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The impact of severity of initial illness, determined by SOFA score, and presence of anemia on outcomes among patients requiring Extra Corporal Membrane Oxygenation (ECMO) support: A single center experience

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ABSTRACT

Introduction: ECMO provides respiratory and circulatory support in critically ill patients. In our study, we report on a single center experience with ECMO and aim to identify the prognostic markers for survival to discharge from hospital.
Methods: A registry was maintained on all patients who underwent ECMO implantation from September 2012 till January 2016 at a single institution. The collected data was analyzed to identify baseline characteristics, outcomes including clinical variables predictive of poor outcome.
Results: A total of 29 patients underwent ECMO implantation. The average age of patients was 42 ± 18 years. 59% were males (N = 17). 19 cases had a cardiac indication for ECMO (66%) while 10 cases had a pulmonary indication (34%). On univariate analysis; presence of Multi-organ failure, SOFA score more than 18 and hemoglobin less than 10 g/dl at baseline and after ECMO removal were associated with increased 30 day mortality. Pearson correlation with 30 day mortality showed a positive correlation with MOF (+0.562, p = 0.002) and SOFA score >18 (+0.448, p = 0.015) and a negative correlation with anemia (−0.507, p = 0.005). 15 out of the total 29 patients (52%) died within 30 days of admission. Patients with MOF (log rank: 10.926, p = 0.001), SOFA score >18 (log rank: 7.758, p = 0.005) and hemoglobin <10 g/dl (log rank: 5.595, p = 0.018) had decreased survival on 30 day follow up.
Conclusions: Although the use of ECMO as a last line in the treatment of critical patients refractory to conventional treatment measures constitutes an important improvement in their care; with 48% overall survival; patient selection and timing of ECMO initiation remains challenging.
Patients who already had signs of MOF and a high SOFA score portended a poor response. Similarly for anemic patients. Hence the importance of consideration for ECMO use earlier in course of illness rather than later. Screening and aggressive treatment of anemia in those patients may help improve the outcomes.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) uses a modified cardiopulmonary circuit to provide respiratory and circulatory support in critically ill patients. Recent advances in circuitry has improved its safety profile, made it easier to use in terms of implementation and decreased the number of staff needed to manage the device. Increasing evidence and experience with ECMO resulted in a steady incline in its popularity for the management of cardiopulmonary diseases[1,2]. ECMO is being utilized as the supportive treatment of choice for conditions with high morbidity and mortality, yet they are potentially reversible. This encompasses both cardiac and respiratory conditions such as ARDS, cardiogenic shock due it ischemia or otherwise. The 2012 the extracorporeal life support organization (ELSO) registry reported a

Abbreviations: ECMO, extracorporeal membrane oxygenation; SOFA score, sequential Organ Failure Assessment score; MOF, multi-organ failure; ARDS, adult respiratory distress syndrome; LVAD, left ventricular assist device.

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survival to discharge rate of 55% and 39% among adults treated with ECMO for respiratory and cardiac causes, respectively2.

The CESAR trial demonstrated a significant reduction in mortality among patients with ARDS treated with ECMO compared to conventional treatment (37% versus 53%).3 ECMO use in refractory cardiogenic shock reported an overall survival of 49% 4. In cardiac arrest, patients demonstrated a survival to discharge rate of 27%2. Our group has reported earlier on use of ECMO among patients with severe cardiotoxicity due to Aluminum Phosphide intoxication8. In another series among 45 patients with Aluminum Phosphide induced cardiac intoxication and shock; those treated with ECMO had an improved survival of 33% vs. 14% among patients treated conventionally9. Albeit this there are no large randomized controlled trials demonstrating the benefit of ECMO for cardiac causes.

Furthermore there is a paucity of data guiding the selection of patients who can benefit the most from ECMO support. In our study, we report a single center experience with ECMO in patients for both cardiac and pulmonary indications and aim to identify the prognostic markers for 30 day survival.

