An investigation into the contributing factors to survival of ARDS patients supported by veno-venous ECMO.

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Abstract

Introduction: This study aimed to identify characteristics associated with survival during and post Extra Corporeal Membrane Oxygenation (ECMO) therapy, in patients with acute respiratory distress syndrome (ARDS) during the COVID-19 pandemic.

Methods: A retrospective observational study on 94 consecutive patients with confirmed COVID-19 induced ARDS supported by ECMO was carried out.

49/94 (52.7%) patients survived to hospital discharge.

Results: Non-survivors were found to have significantly (p<0.05) higher: Pre-ECMO International normalized ratios (INR), carbon dioxide partial pressure (pCO_2), Acute Kidney Injury (AKI) scores and blood urea levels. Also, lower pre-ECMO peak inspiratory pressures (PIP), mean arterial pressure, saturation of arterial oxygen (SaO_2), blood bicarbonate levels (HCO3), blood pH and fewer trials off ECMO with shorter combined trial off times. Patients that did not survive were more likely to have renal impairment and have received peri-ECMO haemofiltration.

Poor prognosis was significantly associated with: receiving pre-ECMO nitric oxide (HR=3.047,CI=1.247-7.447,*p*=0.015), renal impairment (HR=3.023, CI=1.586-5.763,p<0.001), AKI of 2 (HR=3.611,CI=1.382-9.441,p=0.009) or 3 (HR=3.275,CI=1.235-8.685,p=0.017), peri-ECMO haemofiltration (HR=2.412,CI=1.310-4.442,*p*=0.005) and the ABO blood group B (HR=3.103,CI=1.335-7.212,*p*=0.008). pre-ECMO high CO_2 (HR=1.134,CI=1.031-1.248,*p*=0.010), blood lactate (HR=1.350,CI=1.156-1.576,*p*<0.001), INR (HR=2.571,CI=1.438-4.598,*p*=<0.001) and lower blood pH (HR=0.023 CI=0.002-0.210,*p*<0.001).

Conclusions: Commonly used mortality scores may not be of use in a COVID-19 cohort of ECMO patients. The initiation of ECMO needs to be implemented prior to metabolic derangements, renal and fulminant respiratory failure.

Keywords:
ECMO, extracorporeal membrane oxygenation, ARDS, acute respiratory distress syndrome, survival

Introduction

Since the onset of the recent 2020 COVID-19 pandemic, healthcare providers worldwide have witnessed an unprecedented increase in hospitalisations. The presentation of this disease ranges from asymptomatic viral colonisation, to severe ARDS[1] requiring extended periods of mechanical ventilation. Concomitant ventilator-induced pulmonary barotrauma[2] is associated with the aggressive positive pressure ventilator strategies, often seen in COVID-19 positive patients[3]. Strategies using ventilation as a sole treatment modality were associated with high mortality rates (61-81%)[4].

The use of VV-ECMO therapy for patients with refractory respiratory failure, has been shown to be a viable modality of advanced respiratory support in the treatment of ARDS.[5] ECMO provides adequate pulmonary gas exchange, while minimising ventilator-induced lung injury by employing reduced ventilation rest settings. The use of ECMO, as a bridge to lung recovery, was implemented under the guidance of the World Health Organisation

(WHO), specifically in high-volume centres with prior clinical expertise. This utilization of ECMO by centres with more experience with this modality was deemed to produce better outcomes in the more severely affected patients worldwide[6]. However, this had varying results[7]. The mortality rate of COVID-19 positive patients on VV-ECMO in Germany was high by international comparison[8] as was in China[9], but North America reported comparable survival rates to pre-pandemic times[10].

The provision of ECMO is a resource intensive treatment, with finite numbers of equipment, trained staff, and intensive care beds available. It is further compounded by the extreme financial and logistical pressures of maintaining an acute care service. The provision of ECMO to critically ill patients throughout the pandemic was bounded by such constraints. Such a relatively scarce resource requires an allocation strategy based upon a risk-benefit evaluation; prioritising patients with the highest likelihood of recovery[11]. Therefore, there is a real need to identify risk factors that pre-dispose prospective patients to a good outcome.

The aim of this study was to identify specific, contextual characteristics associated with survival during and post ECMO therapy, in patients with COVID-19 induced ARDS.

Methods

Study Design and Participants

A retrospective, observational study was performed on all patients requiring VV-ECMO for COVID-19 disease at Glenfield Hospital, University Hospitals of Leicester, UK, between March 2020 and March 2021. The study was approved by institutional review board and requirement for Ethical committee approval waived due to the retrospective and anonymised nature of the study. SARS-CoV-2 infection was confirmed by a positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) test. The decision to implement VV-ECMO was undertaken by the on-duty clinician from a pool of 7 intensivists, adhering to a

combination of the Extracorporeal Life Support Organisation (ELSO) guidelines[12] and personal clinical experience. Deviation from the proposed guidelines for treatment was at the discretion of the attending physician. Once on ECMO support, the mechanical ventilation strategy was modified to protective lung management.

Data

Routine clinical data were extracted from patients' medical records. These included demographic information, laboratory results, intensive care unit charts, ECMO management charts and haematology records, as well as information on hospital admission, length of stay and outcomes. Patient data recording began on the hospital ward to which the patient was admitted, either at Glenfield hospital or the referring hospital from which the patient was transferred.

Pre-ECMO variables were generated from the time of hospitalisation in the referring centre, to the implementation of ECMO support where the peri-ECMO period began and ended upon cessation of ECMO support. The primary outcome for this study was the weaning off ECMO support and survival indicating lung recovery.

ECMO Cannulation and Circuit

VV-ECMO was facilitated by cannulation of the right internal jugular with either a single caval, dual lumen cannula (Crescent, Medtronic, Minnesota, USA) sizes 28fr to 32fr or a bicaval dual lumen cannula (Avalon Laboratories, California, USA) sizes 29fr to 31fr. All dual lumen cannulation was performed under fluoroscopic guidance. Femoral-jugular cannulation using Arterial/Venous cannulae (Biomedicus, Medtronic, Minnesota, USA) was used for a minority of patients. The ECMO circuit consisted of a 2nd generation console (Levitronix Centrimag, Thoratec, Zurich, Switzerland) utilising a centrifugal pump (Centrimag, Abbott, Illinois, USA) and a polymethylpentene Oxygenator (Paragon Adult Maxi, Chalice Medical, Worksop, UK) and 3/8" polyvinyl chloride tubing pack (Chalice Medical, Worksop, UK). None of the components had surface modification. During ECMO support, blood flows were

maintained between 3.6l/min and 4.8l/min for all patients irrespective of the modality of their cannulation. Anticoagulation was controlled by measuring anti-Xa levels, maintaining a therapeutic range between 0.2-0.4 units/ml.

