An investigation into the contributing factors to survival of COVID-19 induced ARDS patients supported by veno-venous ECMO.

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I would like to dedicate this work to the memory of Sister Carol Warboys, an exceptional theatre sister who always believed in my ability to excel from the very first day of my journey in the NHS.

Abstract

This study aimed to identify characteristics associated with survival and prognosis during/post Veno-Venous Extracorporeal Membrane Oxygenation (VV-ECMO) therapy, a modality of treatment suggested by the World Health Organisation (WHO), in patients with COVID-19 induced Acute Respiratory Distress Syndrome (ARDS). Also, we aimed to identify pre and peri-measures that have an influence on and affect the survival times of this cohort and to see how changes in these variables influenced the risk of not surviving ECMO treatment.

A retrospective observational study on 93 consecutive patients with confirmed COVID-19 induced acute respiratory distress syndrome (ARDS) supported by Extra Corporeal Membrane Oxygenation (ECMO) was carried out. 49/93 (52.7%) patients survived to hospital discharge.

All proposed objectives were met to provide a valuable insight into the efficacy of ECMO for this specific cohort.

Non-survivors, in comparison to 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, blood urea levels and peri-ECMO fresh frozen plasma (FFP) and platelet transfusion volumes. Also, lower pre-ECMO peak inspiratory pressures (PIP), mean blood pressure, saturation of arterial oxygen (SaO_2), blood bicarbonate levels (HCO_3), 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, renal impairment, AKI staging score of 2 or 3, peri-ECMO haemofiltration, receiving transfusions

of albumin, red blood cells (RBC), Fresh Frozen Plasma (FFP), platelets, cryoprecipitate and the ABO blood group B, pre-ECMO high CO_2, blood lactate, and lower blood pH. It was seen that commonly used mortality scores may not be of use in a COVID-19 cohort of ECMO patients. These findings indicated that the initiation of ECMO needs to be implemented prior to metabolic derangements, renal and fulminant respiratory failure.

By utilising the findings of this study, one can make best use of finite resources to provide the greatest utility at a time of excessive demand. As well as filling a known knowledge gap in the use of VV-ECMO for COVID-19 induced ARDS patients, it also highlights further requirements to investigate the use of ECMO in the ARDS setting.

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1 Introduction

During the 2020 COVID-19 pandemic, the services at the Glenfield Hospital Leicester were called upon as a specialist advanced respiratory care provider to treat the abnormally high influx of COVID-19 positive patients from around the country. Our ability to provide a specific form of treatment known as Veno-Venous ExtraCorporeal Membrane Oxygenation, or VV-ECMO, singled us out as 1 of 6 speciality centres in the UK with the ability and experience to facilitate this. In no time our intensive care beds were full and ECMO provision saturated, demand outstripped supply, which led to the unfortunate necessity to redirect patients to other hospitals and/or consider other forms of treatment other than VV-ECMO.

The presentation of ARDS associated refractory respiratory failure had never been seen on this scale before, and other than a small number of studies attributed to the H1N1 pandemic, very little was known about how to manage this situation. Pertinent questions were asked such as ‘how should we allocate ECMO as a finite resource?’, ‘should we allocate VV-ECMO for COVID-19 positive patients in the same way as patients as with ARDS of non-COVID-19 origin?’, and ‘are there factors that predispose COVID-19 positive patients to a poorer outcome on VV-ECMO?’. Having this knowledge would augment the successful triaging of prospective ECMO patients and help to manage patients while being supported by ECMO thus maximising the utility of VV-ECMO.

The conception of this study came about in order to address these questions and as such, augment the efficacy of the triaging process for this cohort of patients making the best use of a finite resource.

Hence, the aim of this study was to identify the factors that can give an indication as to the probable outcome of Covid-19 induced ARDS patients on VV-ECMO.

The study objectives were:

1. To investigate the differences in characteristics of Covid-19 induced ARDS patients who survive VV-ECMO vs those who don't.
2. To identify pre and peri-ECMO measures that have an influence on the outcome of VV-ECMO in Covid-19 Induced ARDs patients.
3. To investigate the differences in survival time between patients with certain risk factors.
4. To assess how changes in peri-ECMO and Pre-ECMO variables (risk factors) influence the risk of not surviving the ECMO treatment in Covid-19 induced ARDS patients.