2. Method

2.1. Study design

A prospectively maintained registry for all patients implanted with ECMO at Al Qassimi Hospital, Sharjah; since December 2012, till January 2016. We collected all baseline and outcome data on enrolled patients who underwent ECMO implantation with Cardiohelp system (Maquet Cardiovascular). Patients had either a cardiac or a respiratory indication for ECMO use. Respiratory indication included refractory respiratory failure of any cause and immediate respiratory collapse with or without cardiovascular instability. Cardiac indication included cardiogenic shock despite adequate other treatment measures such as volume resuscitation, inotropic and vasopressor support, and intra-aortic balloon counter-pulsation.

Table 1
List of patient with ECMO indication, MOF, SOFA score and 30 day mortality.

Patient #	Sex	Age	Indication	ECMO mode	SOFA score	MOF	30 day outcome
1	Female	32	Postpartum cardiomyopathy following third pregnancy complicated with cardiogenic shock, acute kidney and liver injury.	VV	18	YES	died
2	Female	11	Dilated cardiomyopathy following Aluminum phosphate poisoning Complicated with acute kidney and liver injury.	AV	20	YES	died
3	Female	48	Dilated cardiomyopathy following Aluminum phosphate poisoning Complicated with acute kidney injury	AV	14	NO	survived to discharge
4	Male	60	ACS complicated with LVF,Papillary muscle rupture and Acute kidney injury.	AV	13	NO	survived to discharge
5	Male	21	Dilated cardiomyopathy following Aluminum phosphate poisoning.	AV	15	NO	survived
6	Male	63	Acute anterior wall MI complicated by cardiogenic shock	AV	16	NO	died
7	Female	48	Acute respiratory distress syndrome due to H1N1.	VV	23	YES	died
8	Male	29	Acute respiratory distress syndrome due to sever community acquired pneumonia.	VV	12	NO	survived
9	Female	31	Acute respiratory distress syndrome due to H1N1.	VV	17	YES	died
10	Male	60	Acute myocardial infarction complicated with VT, cardiogenic shock	AV	22	No	died
11	Female	16	Idiopathic dilated cardiomyopathy awaiting heart transplant,complicated by acute liver and kidney injury	AV	20	YES	Survived to transfer to another centre for heart transplant.
12	Male	75	Acute posterior wall MI complicated with cardioogenic shock	AV	15	NO	died
13	Female	50	Acute respiratory distress syndrome due to H1N1 virus Complicated with acute liver and kidney injury	VV	21	YES	died
14	Male	60	Acute inferior posterior MI complicated with cardiogenic shock	AV	18	NO	died
15	Male	27	Acute respiratory distress syndrome due to H1N1 virus	VV	15	NO	discharged alive
16	Male	62	Acute myocardial infarction complicated with cardiogenic shock	AV	15	NO	discharged alive
17	Male	62	Late presenting Inferior wall MI complicated by VSD,Right side heart Failure, acute kidney and liver falilure	AV	22	YES	died
18	Male	21	Idiopathic dilated cardiomyopathy, failed weaning from inotropes and crashed, latter implanted with LVAD.	VA	11	NO	survived; waened off ECMO and latter LVAD implanted
19	Male	50	NSTEMI complicated with torsades de point, cardiogenic shock.	VA	17	NO	discharged alive
20	Female	38	Dilated cardiomayopathy following fall from hight with multiple fractures developed ARDS complicated with AKI and liver	VA	21	YES	died
21	Male	21	Idiopathic dilated cardiomayopathy,implanted LVAD as a bridging to the heart transplant developed ARDS due to Klebsiella Pneumoniae	VV	23	NO	waened off ECMO and transferred to other hospital alive
22	Male	59	Acute anterior wall Mi complicated with cardiogenic shock	AV	20	NO	discharged alive
23	Female	14	Sudden arrest at school, prolonged CPR, discovered HOCM complicated with acute liver and kidney injury, DIC.	AV	20	YES	died
24	Male	29	Cardiopulmonary arrest following ARDS due to sever pneumonia	AV	18	YES	died
25	Male	39	Acute respiratory distress syndrome, unknown etiology.	VV	9	NO	discharged alive
26	Male	27	Acute respiratory distress syndrome due to community acquired pneumonia and sepsis.	VV	20	NO	died
27	Female	46	Acute respiratory distress syndrome due to H1N1 virus	VV	11	NO	discharged alive
28	Female	35	Acute respiratory distress syndrome due to community acquired pneumonia.	VV	15	NO	discharged alive
29	Female	72	Acute posterior MI complicated with Pulmonary edema and cardiogenic shock.	AV	17	NO	died

AV: Arteriovenous.
VV: Veno-venous.
VT: Ventricular Tachycardia.
VSD: Ventricular Septal Defect.