Regarding the cessation of ECMO support, radiological, organ function and lung compliance improvement with a circuit sweep below 5l/min together were considered indications that the patient may be ready for a trial off period.

Statistical Analysis

Continuous variables were described by their median and interquartile range (IQR) if non-normal distributed, or mean and standard deviation (SD) if normally distributed. Categorical variables were described by their counts and percentages. A non-significant ($p \geq 0.05$) Shapiro-Wilk test along with consultation of the Q-Q plot and histogram was used to identify normal distribution. Differences between groups were examined using a Chi square test of independence or Fisher Exact test with Yates continuity correction for non-parametric comparisons of categorical data. For 2 category parameters, effect size was estimated by the Phi Coefficient where 0.1, 0.3 and 0.5 indicated a small, medium or large effect respectively. For 3 or more category parameters, Cramer's V coefficient was used. Effect sizes used were small=0.07, medium= 0.21 and large=0.35, for 3 categories, and small=0.06, medium=0.17 and large=0.29 for four or more categories. Differences between groups in normally distributed continuous data were evaluated using Students Independent T-test with a Levenes test significance >0.5 to assume equal variance. Non-normally distributed continuous data used Mann Whitney U test with a median and range to indicate the direction of difference. Effect size (r) was calculated by dividing the standardised test statistic value by the square root of the total number of cases. Effect sizes < 0.3 were considered to be small, between 0.3 and 0.5 were medium and > 0.5 large. Cox univariate survival analysis was used to identify and assess the contributing factors from the study variables to the study end point, namely death Hazard Ratio (HR) using 95% confidence

intervals (CI). In addition, Kaplan-Meier survival analysis utilising the Log Rank test was used to compare median survival times between the two groups. Cox multivariable survival analysis was used to control for confounding variables. Variables that had a univariate $p<0.2$ were assessed as possible confounders. Those that were associated with the outcome and were not in the causal pathway were analysed[13]. Using this method, the '1 in 10 rule' was not exceeded, keeping the risk of overfitting the model low. Multicollinearity was assessed using a Variance Inflation Factor (VIF) value >10 indicating significant multicollinearity. Statistical tests were conducted assuming a 0.05 significance level. All analyses were performed using SPSS Statistics version 28.0.1.1 (IBM ,New York, USA).

Results

Demographics

A total of 94 patients from wave 1 and 2 of the COVID-19 pandemic were treated during the study period (Table I). The study group had a median age of 46 (13) and was predominantly male 69 (72.4%). There was an equal split between white (n=47) and Black, Asian Minority Ethnic (BAME) groups (n=46), and between the cannulation and implementation of ECMO occurring at the referring hospital and the study hospital (n=46 vs n=47). The survival rate for patients treated with ECMO was 52.7% (n=49).

Most patients (85%) in the study possessed the rhesus positive blood type, possession of the rhesus factor was not shown to contribute to the outcome of ECMO or to the prognosis. The distribution of ABO blood groups of patients in the study were comparable to that found in the UK population according to the NHS Blood and Transplant Service[14]. The ABO blood type did not differ significantly between the two groups (p=0.134), but univariate analysis showed that group B had a significantly poorer prognosis than the others. With group B as the reference group, group AB had the best prognosis (HR=0.215 (CI=0.047-0.992, p=0.049) followed by group O (HR=0.267, CI=0.118-0.606, p=0.002) and then group A (HR=0.325, CI=0.140-0.775, p=0.009). In the multivariable model ethnicity (BAME variable) was controlled while assessing ABO blood groups on prognosis. A similar outcome

was seen, group A (HR=0.322, CI=0.138-0.784, p=0.008) and group O (HR=0.275, CI=0.112-0.590, p=0.001) had a better prognosis than group B but group AB showed no significant difference (HR=0.237, CI=0.051-1.097, p=0.065). Kaplan-Meier analysis showed a significantly shorter mean time to death of 11 days for the group B patients than groups AB (22.0 days), O (23 days) and A (20.0 days) (p=0.005).
Other than ABO blood group, none of the patient demographics were shown to contribute to death or was associated with shorter survival times.

All patients in the survival group were alive as of 30 days and 6 months post ECMO decannulation.

Pre-ECMO Parameters

Pulmonary Function (Table 2)

Survivors were seen to have higher peak inspiratory pressure (PIP) values before the initiation of ECMO (p=0.040) than non-survivors (Md=30.0). The percentage of patients receiving nitric oxide was not significantly different (p=0.143) in patients who survived compared to those who didn't, however, it was associated with a poorer prognosis with shorter survival times (HR=3.047, CI=1.247-7.447, p=0.015). This was conversely the case for the variables 'total duration of ventilation' (HR=0.895, CI=0.863-0.928; p<0.001) and 'lung consolidation of 4 quadrants' (HR=0.117 CI=0.015-0.921; p=0.042) which was associated with a better prognosis. The choice of mechanical ventilation mode had no significant effect on the outcome of ECMO, although multivariable analysis controlling for referral region and lung consolidation showed a poorer prognosis for pressure control ventilation (HR=25.204, CI=0.300-488.694; p=0.033) albeit with wide confidence intervals.

Blood Gas Analysis and Pressure

Pre-ECMO blood gas results were analysed using the most recent results before the implementation of ECMO (all within 24 hours of cannulation). Blood pressure measurements were the last taken before ECMO cannulation (within 30 mins). Non-survivors were seen to be more acidotic (p=0.015) (HR=0.023 CI=0.002-0.210, p<0.001) and have lower bicarbonate (HCO_3) concentrations (p=0.045, two tailed) than survivors (M=27.512, SD=4.748). Non-survivors also had lower arterial saturations (SaO_2) (p=0.030) and higher International Normalised Ratios (INR) (p=0.004) (HR=2.571, CI=1.438-4.598, p=0.001) than survivors. Higher carbon dioxide partial pressure (pCO_2) (HR=1.134,CI=1.031-1.248, p=0.010) and lactate (HR=1.350, CI=1.156-1.576, p<0.001) concentrations were associated with a decreased survival time (Table 5). Pre ECMO mean arterial systemic blood pressures were seen to be significantly lower in the non-survivor group (M=77.280, SD=13.900) in comparison to the survivor group (p=0.026, two tailed), the magnitude in the difference in the means (mean difference=7.457, 95% CI[0.917-13.996]) was moderate (Cohen's d=0.50) (Table 4).

