the data behind VA ECMO as much as there is it utilizing the treatment.

The data rejected our first hypothesis. We were surprised to find that there was no significance between survivors and nonsurvivors with regards to platelet counts of any kind. While the average platelet count was relatively close to significance ($p = 0.099$), we cannot say that any of the platelet counts we looked at have any effect on patient mortality or can be used as an indicator for increased risk of VA ECMO. We think that one of the reasons why this may also show no significance, is that our platelet transfusion thresholds may not allow such a finding without a larger population to rely on. The average platelet counts for nonsurvivors vs survivors (98 vs 106, respectively) were both very close to the transfusion threshold for our center, but nonsurvivors received much more platelets on average than survivors (1900ml vs 556 ml). We feel that the fact that we could find no significance between these two groups was due primarily to the fact that the nonsurvivors received much more products and that kept them close to the transfusion threshold with plenty of clinical support, while survivors were at this same point with very little clinical support. Lowering the transfusion thresholds for these patients would help to solve this issue, and since there is no difference in bleeding between groups, there should be room to lower our thresholds in this regard.

Our second hypothesis was confirmed to be correct, in that kidney function is a significant indicator of risk and mortality to the patient. With our initial and average BUN showing a significant difference between the groups, this fall in line with other studies that show similar results regarding these values [28, 29]. We were surprised to see significance in both initial and average, but not final BUN. Our idea that CRRT utilization is a major indicator for mortality of patients was confirmed as well. Kielstein, et al. (2013) observed that patients that undergo CRRT during ECMO have significantly lower survival rates at 3 months, as lower than 1/3 the survival rates than those who did not receive CRRT. It should be noted that it is most likely not the treatment of CRRT that is causing the increased mortality, but rather the condition the patients are in to require such multi-organ support. One of the biggest limitations in this study is that it is retrospective and that we cannot change or add tests or samples to be collected to further our look into the kidneys. We had no recording of urine output, nor lab testing for serum creatinine or total bilirubin. These are a major component of the RIFLE criteria for predicting acute kidney injury, and have also seen to increase patient mortality when their levels fall out of normal ranges due to kidney dysfunction [30-32].

Our study confirmed our hypothesis that survivors were transfused with significantly less amounts of FFP, pRBCs, and platelets. We saw no difference in the administration of cryoprecipitate, which was counter to our hypothesis regarding that. We also saw that there was no difference between survivors and nonsurvivors when it came to incidence of bleeding, both having an occurrence of 60% of patients that did not bleed at all during their ECMO run ($p = 0.393$). This, coupled with the fact that the nonsurvivor group received much more platelets and FFP makes us think that we may be giving patients products, increasing their

exposure and risk, when it may not be necessary to do so and we should experiment with lowering the parameters at which we start to transfuse patients.

Some of the markers we found as indications of increased mortality were an unexpected surprise. For us, both the presence of atrial fibrillation being a significant indicator of increased mortality was something we would not have related unless this study was carried out. The drastic difference in heparin dosing was also a shock. The dosage difference can be argued two ways: 1) The patients who survived were more capable to handle higher doses of heparin due to a more intact coagulation system, and 2) The increased dosage of heparin better allowed these patients to have less complications that would lead to an increased mortality. It is unclear which argument has more weight, but think that it should be looked at in much greater detail for anticoagulation over long periods with ECMO.

Overall, we have come to the conclusions that nonsurvivors receive much more blood product transfusions, yet require much less anticoagulation. We only had biomarkers for the kidneys available and the patient's kidney function was seen to have a significant effect on patient mortality. It has been shown that patients commonly experience multi-organ failure while on ECMO and its occurrence significantly increases patient mortality [33, 34]. We are inclined to believe that a sizeable percentage of the nonsurvivors were most likely suffering from multi-organ failure, including the liver. The liver is the producer of many of the coagulation factors and dysfunction of the organ would explain many of the differences between the groups regarding the needs for blood product transfusions. While we also proved kidney dysfunction increases patient mortality, kidney dysfunction also affects heparin elimination from the body

through the non-saturable mechanism of renal excretion [35]. This may help, in part, to explain the difference seen in heparin dosing between groups.

Future Directions

We feel the first step should be to restrospectively include the VA ECMO patients from 2016-2019 at our institution to strengthen our data. Next should be to prospectively change the data collected to include more lab tests that look at kidney function such as serum creatinine, and to include urine output into our systems so that can further help with our findings on the kidney. We also want to look at other vital organs, such as the liver, and add the testing for markers of those such as total bilirubin, alanine transaminase (ALT), and aspartate transaminase (AST). We want to add a patient's heparin concentration as well, to further explore the large difference in heparin dosing between groups. We hope that this increase of patient population would also push those markers that were close to significance, either into or farther away for more definitive terms. We know the sample size was smaller than we would have wanted and the increase in size could also push this from nonparametric testing to parametric testing. Given the heparin dosing being such a significant factor for survival, we feel that the current trend of looking at primarily ACT as an indicator for sufficient anticoagulation may not be enough. We feel that including heparin dosage may improve patient outcomes in the future.

Another step we should be taking as an institution should be to look at the patients that underwent venovenous (VV) ECMO at our institution and analyze them the same way we did here. Our volume of VV ECMO patients during that time was larger than that of our VA ECMO,

so there may be even stronger findings from the data. We would also like to prospectively include new end points in the same way that we would like to for VA ECMO. We feel that the data gathered by both of these new endeavors would provide extremely useful findings that would benefit patient selection and outcomes in the future for ECMO as a whole.

As well as looking at our own patient population, we feel that incorporating this large growth of the patient population across the country would yield significant leaps forward in what we know about the optimization and risk factors of ECMO. We had only 70 patients that qualified for this study in a span of 5 years. If we could pool the patients from other centers to increase this population by ten, or even, one hundred-fold this could be exactly the data that would make a colossal impact in the ECMO field.

Conclusion

The field of VA ECMO has been around for decades but is growing rapidly in the last decade. With this increased growth, there are more patients subjected to it. This allows for more studies and much more information to be obtained regarding VA ECMO. We feel that this growth is the perfect opportunity to fine tune and improve patient survival for this extremely invasive procedure. We have restrospectively analyzed our VA ECMO database and found several markers to be significant that we would've otherwise never known about with regards to our own practice. This practice can, and should be, done by other centers that have the volume of patients to make valuable contributions or to pool resources and have multi-center studies to further our knowledge about a treatment that is used in increasing frequency across

the world. Our efforts hopefully can contribute to the field in a way that will help patients in the future and possibly help with a creation of a better criteria for VA ECMO utilization.

Declaration of Conflicting Interest and Funding

The authors declare there is no conflict of interest within this study. This research has received no grants from any funding agency.

Appendices

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