Standard protocols during ECMO implantation and weaning were followed.

2.2. Predictor variables

Patient demographics and clinical characteristics such as hypertension, diabetes, ischemic heart disease, chronic kidney disease and sepsis were recorded. During the hospital course, the onsets of the following were documented; acute kidney injury was diagnosed if dialysis became required or serum creatinine rose above 3.0 mg/dl with urine output of less or equal to 400 ml per day. Sepsis was labeled if diagnosed by the treating physician and was proven by culture from a body site. Major bleeding was labeled upon requirement of transfusion of at least one unit of packed red blood cell. Minor bleeding was recognized if it culminated in a new onset hematoma, hematuria; but did not require blood transfusion. Heparin induced thrombocytopenia (HIT) was documented if platelet levels dropped after the start of intravenous heparin or low molecular weight enoxaparin and improved after discontinuation. Stroke was labeled if diagnosed by a neurologist with radiological evidence. Cardiac function was examined using conventional 2 D echocardiogram. Multi-organ failure (MOF) was defined as altered function involving two or more organs. In addition, Sequential Organ Failure Assessment (SOFA)5 was calculated for each patient.

2.3. Outcome variables

Patients were followed over the course of their hospital stay up to their discharge. If not discharged then survival at 30 days was recorded. During their period of ECMO use all complications the ensued were recorded.

2.4. Statistical analysis

Continuous variables were reported as mean ± standard deviation while categorical variables were reported as count (percent). Two sided *t*-test was used to assess differences between continuous variables, while discrete variables were assessed with Fisher's Exact test or chi square test as deemed appropriate. Simple correlations between predictor variables with outcomes were conducted. Correlations were expressed with r+ correlation coefficient and p values were placed. P value of <0.05 (two sided) was considered statistically significant. After adjusting for clinical variables, binary logistic regression analysis and forward selection models were used to assess the value of each independent variable to predict 30 day mortality. A Kaplan-Meier method was performed to estimate the cumulative survival at 30 days. A comparative log-rank test was used to compare the survival rates between different subgroups and a stepwise multivariable Cox proportional hazards model was used to identify clinical variables that can predict 30 day mortality. The hazard ratio was estimated within its 95% confidence limit and supported by the significance level. IBM SPSS Statistics for Windows (Version 22.0). Armonk, NY: IBM Corp was used to conduct the statistical analysis.

3. Results

3.1. Patient clinical characteristics

A total of 29 patients underwent ECMO implementation from September 2012 to January 2016 (Table 1). The average age of patients was 42 ± 18years with majority being males (59%, N = 17). 19 cases (66%) had a cardiac indication for ECMO while 10 cases (34%) had a pulmonary indication. 34.5% (N = 10) of patients had ischemic heart disease, 24.1% of patients were hypertensive (N = 7) diabetic (N = 7) and septic before implantation (N = 7); while 6.9% (N = 2) had chronic kidney disease. 37.9% of patients (N = 11) developed MOF with an average SOFA score of 17.1 ± 3.8. (Table 2)

During the course of the inpatient stay 55.2% (N = 16) of patients developed acute kidney injury, 44% (N = 13) developed minor bleed, 38% (N = 11) developed heparin induced thrombocytopenia (HIT), 17.2% (N = 5) developed cerebrovascular accident, and 13.8% (N = 4) developed infection at insertion site. (Table 2)

On univariate analysis, MOF, SOFA score more than 18 and hemoglobin less than 10 g/dl at baseline and after ECMO removal were associated with increased 30 day mortality. Pearson correlation showed a positive correlation between MOF and 30 day mortality (+0.562, p = 0.002) and between SOFA score > 18 and 30 day mortality (+0.448, p = 0.015) and a negative correlation with anemia (-0.507, p = 0.005).