Renal Function (Table 3)

The percentage of patients with renal failure as defined by an Acute Kidney Injury (AKI) staging score of ≥1 was significantly higher in the non-survivor group (p=0.002, phi=-0.35).This was further shown by Cox univariate analysis to significantly (p<0.001) decrease survival time (HR=3.023, CI=1.586-5.763) and also in the multivariable model when controlling for age (HR=2.969, CI=1.551-5.683, p=0.001). When assessing AKI categories individually (p=0.001) an AKI of 2 (HR=3.611, CI=1.382-9.441,p=0.009) and 3 (HR=3.275, CI=1.235-8.685, p=0.017) in the univariate analysis, were associated with a poorer prognosis. The multivariable analysis mirrored these findings when controlling for age, an AKI of 2 (HR=3.520, CI=1.338-9.257, p=0.011) and 3 (HR=3.253, CI=1.227-8.625, p=0.018)

also indicated a poorer prognosis. Kaplan-Meier showed a median time to death of 11 days and 10 days for an AKI of 2 and 3 respectively compared to 23 days for no degree of renal failure (p=0.003). Blood urea values were found to be significantly higher (p=0.041) in the non-survivor group but did not affect the time to death. The use of pre-ECMO continuous Veno-Venous Haemofiltration (CVVH) was not seen to differ between groups, or be related to the prognostic outcome, although there was a significant difference between groups for patients receiving peri-ECMO CVVH (p=0.005) with a 73.3% majority in the non-survivor group (p=0.01). Peri-ECMO CVVH was associated with a poorer prognosis in both the univariate analysis (HR=2.412, CI=1.310-4.442, p=0.005) and in the multivariable model when controlling for age (HR=2.445, CI=1.325-4.510, p=0.004). A significantly ($p<0.05$) reduced median time to death of 19 days was seen for those that received peri-ECMO CVVH vs 25 days (p=0.004) for those that did not.

Pre-ECMO Risk Stratification Scores (Table 6)

Prior to the referral of prospective patients for ECMO, referring centres calculated required mortality and morbidity scores pertinent to the utilisation of veno-venous ECMO. Stratification was applied to scores that had continuous data results. The Murray score for the gradation of lung injury did not differ between the two groups (p=0.432) and Cox survival analysis showed no difference in prognosis. Patients with a Murray score of 1.0-1.9 and 4.0 showed a decreased (16 and 13 days respectively) median time to death than other strata (p=0.03). The Respiratory ECMO Survival Score (RESP) was calculated for all study patients to give a RESP class (1 to 3), RESP points (-1 to 7) and in-hospital survival score (57%-92%). All 3 outcome metrics showed no significant difference between outcome groups. Better prognostic outcomes were seen in patients with a RESP in hospital survival score of 76% (HR=0.307, CI=0.131-0.717, p=0.006) although median time to death for this group was seen to be 22 days in comparison to 16 days for 57% and 23 days for 92% (p=0.012). RESP class showed no prognostic difference between groups but showed a decreased median time to death as the class increased (p=0.012). Patients with a RESP

point score of 4 showed a marginally better prognostic tendency (HR=0.095, CI=0.010-0.862, *p*=0.036) than other groups.

Pharmacological intervention was applied to some patients. These patients were treated with Tocilizumab (n=18), Remdesivir (n=15), Hydroxychloroquine (n=3) and Tamiflu (n=1). No significant difference between these groups was seen and no effect on prognosis.

Peri-ECMO Parameters

Intra-ECMO Variables (Table 4)

Modality of ECMO cannulation showed no influence on therapy outcome, most patients (n=75) received dual lumen cannulation of the right internal jugular (RIJ) vein. Half of the patients (n=46) were cannulated and put on ECMO at the referring hospitals, this too showed no effect. The majority of patients did not require an ECMO circuit change while receiving ECMO support but patients that received one circuit change had a poorer prognosis than those that did not require one (HR=0.255, CI=0.089-0.731, *p*=0.011). Standard procedure when considering the cessation of ECMO support was to undergo a 'trial off' period where the gasses to the ECMO oxygenator were turned off in order to simulate no VV support, we found a significant association between survival and number of trial off periods (*p*=0.035) and there was a better prognosis for patients that had 1 (HR=0.377, CI=0.183-0.778, *p*=0.008) and 3 (HR=0.690, CI=0.009-0.516, *p*=0.009) periods of trial off when compared to none. When combining the duration of trial off periods each patient had, we also saw an association between the combined trial off time and survival, the survivor group had a greater combined trial off time (*p*<0.001) than the non-survivors, and the greater the combined trial off time the better the prognosis (HR=0.997, CI=0.994-1.000, *p*=0.034).

It was found that the use of red blood cells (RBC) (HR=1.266, CI=1.147-1.397, *p*=<0.001), albumin (HR=1.395, CI=1.157-1.681, *p*=<0.001) and cryoprecipitate (HR=23509.940, CI=51.968-10635757.2, *p*=0.001) transfusions whilst they did not differ between the two groups, were associated with a poorer prognosis, most notably Cryoprecipitate, which demonstrated a very high HR. The transfusion volumes of Fresh Frozen Plasma (FFP) (*p*<0.001) and Platelets (p=0.010) (HR=1.797, CI=1.616-2.783, *p*=0.009) were found to be significantly lower in the survivor group and also indicated poorer outcomes.

Discussion

To date, there have been many publications addressing the application of ECMO as a viable, cost-effective bridge to recovery for patients with COVID-19 induced ARDS. Few have sought to ascertain risk factors that could predetermine patients to a poorer prognosis and outcome from the treatment of ECMO.