2 Background

2.1 ARDS

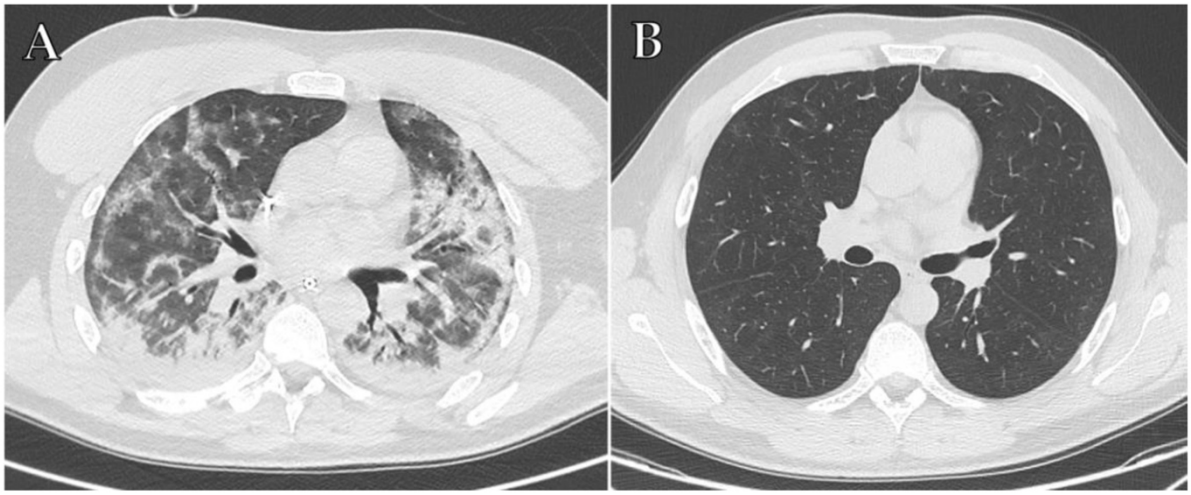
ARDS is a potentially fatal condition in which the lungs sustain a significantly extensive injury that severely limits their efficacy to provide the bodies organs with the oxygen supply they require for a normal function. The genesis of ARDS is always from an injury to the lung. The exact nature of the injury is not always clear but common causes are sepsis, trauma, aspiration, pneumonia, viral infection of the lungs (e.g., SARS-CoV-2) blood transfusions, pancreatitis and near drowning to name a few. Most people that develop ARDS are already in hospital because of the causative injury/illness, while it is not clear who will develop this condition, certain risk factors may increase the risk such as advanced age, alcoholism, extensive surgery and a history of smoking. ARDS causes an inflammation of the lungs which results in the damage to the alveoli. The inflammation causes fluid from nearby blood capillaries to leak into the lung tissue, this increased alveolocapillary permeability causes bilateral pulmonary oedema which prevents them from filling with air, therefore eventually depriving the body of the necessary oxygen it requires.

2.1.1 Diagnostic considerations

These is no specific single test that confirms a diagnosis of ARDS, as ARDS is a syndrome rather than a specific, standalone pathologic condition it is identified solely by clinical criteria(Herrero, Sanchez and Lorente, 2018). As can be seen in the Berlin definition (Figure: 2), a clinical diagnosis of ARDS requires a new or worsening respiratory distress in the presence of bilateral chest radiographical abnormalities that have been present for 7 days

or fewer, that heart failure cannot fully explain the observed hypoxaemia and radiographical infiltrates and that the impairment of oxygen be clinically significant (Meyer, Gattinoni and Calfee, 2021). Computerised Tomography (CT) imaging can identify aspects of the ARDS criteria and can quantify lung oedema and recruitability of lung parenchyma (Cressoni *et al.*, 2014).

Figure 1: CT Scan



Axial HRCT images of a 38-year-old man with COVID-19 ARDS admitted to ICU at the same level, performed at different times: baseline scan (**A**) and 7-month follow-up (**B**). The baseline scan (**A**) shows typical imaging features indicative of severe COVID-19 pneumonia, including extensive bilateral parenchymal consolidations, mainly affecting the posterior regions of lower lobes, bilateral focal ground-glass opacities in the anterior regions and patchy consolidation, peripherally distributed, resembling pulmonary fibrosis. The 7-month scan (**B**) shows a complete resolution of the parenchymal consolidations and the apparent fibrotic abnormalities.