3.2. Overall survival

At 30 days, 14 out of the total 29 patients (48%) survived to discharge from hospital. Looking at the 15 patients who where deceased (52%); factors associated with decreased survival where presence of MOF (log rank:10.926, p = 0.001), a SOFA score > 18 (log rank:7.758, p = 0.005) and hemoglobin $<$ 10 g/dl (log rank:5.595, p = 0.018) (Fig. 1).

4. Discussion

ECMO is a powerful treatment option for critically ill patients. While in many centers in the first world it can be used as a bridge for left ventricular assist device or for heart and lung transplantation, in our center, among other centers around the world, its use is limited due to limited availability of ECMO resources and decreased availability of these transplant options. Two patients fitted with ECMO became crucially dependant on it for survival and finally died due to lack of readily available transplant options. The first patient was a case of severe postpartum dilated cardiomyopathy, who could not be transferred for subsequent heart transplant and died after 3 weeks due to peripheral complications. An ECMO placed in VA configuration intakes blood from a large vein such as Inferior vena cava and pumps it continuously into a large peripheral artery such as common iliac. In doing so it tends to pump against the flow of blood from the left ventricle, which would then be preferentially diverted to the head and upper extremities while the abdomen and lower extremities become preferentially perfused by flow from ECMO. In some cases the acute increase in afterload would be large as to cause an extra burden on an already weakened Left ventricle and cause further deterioration of its systolic function. In our specific patient her aortic valve had ceased to open and she eventually developed a thrombus in her left ventricle.

In similar cases, when VA ECMO is used, LV systolic function needs careful monitoring and follow up with serial echocardiograms and consideration for use of inotropes to aid the left ventricle and if possible quick weaning of ECMO as tolerated.

The other patient had developed end stage lung disease following a prolonged course of ventilation due to H1N1 pneumonia and ARDS and could not be transferred for lung transplant and died after 2 weeks due to sepsis

Hence most of our emphasis lies upon its use as a bridge for recovery and the ability to foresee who would be a potential candidate in order to achieve a favorable final outcome. To our knowledge this is the first report from our region in the Middle East that details the indication for ECMO use, baseline patient characteristics, and short term outcomes for patients treated by it.

In our series, we present 29 patients who required ECMO for both pulmonary and cardiac indications. The mean age of the study population was comparatively younger than reported elsewhere in

Table 2
Patient Clinical Characteristics.