From assessing the pre-ECMO data, we identified a cohort of patients that had a poorer outcome on ECMO support. These patients displayed a significant pre-ECMO acidaemia with a low HCO_3, SaO_2, and mean systemic arterial blood pressure, a higher PIP and an elevated INR, essentially indications of severe ARDS and inflammation. INR may have been elevated due to therapeutic anticoagulation regimens of referring hospitals, ECMO requires systemic anticoagulation so will eventually be elevated on ECMO. Higher pCO_2 and lactate levels also contributed to a poorer prognosis. Changes in blood lactate levels after the initiation of ECMO support was beyond the scope of this study, however, this would be an interesting and valuable measure to assess in future studies. No significant difference was seen in the Murray Score, Sequential Organ Failure Assessment (SOFA) Score, Predicting Death for severe ARDS on VV-ECMO (PRESERVE) score, and the Horowitz index for ARDS prognostic markers highlighting a questionable efficacy in their prognostic use for the

COVID-19 patient. Only the RESP score 4 (76% class survival) showed a relatively improved prognosis. However, it has been shown that these prognostic markers are frequently used incorrectly, thereby negating their clinical utility in efficacy of outcome[15]

It was expected that our study would confirm commonalities between our data and that of other authors. Common findings relating to renal function and surrogate markers of renal disfunction/ failure were mirrored in our study to previous research. Increases in mortality for patients that receive CVVH support during ECMO but not pre-ECMO also have been reported[16],[17] for patients with COVID-19 on ECMO. Our findings of a statistically significant increased pre-ECMO urea, renal impairment, an AKI score of 2 and 3 and peri-ECMO CVVH therapy (with a poorer prognosis in the latter 3) in the non-survivor group highlighted the detrimental implications of renal dysfunction on the outcome of ECMO in the COVID-19 positive cohort. Creatine was higher in the non-survivor group, although not significantly.

Our findings were contradictory to that of other authors in that we did not find age to be correlated with prognosis[18],[19] in the COVID-19 ECMO group, age has been reported to be a significant predictor of mortality in ECMO patients before the COVID-19 outbreak[20],[21]. Longer times to cannulation (the time from ICU admission to ECMO) have been seen to reduce survival rates[22],[23],[24] which we did not reproduce. Current epidemiological understanding of the virus suggests an over-representation in the BAME community with death 2-4 times greater than those among the white population[25]. This was not seen in the ECMO setting, the incidence of death in both cohorts were comparable (white=48.9%, BAME=45.7%) and ethnicity was not shown to influence treatment outcome.

The use of inhaled nitric oxide showed no effect in outcome between the survivor and non-survivor groups, although patients receiving nitric oxide therapy exhibited a poorer prognosis and a significantly shorter median time to death. The Cox analysis showed this group to be 3 times more likely to die than patients not receiving this treatment with almost half the survival time (median time to death 13 days vs 22 days). Research has shown that inhaled nitric oxide may increase the risk of renal dysfunction[26],[27], especially in patients with ARDS,

this may be a contributing factor to the renal dysfunction we observed. The consolidation of 4 lung quadrants was seen to confer better prognostic outcome according to Cox univariable analysis. When consulting the prevalence of lung consolidation among the study participants one can see that the number of patients with 4 quadrant consolidation (n=73) was far greater than that of all other lung consolidation groups combined (n=20), this may have an effect on the statistical analysis.

The prevalence of the ABO blood group A has been shown to be higher among COVID-19 positive patients than other blood types and conversely blood group O appears to confer a protective effect[28],[29],[30],[31] however, our data did not reflect this. Research pertaining to ABO blood group and COVID-19 mortality has been inconclusive[32]. No significant difference in blood groups was found between survivors and non-survivors but patients with blood group B had a significantly poorer prognosis than others. When performing cox univariate analysis using all of the other blood groups as the reference group we found that patients with group B had consistently poorer outcomes than the other groups with a median time to death of around half of that of groups A,O and AB (p=0.005). Due to the prevalence of blood group B amongst the black and Asian community[33] a multivariable analysis was performed controlling for ethnicity (BAME) and the prognostic outcomes were found to be very similar, group B still exhibited a detrimental effect on outcome against all other blood groups except group AB which was insignificant. To date the authors are not aware of any prior research having been published regarding prognostic impact of ABO blood groups in the provision of ECMO.

It is important to iterate that the COVID-19 pandemic was used as a ‘test bed’ in order to accrue a consistent flow of ARDS patients over a relatively small period of time. Pre-pandemic, a time period of 8 years would have been required to collect data from 94 ARDS patients in the study hospital. The ability to collect and collate date from a relatively small period of time negates the effects of changes in clinical practice, the cause of ARDS, the throughput of staff and variations in equipment used. This control of variables gives a more accurate statistical analysis.

Limitations

This study had several limitations. The monocentric nature of this study may impact the generalisability of the findings. The relatively limited number of patients included along with the retrospective study design could limit the validity of the data.

Conclusions

The findings of this study show that triage decision making with a pragmatic approach to patient selection is necessary to decide whether this resource intensive therapy is of utility[34], a liberal approach to patient selection for the COVID-19 patient should be avoided. Commonly used mortality scores may not be of use in a COVID-19 cohort of ECMO patients. We found that it is imperative that the initiation of ECMO is implemented prior to metabolic derangements, renal and fulminant respiratory failure in order to benefit from ECMO in the support of COVID-19 induced ARDS.

Disclosure Statement

The authors declare no conflicts of interests. The study sponsor/funder had no role or influence in the study design, in the collection, analysis, and interpretation of data, in the writing of the report or in the decision to summit the paper for publication.