(Brandi *et al.*, 2022)

CT can at times, be challenging to obtain in patients with severe hypoxaemia who are receiving ITU interventions. It exposes patients to ionizing radiation which limits its repeatability and is also expensive.

ARDS can be diagnosed by using the Berlin Criteria for ARDS-

Figure 2:The Berlin criteria for ARDS

Characteristics	1994 AECC definition	2012 Berlin definition
Onset	Acute	≤7 days since onset of predisposing clinical condition
X-ray abnormalities	Bilateral opacities	Bilateral opacities on X-ray or CT scan not attributed to pleural effusion, atelectasis or nodules
Non-cardiogenic pulmonary oedema	No evidence of increased pressure in left atrium or pulmonary wedge pressure ≤ 18 mmHg	Respiratory failure that cannot be attributed to heart failure or volume overload
Oxygenation	$PaO_2/FiO_2 \leq 300$ mmHg acute lung injury $PaO_2/FiO_2 \leq 200$ mmHg ARDS	PaO_2/FiO_2 ratio with use of ≥5 cm H_2O of PEEP: 201–300 mmHg mild ARDS 101–200 mmHg moderate ARDS <100 mmHg severe ARDS
Predisposing condition	Not specified	Perform additional studies to rule out cardiogenic oedema (echocardiography, determination of BNP*)

* Brain natriuretic peptide.

(Amezcua-Gutiérrez *et al.*, 2018)

2.2 Underlying pathologies

2.2.1 Endothelial permeability

Normal lung vasculature has several safety features that prevents the lungs from flooding due to a range of vascular hydrostatic pressures. The fluid that is filtered from the pulmonary microvasculature in the interstitium is mostly reabsorbed into the circulation due to a low alveolar epithelial permeability, a protein osmotic gradient between the blood vessels and the interstitium, lymphatic flow, the hydrostatic pressure from peripheral to central vessels and the pleural and mediastinal sinks if the hydrostatic pressure becomes elevated (Rogol, 1991). When the barrier created by the vasculature becomes highly permeable to solutes and proteins, the osmotic gradient, mainly a product of protein concentration, is lost, the interstitium can become flooded with fluid.