Baseline characteristics of patients receiving ECMO					
		All	status		P Value
			Survived	Died	
Gender	**Female**	12(41%)	3(10.3%)	9(31%)	0.07
	Male	17(59%)	10(34.5%)	7(24.1%)	
Age (years)		42 ± 18	37 ± 17	45 ± 19	0.27
Indication for ECMO	**Cardiac**	19(66.0%)	9(31.0%)	10(34.5%)	0.7
	Pulmonary	10(34.0%)	4(13.8%)	6(20.7%)	
Baseline Characteristics	**Hypertension**	7(24.1%)	3(10.3%)	4(13.8%)	0.9
	Diabetes	7(24.1%)	3(10.3%)	4(13.8%)	0.9
	Chronic renal failure	2(6.9%)	1(3.4%)	1(3.4%)	0.87
	Ischemic heart disease	10(34.5%)	4(13.8%)	6(20.7%)	0.7
	Sepsis	7(24.1%)	2(6.9%)	5(17.2%)	0.32
	Multi-organ failure	11(37.9%)	1(3.4%)	10(34.5%)	**0.02**
	SOFA score	17.1 ± 3.8	15.3 ± 3.9	18.6 ± 3.1	**0.015**
Lab parameters (Mean ±SD)	**White blood cell(×109/L) on admission**	13.64 ± 7.4	13.67 ± 7.1	13.61 ± 8.04	0.57
	Hemoglobin(g/dl) on admission	11.7 ± 2.4	13 ± 2	10.5 ± 2	**0.02**
	Platelet ($\times 10^9$)/L) on admission	222.9 ± 118.5	228.7 ± 85.5	218 ± 142.6	0.82
	Creatinine (umol/L) on admission	125.7 ± 79.73	132.8 ± 71.31	119.9 ± 87.9	0.67
	White blood cell(×109/L) after ECMO	15.7 ± 9.97	17.7 ± 10.4	13.4 ± 9.5	0.29
	Hemoglobin(g/dl) after ECMO	10 ± 2	10.8 ± 1.54	9 ± 2	**0.026**
	Platelet(×109/L) after ECMO	145.25 ± 129.1	167 ± 102	120 ± 156	0.392
	Creatinine (umol/L) after ECMO	191.5 ± 136.7	196.3 ± 156.88	185.3 ± 113	0.85
Mode of Insertion	**VV**	10(34.5%)	5(17.1%)	5(17.1%)	0.68
	VA	19(65.5%)	8(27.6%)	11(37.9%)	
Average SOFA score associated with mode of insertion	**VV**	16.6 ± 5			0.568
	VA	17.5 ± 3			
IABP		13(44.8%)	7(24.1%)	6(20.7%)	0.38
Hemodynamics	**HR**	68.4 ± 47.8	61.5 ± 55	74 ± 41	0.49
	SBP	78.4 ± 31	81.2 ± 34	76 ± 28	0.68
	DBP	43.8 ± 25.6	43 ± 30	43 ± 23	0.99
Complications	**Acute kidney injury**	16(55.2%)	7(24.1%)	9(31%)	0.89
	Minor bleed	13(44%)	7(54%)	6(48%)	0.45
	Major bleed	5(16%)	1(15%)	4(24%)	0.09
	Infection at insertion site	4(13.8%)	2(6.9%)	2(6.9%)	0.82
	Heparin induced thrombocytopenia	11(38%)	2(16%)	9(24%)	0.07
	Cerebrovascular accident	5(17.2%)	1(3.4%)	4(13.8%)	0.22
Length of stay		13.9 ± 12.1	14.2 ± 11	10.1 ± 8	0.67
LVEF		35% ± 12	36% ± 6	28% ± 4	0.08

literature. 31% of our patients (N = 9) had ongoing CPR while ECMO was being implanted out of which 34% (N = 3) survived to hospital discharge which is similar to the rate reported in literature6. However, this came at the expense of potential complications such as access site infection, HIT, bleeding. In univariate analysis we found that a hemoglobin level less than 10 g/dl on admission and after ECMO removal is associated with increased 30 day mortality. ECMO circuits require the introduction of large bore catheters into venous and arterial peripheral circulation and this can invariably invite complications such as bleeding from multiple initial puncture attempts or due to patients being on heparin intravenously with high Activated clotting times. ECMO may also induce hemolysis by a number of mechanisms the most common ones being due to generation of negative pressure by the pump in hypovolemic patients, the development of clot within the circuit or near the cannula orifices or excessive centrifugal pump speed >3000 revolutions per minute (RPM)7. Therefore, ECMO can exacerbate pre-existing anemia and patients undergoing ECMO implantation should be aggressively screened for anemia and transfused to improve outcomes. It is also conceivable that anemia is a marker for sicker patients who would faire worst. The link between mortality and anemia among patients requiring ECMO needs further validation, and if so postulation of treatment goals.