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Table 1: Demographics

Variable	All n=93		Survived	n=49 (52.7%)	Median	Mean	Died	n=44 (47.3%)	Median	Mean (SD)	Diffrence between groups	Cox univariate survival analysis		Kaplan-Meier Survival Analysis	
	Count	%	Count	%	(Range)	(SD)	Count	%	(Range)		P Value	HR (95% CI)	P Value	Median Time to Death (days)	P Value[g]
Age (Years)	46 (13)[b]				46.00 (35)				46.00 (38)		0.414[c]	1.015 (0.976-1.054)	0.458		
Sex											1.000[d]				0.841
Male	69	74.2	36	52.2			33	47.8				Ref		22.000 (18.570-25.430	
Female	24	25.8	13	54.2			11	45.8				1.071 (0.539-2.128)	0.844	20.000 (16.658-23.342)	
Wave of Pandemic											0.584[d]				0.187
First	44	47.3	25	56.8			19	43.2				Ref		18.000 (16.331-19.669)	
Second	49	52.7	24	49			25	51				0.663 (0.355-1.239)	0.198	23.000 (19.209-26.791)	
Ethnicity group											0.913[d]				0.975
White	47	50.5	24	51.1			23	48.9				Ref		22.000 (18.420-25.580)	
BAME	46	49.5	25	54.3			21	45.7				0.991 (0.544-1.805)	0.975	20.000 (15.656-24.344)	
ABO type											0.134[d]				**0.005**
A	33	35.5	20	60.6			13	39.40				Ref		20.000 (17.523-22.477)	
B	13	14	3	23.1			10	76.90				**3.103(1.335-7.212)**	**0.008**	11.000 (7.962-14.038)	
O	42	45.2	23	54.8			19	45.20				0.860(0.418-1.768)	0.681	23.000 (20.364-25.636)	
AB	5	5.4	3	60			2	40.00				0.723(0.162-3.224)	0.671	22.000 (8.918-35.082)	
Rhesus											1.00[e]				0.689
Positive	85	91.4	45	52.9			40	47.10				Ref		22.000 (19.020-24.980)	
Negative	8	8.6	4	50			4	50.00				1.229(0.437-3.454)	0.696	19.000 (13.120-24.880)	
Weight (Kg)	96.42 (20.68)[a]					97.114 (20.168)				96.095(21.426)	0.814[f]	0.997 (0.982-1.013)	0.749		
BMI (Kg/m^2)	32.60 (6.64)[a]					33.155(7.114)				32.275(6.368)	0.533[f]	0.996 (0.948-1.046)	0.876		
Obesity Category											0.858[d]				0.175
Normal weight	10	10.8	5	50			5	50				Ref		17.000 (15.057-18.943)	
Over weight	18	19.4	11	61.1			7	38.9				0.318 (0.095-1.062)	0.063	83.000 (-)	
Obese	38	40.9	20	52.6			18	47.4				0.610(0.222-1.673)	0.337	22.000 (17.857-26.143)	
Extremely obese	27	29	13	48.1			14	51.9				0.797 (0.285-2.230)	0.666	19.000 (15.629-22.371)	
Diabetes	26	28	11	42.3			15	57.7			0.309[d]	1.082(0.571-2.050)	0.809	22.000 (18.265-25.735)	0.805
Smoker	7	7.5	5	71.4			2	28.6			0.440[e]	0.431(0.104-1.789)	0.247	35.000 (3.021-66.979)	0.222
Infections											0.309[d]				
None	88	94.5	45	51.1			43	48.9				Ref			
Legionella	1	1.1	1	100			0	0				0.000(0.000-0.000)	0.994		
Pneumococcus	2	2.2	2	100			0	0				0.000(0.000-0.000)	0.979		
MRSA	1	1.1	1	100			0	0				0.000(0.000-0.000)	0.994		
HIV	1	1.1	0	0			1	100				4.73 (0.62-35.89)	0.130		
Immunocompromised	1	1.1	0	0			1	100			0.473[e]	4.875(0.642-36.989)	0.126	12.000 (-)	0.087
Cardiac arrest	2	2.2	1	50			1	50			1.000[e]	0.543(0.074-3.963)	0.547	19.000 (-)	0.532
Time to ECMO (days)	7 (5)[b]				7.00 (21)				7.00 (15)		0.871[c]	0.944 (0.867-1.027)	0.183		

[a]=mean (SD), [b]=median (IQR), [c]=Mann-Whitney U test, [d]=Chi-square test, [e]=Fisher exact test, [f]=Independent T-test, [g]=p value based on Log Rank test

BMI=Body Mass Index, HIV= Human Immunidefeciency Virus,

Obesity Cat-Normal Weight= <25Kg/m^2, Over Weight= >24Kg/m^2, Obese=29-39Kg/m^2, Extremely Obese=>39Kg/m^2. Based on WHO guidelines (2022)