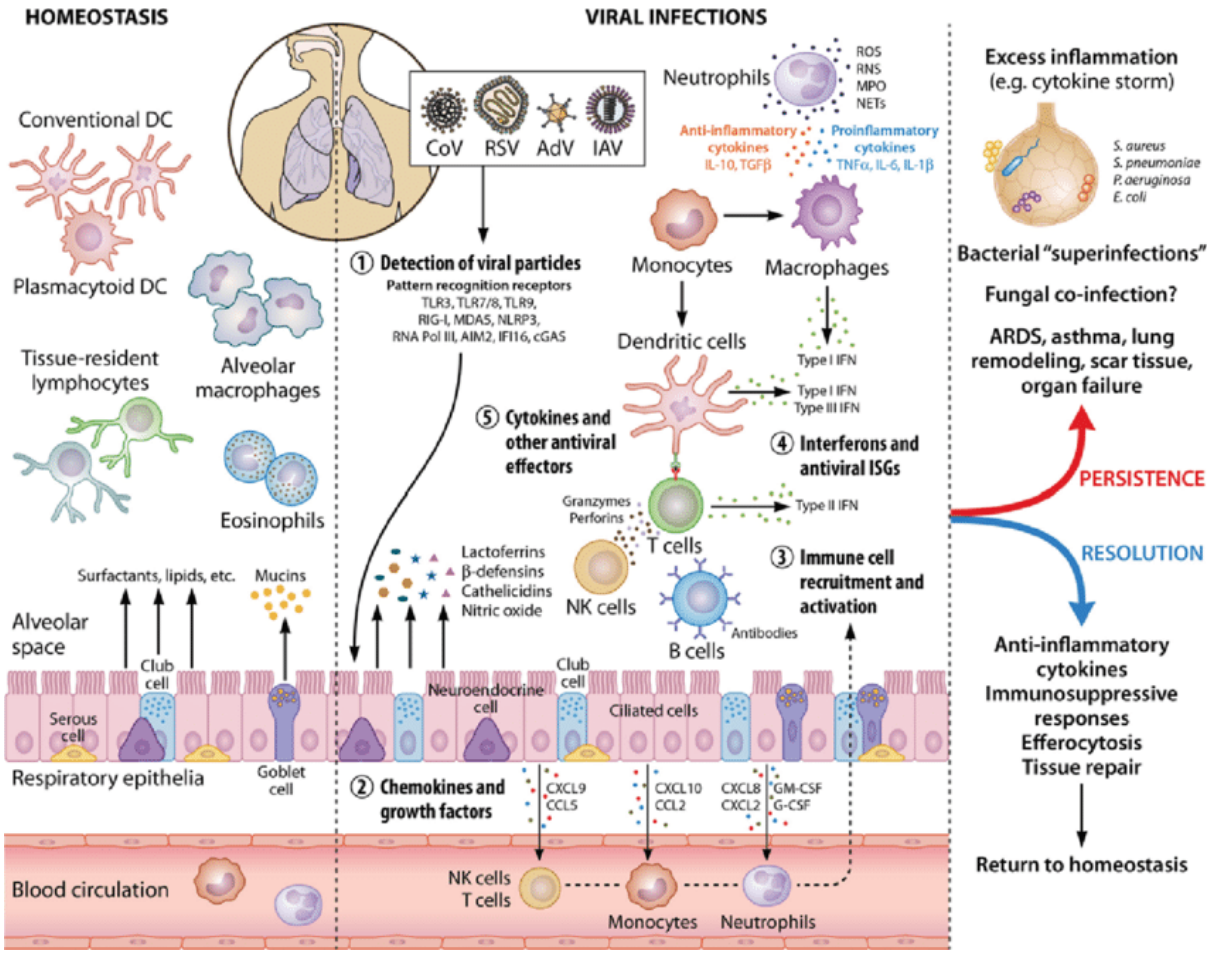
Normal pulmonary endothelium inhibits inflammation and coagulation due to an array of surface markers and exogenously produced factors, whereas activated endothelium does the opposite (Matthay and Wiener-Kronish, 1990). Stimuli such as cytokines, chemokines, regional hypoxia, leukocytes, thrombin, lipopolysaccharides which are found in patients with ARDS due to the inflammatory response, can alter the endothelium into a dysregulated, “leaky” state which attracts inflammatory cells (Millar *et al.*, 2016). The concomitant disruption between endothelial cells and the changes in the cytoskeleton causes adjacent cells to retreat away from each other and allow endothelial gaps to form (Abadie *et al.*, 2005). This activated endothelium recruits activated neutrophils and via margination, diapedesis and chemotaxis, the neutrophils move across the endothelial gap.

In ARDS the epithelial barrier, function and fluid clearance are either weakened or inactive (Short *et al.*, 2016). Epithelial injury can be induced by pathogens such as bacteria and viruses, acid injury from aspiration of gastric contents or excessive mechanical stretch as seen in Mechanical Ventilation (MV). These injuries can cause epithelial apoptosis or necrosis and disrupt endothelial integrity (Bachofen and Weibel, 1982).

2.2.2 Lung Inflammation

The accumulation of leukocytes, particularly neutrophils, in the lungs and alveoli is clinically and pathologically significant in ARDS. The neutrophils from patients with ARDS are activated and functionally specific, they have an augmented chemotactic and metabolic ability and a delayed apoptosis

Figure 3:Mechanism of inflammation



(Clementi *et al.*, 2021)

2.2.3 Mechanical trauma

Biomechanical stress sometimes seen in patients receiving MV therapy can contribute to lung injury and ARDS. The treatment of patients with severe hypoxia has mostly relied on MV. Excessive or prolonged MV in hypoxic patients can cause physical barotrauma to the lung tissues and ventilatory strategies have been adopted to ameliorate this phenomena such as low tidal volume ventilation and reduced plateau pressures.