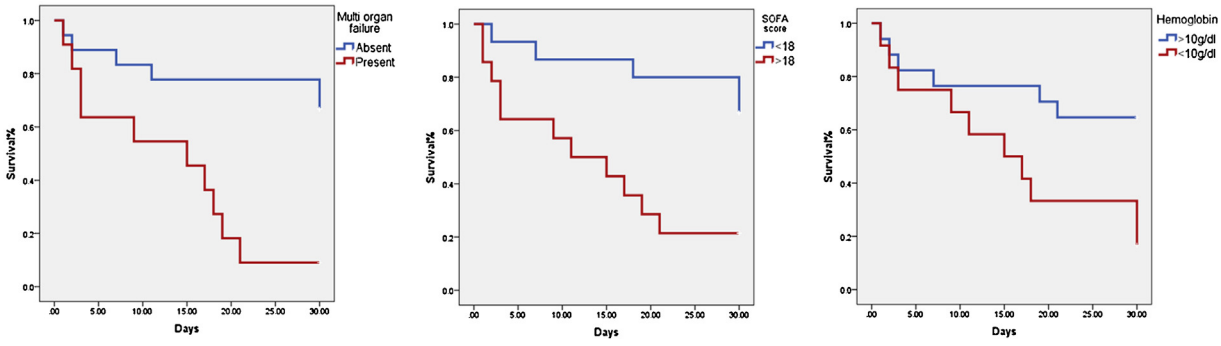

Fig. 1. Kaplan meier curve showing percentage survival over 30 day period for MOF, SOFA score >18 and hemoglobin <10 g/dl.

The other factors associated with poor 30 day survival were presence of MOF at implantation time, and a SOFA score more than18. SOFA score is a quantitative measurement of degree of MOF and describes the spectrum of the same pathologic process. Persistent organ failure is a common pattern seen before death7 and a marker for poor prognosis. SOFA score is a scoring system which describes the status of patients organ function and higher scores are predictive of mortality5. What we can infer from our finding is that ECMO does not offer any mortality benefit in patients with high SOFA score or MOF. This highlights the question of timing of implantation; are we actually doing any good to patients when we implant ECMO in patients when their illness becomes resistant to all other treatment options and they are already in refractory MOF. This is especially relevant in developing countries where there are no options for organ transplantation and emphasis is on "bridge to recovery" pathway. Earlier implantation of ECMO may help improve patient outcomes. Furthermore the use SOFA score when screening patients for ECMO implantation can help quantify when is timing appropriate before it becomes too late. To our knowledge this is the first report that highlight the use of SOFA score for this indication.

4.1. Limitation

The most important limitation of this registry is the sample size. When analyzed with logistic regression and Cox regression; there is a statistically significant odds ratio and hazard ratio for MOF, SOFA score and anemia. However, due to the small sample size the confidence intervals are very wide and hence the results are not included in the final report. Moreover, our population varied in terms of age and ECMO indication as a result of which our distribution might have been skewed. Nonetheless, we shed light on use of ECMO from our region and obstacles to which we are exposed and the outcomes that are attainable. This registry is continuous and as the patient number grows any significant associations can be reaffirmed and reported.

5. Conclusion

ECMO is a supportive option for patients with refractory cardiogenic shock and respiratory failure. The patients who will benefit the most are still not defined in the literature. From our report, we infer that patients who develop advanced multi organ dysfunction and have a SOFA score more than 18 are poor candidates to benefit from ECMO as a bridge to recovery. Moreover, we also show the importance of screening and treating anemia in patients who will undergo ECMO implantation.

References

1. MacLaren G, Combes A, Bartlett RH. Contemporary extracorporeal membrane oxygenation for adult respiratory failure: life support in the new era. *Intensive Care Med*. 2012;38:210–220.
2. Paden ML, Conrad SA, Rycus PT, Thiagarajan RR, Registry E. Extracorporeal life support organization registry report 2012. *ASAIO J*. 2013;59:202–210.
3. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure CESAR: a multicentrerandomised controlled trial. *Lancet*. 2009;374:1351–1363.
4. Takayama H, Truby L, Koekort M, et al. Clinicaloutcome of mechanical circulatory support for refractorycardiogenic shock in the current era. *J Heart Lung Transplant*. 2013;32:106–111.
5. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22:707–710.
6. 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(September (33))2246–225610.1093/eurheartj/ehv194 [Epub 2015 Jun 1].
7. Toomasian JM, Bartlett RH. Hemolysis and ECMO pumps in the 21st Century. *Perfusion*. 2011;26(1):5–610.1177/0267659110396015.
8. Elabbassi W, Chowdhury MA, Al Nooryani A. Severe reversible myocardial injury associated with aluminum Phosphide toxicity: a case report and review of literature. *J Saudi Heart Assoc*. 2014;26(4):216–222.
9. Mohan B, Singh B, Gupta V, et al. Outcome of patients supported by extracorporeal membrane oxygenation for aluminum Phosphide poisoning: an observational study. *Indian Heart J*. 2016;68:295–301.