P<0.05 indicates statistical significance

Table 2: Pulmonary function

Variable	All n=93		Survived n=49 (52.7%)		Median (Range)	Died n=44 (47.3%)		Median (Range)	Diffrence between groups	Cox univariate survival analysis		Kaplan-Meier Survival Analysis	
	Count	%	Count	%		Count	%		P Value	HR (95% CI)	P Value	Median Time to Death (days)	P Value[g]
Duration of MV before cannulation (Days)	4.00 (4.00)[b]				4 00(7)			4.00 (9)	0.409[c]	0.959 (0.833-1.105)	0.565		
Mechanical ventilation mode									0.124[d]				
CPAP	2	2.20	1	50.00		1	50.00			Ref			
Hand Bagged	1	1.1	1	100		0	0			0.000 (0.000-0.000)	0.993		
BIPAP	33	35.5	10	30.3		23	69.7			0.772 (0.098-5.829)	0.806		
SIMV	26	28	16	61.5		10	38.5			0.77 (0.980-6.077)	0.810		
PC	1	1.1	1	100		0	0			0.000 (0.000-0.000)	0.993		
APRV	21	22.60	14	66.70		7	33.30			0.471 (0.570-3.878)	0.484		
VCAC	1	1.10	1	100.00		0	0			0.000 (0.000-0.000)	0.988		
PRVC	4	4.30	3	75.00		1	25.00			0.437 (0.270-7.027)	0.559		
CMV	1	1.10	1	100.00		0	0			0.00 (0.00-0.00)	0.979		
PCV-VG	3	3.20	1	33.30		2	66.70			8.157 (0.665-100.127)	0.101		
FiO2 on MV (%)	100.0 (4)[b]				100 (50)			100 (30)	0.046[c]	1.021 (0.977-1.067)	0.366		
Respiratory rate on MV (Breaths/min)	20.0 (6)[b]				20.00 (23)			20 (21)	0.902[c]	1.008 (0.951-1.069)	0.783		
Tidal volume on MV (mls)	460.0 (136.0)[b]				460.00 (399)			455.00 (651)	0.434[c]	1.001 (0.998-1.004)	0.482		
Peak inspiratory pressure on MV (cmH2O)	30.0 (7.0)[b]				31.5 (24)			30.00 (29)	**0.040**[c]	0.980 (0.939-1.024)	0.370		
Possitive end expiratory pressure on MV (cmH2O)	10.5 (4.0)[b]				10.00 (17)			12.00 (12)	0.671[c]	1.013 (0.920-1.116)	0.788		
Lung Compliance	23.850 (12.7)[b]				22 (36.5)			25.35 (77.1)	0.147[c]	0.999 (0.977-1.021)	0.905		
PaO_2 / FiO_2ratio, Horrowitz index	61.5 (17)[b]				62.0 (166.0)			60.5 (81.0)	0.253[c]	0.993(0.972-1.014)	0.497		
Patient on Nitric oxide	8.00	8.60	2	25.00		6	75.00		0.143[e]	**3.047(1.247-7.447)**	**0.015**	**13.000 (3.161-22.839)**	**0.009**
Patient proned	89.00	95.70	45	91.80		4	8.20		0.119[e]	0.045 (0.00-12.587)	0.280		
Lung consolidation (Quadrants)									0.422[d]				
1	1	100	0	0.00		1	100.00			Ref			
2	9	9.7	3	33.30		6	66.70			0.141(0.016-1.261	0.800		
3	10	10.8	6	60.00		4	40.00			0.128(0.013-1.214)	0.073		
4	73	78.5	40	54.80		33	45.50			**0.117(0.015-0.921)**	**0.042**		
Pneumothorax	8.00	8.60	2	25.00		6	75.00		0.143[e]	0.710 (0.299-1.686)	0.438	20.000 (15.080-24.920)	0.426
Chest drains in situ	8.00	8.60	2	4.10		6	13.60		0.143[e]	0.710 (0.299-1.686)	0.438	20.000 (15.080-24.920)	0.426
No. of chest drains (n)									0.260[d]				0.728
0	85	91.4	47	55.3		38	44.7			Ref		22.000 (18.634-25.366)	
1	4	4.3	1	25		3	75			1.392 (0.426-4.549)	0.584	20.000 (16.799-23.201)	
2	4	4.3	1	25		3	75			1.425 (0.438-4.632)	0.556	8.333 (0-27.333)	
Total Duration of MV (Days)	21.5 (18)[b]				23.0 (111)			21.0 (90)	0.128[c]	**0.895(0.862-0.928)**	**<0.001**		

[a]=mean (SD), [b]=median (IQR), [c]=Mann-Whitney U test, [d]=Chi-square test, [e]=Fisher exact test, [f]=Independent T-test, [g]=p value based on Log Rank test

APRV=Airway pressure release ventilation, BIPAP=Bilevel positive airway pressure, CMV=continuous mandatory ventilation, CPAP=Continuous positive airway pressure, FiO_2=Fraction of inspired oxygen, MV=Mechanical ventilation, PaO_2=Partial pressure of oxygen, PC=pressure control, PRVC=Pressure regulated volume control, PCV-VG=Pressure control ventilation volume guaranteed, VCAC=Volume control assist control

P<0.05 indicates statistical significance

Table 3: Renal/Liver Function

Variable	All n=93		Survived n=49 (52.7%)		Median (Range)	Died n=44 (47.3%)		Median (Range)	Diffrence between groups	Cox univariate survival analysis		Kaplan-Meier Survival Analysis	
	Count	%	Count	%		Count	%		P Value	HR (95% CI)	P Value	Median Time to Death (days)	P Value[g]
Renal impairment	18	19.4	3	6.1		15	34.1		**0.002[d]**	**3.023 (1.586-5.763)**	**<0.001**	**19.000 (9.466-28.534)**	**<0.001**
AKI	18	19.4	3	16.7	2.00(1.00)	15	83.3	2.00(1.00)	**0.001[d]**				**0.003**
0	75	80	46	93.9		29	65.5			Ref		23.000 (19.795-26.205)	
1	6	6.5	1	2		5	11.4			2.403 (0.906-6.374)	0.078	20.000 (19.133-20.867)	
2	6	6.5	1	2		5	11.4			**3.611(1.382-9.441)**	**0.009**	11.000 (0-24.720)	
3	6	6.4	1	2		5	11.4			**3.275(1.235-8.685)**	**0.017**	10.000 (0-26.803)	
Patient on Haemofiltration (Pre)	9	9.7	2	4.1		7	15.9		0.079[e]	1.927(0.851-4.365)	0.116	20.000 (0-40.444)	0.102
Patient on Haemofiltration (Peri)	30	32.3	8	26.7		22	73.3		**0.001[e]**	**2.412(1.310-4.442)**	**0.005**	19.000 (17.192-20.808)	0.003
Creatinine (micmol/L)	73.00(61.5)[b]				79 (383)			86 (339)	0.595[c]	1.002 (0.998-1.005)	0.289		
Urea (mmol/L)	8.30 (7.40)[b]				**8.4 (29.7)**			**9.9 (103.1)**	**0.041[c]**	1.008(0.992-1.024)	0.351		
Amylase (iu/L)	61.0 (85.5)[b]				56 (564.0)			64 (631.0)	0.360[c]	1.001 (0.999-1.003)	0.475		
Bilirubin (micmol/L)	10.0 (11.0)[b]				10 (77)			10 (39)	0.917[c]	0.994 (0.973-1.017)	0.618		
Alkaline Phosphatase (iu/L)	80.0 (55.5)[b]				85 (393.0)			75.5 (247.2)	0.181[c]	0.995 (0.989-1.001)	0.137		
Alt (iu/L)	42.0 (53.5)[b]				48.8 (292.0)			51 (2434.0)	0.633[c]	1.000 (1.000-1.001)	0.384		
Albumin (g/L)	27.0 (9.0)[b]				28.0 (266.0)			27.0 (49.0)	0.778[c]	0.983 (0.944-1.023)	0.399		

[a]=mean (SD), [b]=median (IQR), [c]=Mann-Whitney U test, [d]=Chi-square test, [e]=Fisher exact test, [f]=Independent T-test, [g]=p value based on Log Rank test
Alt=Alanine transaminase, AKI=Accute kidney injury,