2.3 ARDS outcomes

ARDS is more common than generally believed. A study by Bellani *et al*. from 50 countries reported that 10% of ITU patients and 23% of patients receiving MV support fulfilled the criteria for ARDS (Bellani *et al.*, 2016). Hospital mortality was shown to be in the region of 35%-45% in a study cohort closely resembling the dataset used to validate the Berlin definition (Ranieri *et al.*, 2012). The common cause of death observed in ARDS patients has been shown to be from sepsis and multi organ failure rather than respiratory failure (DiFonzo and Bordia, 1998), survivors recover normal to near-normal lung function although many suffer the burden of functional limitations related to the muscle weakening, deconditioning or psychological sequelae of severe Illness (Margaret S. Herridge *et al*., 2011). A degree of psychiatric morbidity is recognised post ARDS, Cognitive impairment is common, affecting almost 50% of survivors at 2 years (Mikkelsen *et al.*, 2012).

2.4 Treating ARDS

2.4.1 Mechanical Ventilation

A deteriorating tissue oxygen status from a non-invasive oxygen therapy regimen with an inability to provide sufficient oxygenation brings about the need for a more invasive therapy, namely MV.

In a comparison of epidemiological studies, rates of MV among patients admitted to ITU's with ARDS during the COVID-19 pandemic range from 29.1% in one Chinese study (Wang *et al.*, 2020) to 89.9% in a study from the U.S (Richardson *et al.*, 2020).

Mechanical ventilators are generally used for conditions that cause either low oxygen levels (e.g., pneumonia) or high carbondioxide levels (e.g., chronic obstructive pulmonary disease (COPD)).

There are two types of MV that are highlighted as follows. -

2.4.2 Non-invasive MV (NIMV)

This involves a ventilator that delivers oxygen through a face mask. This type of MV is generally used for patients with mild to moderate breathing difficulties and creates a positive airway pressure to lessen the respiratory effort required to breathe. Examples of this are Bilevel positive airway pressure (BIPAP) and Continuous positive airway pressure (CPAP).

2.4.3 Invasive MV

Invasive MV (IMV) involves the placement of an endotracheal (ET) tube into the patients trachea to provide an airtight seal within the airway. The ventilator delivers a prespecified volume of gas with a set number of breaths per minute at a specified pressure, these are adjusted according to the patients requirements (Walter, Corbridge and Singer, 2018). As gas enters the lungs the interalveolar pressure increases until a change in flow or pressure is

detected by the ventilator or a pre specified volume of gas has been delivered to indicate the end of a breath. The expiration phase of breathing happens passively. IMV is required for patients that are critically ill that are hypoxic and/or hypercapnic and cannot adequately meet their gas exchange requirements where NIMV will not be effective .

There are unwanted issues that can result from MV, the main detrimental effects are-

2.4.4 Ventilator associated pneumonia

By far the most common infection among the MV patient receiving positive pressure ventilation (PPV) is ventilator associated pneumonia (VAP). The mortality rate is between 20% to 50% (Kunis and Puntillo, 2003). Although the ET tube is necessary for the implementation of IMV, it also acts as a conduit between the outside environment and the normally sterile lower respiratory tract. In the immunologically compromised patient that has a dysfunctional immune system, invading bacteria (via the ET tube) often colonise the lower respiratory tract of patients. This can further complicate the medical management of patients.

2.4.5 Ventilator associated barotrauma (VAB)

High pressures and tidal volumes entering the lungs from the ventilator can cause barotrauma resulting in alveolar damage. Damage to the alveolar epithelial lining occurs initially, on a microscopic level until it is severe enough to cause a pneumothorax, pneumomediastinum, and subcutaneous emphysema. All of these conditions are associated with high mortality rates (Sánchez García, Sanz Díaz and Rubio Solís, 2017). In the already

damaged lungs of patients with ARDS, greater and greater pressures and volumes of gas are required to fulfil the gas exchange needs of the body, this predisposes these patients to a greater risk of VAB.

2.5 Treatment of ARDS

MV does not cure ARDS, however, it does allow time for the patient to recover from the pathologies that led to respiratory failure while providing adequate oxygenation and CO_2 removal. It is clear that ventilator-associated strategies were necessary in order to minimize ventilator-induced lung injury (VILI).