Table 4: ECMO Data

Variable	All n=93		Survived n=49 (52.7%)		Median (Range)	Mean (SD)	Died n=44 (47.3%)		Median (Range)	Mean (SD)	Diffrence between groups	Cox univariate survival analysis		Kaplan-Meier Survival Analysis	
	Count	%	Count	%			Count	%			P Value	HR (95% CI)	P Value	Median Time to Death (days)	P Value[g]
Vascular access											0.309[d]				0.801
Right Internal Jugular	75	80.6	42	56.00			33	44.00				Ref		22.000 (17.707-26.298)	
Right Internal jugular/Femoral Vein	17	18.3	7	41.20			10	58.80				1.238(0.608-2.522)	0.557	20.000 (15.628-24.372)	
Left Internal Jugular/Femoral Vein	1	1.1	0	0.00			1	100.00				1.395(0.189-10.321)	0.744	22.000 (-)	
Cannulated at the refering Hospital	46	49.5	26	53.10			20	45.50			0.600[d]	1.213(0.665-2.211)	0.529	23.000(20.512-25.448)	0.519
Circuit change (n)											0.232[d]				**<0.001**
0	76		37	48.70			39	51.30				Ref		19.000 (15.953-22.047)	
1	12		8	66.70			4	33.30				**0.255(0.089-0.731)**	**0.011**	0	
2	5		4	80.00			1	20.00				0.00(0.000-1.415X10^{171})	0.951	83.000 (-)	
Oxygenator change (n)											0.253[d]				
0	87		44	50.60			43	49.40				Ref			
1	4		3	75.00			1	25.00				0.484(0.066-3.524)	0.473		
2	2		2	100.00			0	0.00				0.000(0.000-1.520X10^{285})	0.972		
Time on ECMO (Days)	15.00 (12.00)[b]				13 (52)				17.5 (81)		0.893[c]				
Trial Off (n)											**0.035[d]**				
0	40		12	30.00			28	70.00				Ref			
1	27		17	63.00			10	37.00				**0.377(0.183-0.778)**	**0.008**		
2	11		8	72.70			3	27.30				0.427(0.129-1.410)	0.163		
3	8		6	75.00			2	25.00				**0.690(0.09-0.516)**	**0.009**		
4	3		2	66.70			1	33.30				0.218(0.229-1.615)	0.136		
5	1		1	100.00			0	0.00				0	0.984		
6	1		1	100.00			0	0.00				0	0.989		
7	1		1	100.00			0	0.00				0	0.984		
8	1		1	100.00			0	0.00				0	0.986		
Combined trial off time (min)	4.00 (38.00)[b]				12.0 (1297.0)				0.0 (606)		**<0.001[c]**	**0.997(0.994-1.000)**	**0.034**		
Systoilc Blood pressure (mmHg)	117.09 (25.06)[a]					122.150(25.930)				111.930 (22.650)	0.053[f]	0.990(0.978-1.002)	0.096		
Diastolic blood pressure (mmHg)	66.20 (13.51)[a]					68.400 (12.390)				64.330 (13.710)	0.148[f]	0.992(0.970-1.015)	0.486		
Mean blood pressure (mmHg)	81.57 (15.46)[a]					84.730 (15.600)				77.280 (13.900)	**0.026[f]**	0.986(0.965-1.008)	0.218		

[a]=mean (SD), [b]=median (IQR), [c]=Mann-Whitney U test, [d]=Chi-square test, [e]=Fisher exact test, [f]=Independent T-test, [g]=p value based on Log Rank test

P<0.05 indicates statistical significance

Table 5: Pre-ECMO Blood Results

Variable	All n=93		Survived	n=49 (52.7%)	Median (Range)	Mean (SD)	Died	n=44 (47.3%)	Median (Range)	Mean (SD)	Diffrence between groups	Cox univariate survival analysis	
	Count	%	Count	%			Count	%			P Value	HR (95% CI)	P Value
pH	**7.32 (0.16)[b]**				**7.330 (1.410)**				**7.275 (1.600)**		**0.015[c]**	**0.023(0.002-0.210)**	**<0.001**
PaO_2 (kPa)	7.90 (1.20)[b]				7.900 (9.100)				7.800 (10.800)		0.641[c]	0.971(0.806-1.171)	0.761
PCO_2 (kPa)	7.70 (2.85)[b]				7.500 (10.500)				8.300 (16.100)		0.199[c]	**1.134(1.031-1.248)**	**0.010**
SaO_2 (%)	**89.0 (5.65)[b]**				**91.000 (88.000)**				**88.000 (61.900)**		**0.030[c]**	0.981(0.961-1.003)	0.084
HCO_3 (mEq/L)	**26.96 (4.93)[a]**					**27.512 (4.748)**				**25.302 (5.871)**	**0.048[f]**	0.934(0.872-1.000)	0.050
Lactate (mmol/L)	1.60 (0.60)[b]				1.500 (5.300)				1.800 (14.200)		0.155[c]	**1.350(1.156-1.576)**	**<0.001**
Hb (g/L)	115.36 (16.23)[a]					114.492 (19.236)				115.591 (16.858)	0.771[f]	0.995(0.977-1.014)	0.622
HCT l/L)	35.49 (4.36)[a]					35.006 (4.963)				35.666 (4.756)	0.516[f]	1.001(0.937-1.069)	0.979
Platelets (10x9/L)	271.0 (157.0)[b]				286.000 (517.000)				243.000 (522.000)		0.278[c]	0.998(0.996-1.001)	0.218
Fibrinogen (g/L)	6.50 (2.60)[b]				6.200 (35.100)				6.200 (10.300)		0.752[c]	0.914(0.807-1.036)	0.159
C-Reactive protein (mg/L)	177.0 (204.0)[b]				151.000 (407.000)				159.000 (459.000)		0.832[c]	1.001(0.999-1.003)	0.420
D-Dimers mg/l FEU)	6.20 (17.68)[b]				8.329 (7455.1000)				6.200 (8087.480)		0.969[c]	1.000(1.000-1.000)	0.705
INR (ratio)	**1.10 (0.20)[b]**				**1.000 (0.500)**				**1.100 (5.600)**		**0.004[c]**	**2.571(1.438-4.598)**	**0.001**
PT (sec)	13.70 (3.0)[b]				13.200 (7.000)				14.100 (120.000)		0.109[c]	1.008(0.994-1.021)	0.263
APTT (sec)	31.20 (9.20)[b]				32.400 (30.500)				29.500 (59.300)		0.516[c]	1.030(0.993-1.069)	0.115
White Cell Count (10x9/L)	11.50 (8.50)[b]				12.200 (36.700)				11.950 (29.300)		0.908[c]	1.010(0.969-1.054)	0.638
Glucose (mmol/L)	8.40 (3.0)[b]				8.400 (14.800)				8.650 (17.600)		0.368[c]	1.035(0.942-1.137)	0.478
Calcium (mg/dL)	2.19 (0.21)[b]				2.200 (1.520)				2.180 (1.970)		0.969[c]	1.074(0.351-3.286)	0.901
Potassium mmol/L)	4.60 (0.80)[b]				4.600 (3.700)				4.600 (2.300)		0.954[c]	0.816(0.454-1.466)	0.497
Sodium (mmol/L)	141.82 (4.53)[a]				142.000 (22.000)	141.78(5.17)			141.500 (20.000)	141.70(4.69)	0.934[f]	1.002(0.938-1.070)	0.957
Troponin-I (ng/L)	18.60 (32.10)[b]				20.100 (15749.000)				22.200 (2579.200)		0.960[c]	1.000(1.000-1.000)	0.368

[a]=mean (SD), [b]=median (IQR), [c]=Mann-Whitney U test, [d]=Chi-square test, [e]=Fisher exact test, [f]=Independent T-test, [g]=p value based on Log Rank test

APTT=Activated partial thromboplastin time ,Hb=Haemoglobin, HCO_3=Bicarbonate, HCT=Haematocrit, INR=International normalized ratio, PCO_2=Partial pressure of carbon dioxide, PO_2=Partial pressure of oxygen

PT=Prothrombin time, SaO_2=Saturation of arterial oxygen

P<0.05 indicates statistical significance

Table 6: Pre-ECMO Survival Scores

Scores	All n=93		Survived n=49 (52.7%)		Median (Range)	Died n=44 (47.3%)		Median (Range)	Diffrence between groups	Cox univariate survival analysis		Kaplan-Meier Survival Analysis	
	Count	%	Count	%		Count	%		P Value	HR (95% CI)	P Value	Median Time to Death (days)	P Value[g]
Murray score									0.432[d]				**0.03**
1.0-1.9	2	2.2	0	0		2	100			Ref		16.000 (-)	
2.0-2.9	19	20.7	10	52.6		9	47.4			0.310(0.064-1.507)	0.146	22.000 (17.899-26.101)	
3.0-3.9	68	73.9	37	54.4		31	45.6			0.279(0.064-1.220)	0.090	23.000 (18.533-27.462)	
4.0	3	3.3	1	33.3		2	66.7			1.530(0.211-11.094)	0.674	13.000 (-)	
SOFA score									0.530[d]				0.151
1.0-5.0	39	41.9	21	53.8		18	46.2		0.841[d]	Ref		23.000 (17.497-28.503)	
6.0-10.0	49	52.7	26	53.1		23	46.9			1.424(0.754-2.690)	0.276	22.000 (17.830-26.170)	
11.0-15.0	5	5.4	2	40		3	60			3.097(0.883-10.861)	0.077	17.000 (0-35.896)	
RESP in hospital survival (%)									0.288[d]				**0.012**
57.0	10	10.8	3	30		7	70			Ref		16.000 (8.981-23.019)	
76.0	75	80.6	41	54.7		34	45.3			**0.307(0.131-0.717)**	**0.006**	22.000 (18.795-25.205)	
92.0	8	8.6	5	62.5		3	37.5			0.281(0.070-1.126)	0.073	23.000 (-)	
RESP class									0.288[d]				**0.012**
1.0	8	8.6	5	62.5		3	37.5			Ref		23.000 (-)	
2.0	75	80.6	41	54.7		34	45.3			1.092(0.333-3.576)	0.884	22.000 (18.795-25.205)	
3.0	10	10.8	3	30		7	70			3.559(0.888-14.253)	0.073	16.000 (8.981-23.019)	
RESP score									0.085[d]				
-1.0	1	1.1	0	0		1	100			Ref			
0.0	1	1.1	1	100		0	0			0 .000(0.000-0.000)	0.987		
1.0	2	2.2	2	100		0	0			0.000 (0.000-0.000)	0.981		
2.0	7	7.5	0	0		7	100			0.695(0.083-5.846)	0.738		
3.0	18	19.4	8	44.4		10	55.6			0.221(0.027-1.804)	0.159		
4.0	16	17.2	10	62.5		6	37.5			**0.095(0.010-0.862)**	**0.036**		
5.0	40	43	23	57.5		17	42.5			0.183(0.023-1.438)	0.106		
6.0	4	4.3	3	75		1	25			0.147(0.009-2.439	0.181		
7.0	4	4.3	2	50		2	50			0.161(0.014-1.889)	0.146		
PRESERVE									0.786[d]				
-2.0	15	16.3	8	53.3		7	46.7			Ref			0.816
-1.0	8	8.7	4	50		4	50			1.267(0.371-4.329)	0.706	26.000 (19.182-32.818)	
0.0	26	28.3	11	42.32		15	57.5			1.697(0.684-4.214)	0.254	18.000 (5.701-30.299)	
1.0	16	17.4	10	62.5		6	37.5			1.695(0.562-5.115)	0.349	20.000 (18.787-21.213)	
2.0	15	16.3	9	60		6	40			1.851(0.612-5.601)	0.276	16.000 (9.396-22.604)	
3.0	8	8.7	5	62.5		3	37.5			0.958(0.247-3.709)	0.950	25.000 (10.798-39.202)	
4.0	3	3.3	1	33.3		2	66.7			0.615(0.075-5.010)	0.650	83.000 (-)	
5.0	1	1.1	0	0		1	100			2.702(0.324-22.549)	0.359	19.000 (-)	
Horrowitz Index									1.000[e]				0.328
Moderate	4	4.3	2	50		2	50			Ref		9.000 (-)	
Severe	89	95.7	47	52.8		42	47.2			0.503(0.120-2.107)	0.347	22.000 (18.935-25.065)	

[a]=mean (SD), [b]=median (IQR), [c]=Mann-Whitney U test, [d]=Chi-square test, [e]=Fisher exact test, [f]=Independent T-test, [g]=p value based on Log Rank test
P<0.05 indicates statistical significance