2.5.1 Lung protective ventilation

Gattinoni *et al.* hypothesised that lung protective strategies and permissive hypercapnoea could be more beneficial than the current high volume/high pressure MV methods (Gattinoni *et al.*, 1980). The ARMA trial in 2000 reported a survival advantage with reduced tidal volumes from 12cc/kg predicted body weight to 6 cc/kg thereby limiting the stretch of the lung and thus barotrauma. The findings of that study were that MV with lower tidal volumes than is traditionally used results in decreased mortality and an increase in the number of days without ventilator use (The acute respiratory distress syndrome network, 2001). This concept is now widely recognised as a lung protective strategy for patients with ARDS (Bellani *et al.*, 2016).

2.5.2 PEEP

PEEP has been shown to provide a protective strategy in the hypoxic patient. Subsequent research showed that the combination of a large tidal volume with no PEEP induces haemorrhagic pulmonary oedema (Dreyfuss *et al.*, 1988). However, three large clinical trials tested the hypothesis that a higher PEEP MV strategy would improve survival compared with the commonly used ARDS Clinical Network (ARDSNet) protocol. All three trials showed no significant difference in clinical outcomes indicating that an increased PEEP was not effective for all ARDS patients (Expiratory Pressure Study Group, 2008), (Meade *et al.*, 2008), (Brower *et al.*, 2004).

2.5.3 Prone positioning

Since the observation that oxygenation improved when patients were placed in the prone position (Piehl and Brown, 1976), studies have identified several mechanisms as the cause of this improvement. The improvement of ventilation distribution between anterior and posterior aspects of lung anatomy is a commonly cited mechanism for the justification of this technique, however, a series of randomised trials followed this vogue of proning for ARDS, all failed to show a survival benefit (Guo *et al.*, 2022)(Retracted), (Taccone *et al.*, 2009), (Guerin *et al.*, 2004). Post hoc, It was suggested that potential benefits of proning may be seen in severely hypoxic patients proned for longer periods (>16 hours) and thus a prospective study examined prone MV for 17 hours per day for patients with moderate to severe ARDS and showed a statistically significant survival benefit (Guérin *et al.*, 2013).

2.5.4 Neuromuscular blockade

When the oxygen consumption and carbon dioxide production increases, the patients ventilation must increase to meet these demands in order to maintain a constant arterial $PaCO_2$ and pH. Therefore controlling the oxygen consumption may have a beneficial application in the management of ARDS (Suzuki *et al.*, 2004). Several approaches such as sedation (Kress *et al.*, 1996), a reduction in body temperature (Manthous *et al.*, 1995) and neuromuscular paralysis (Marik and Kaufman, 1996) have been tried. Neuromuscular blockade (paralysis) has an added benefit of reducing MV dyssynchrony, seen when patients try to fight against the ventilator, this can lead to high tidal volumes which as previously stated can lead to barotrauma. A large randomised controlled trial in 2010 showed an adjusted mortality advantage when using neuromuscular blockade in comparison to a placebo in patients with moderate to severe ARDS (Cousin *et al.*, 2021). Neuromuscular blockade should be considered in difficult to ventilate patients with ARDS.

2.5.5 Pharmacological treatment

Decades of clinical trials pertaining to the treatment of ARDS with a pharmacological adjunct to MV have proven inefficacious. Most of the physiological pathways involved in ARDS have been targeted in large clinical trials (*Table 1)* including epithelial injury, dysfunctional coagulation and inflammation (Lewis *et al.*, 2019).

Table 1: Ineffective pharmacotherapies for the treatment of ARDS

Drug	Potential Mechanism
Activated protein C	Anticoagulant, antiinflammatory
Anti-endotoxin antibodies	Reduction in inflammation by binding endotoxin
Aspirin	Anti-inflammatory through anti-platelet effect
Beta agonists	Improved alveolar fluid clearance
Ibuprofen	Anti-inflammatory by inhibition of cyclooxygenase
Interferon Beta-1a	Improved pulmonary endothelial barrier
Keratinocyte growth factor	Promote epithelial repair
Lisofylline	Anti-inflammatory
Neutrophil elastase inhibitor	Anti-inflammatory
Inhaled nitric oxide	Pulmonary vasodilation
Omega-3 fatty acids	Anti-inflammatory
Procysteine and N-acetylcysteine	Reduction in oxidant injury
Prostaglandin E1	Anti-inflammatory
Statins	Anti-inflammatory
Surfactant	Promote epithelial repair, reduce atelectrauma

Modified from Meyer, Gattinoni and Calfee, 2021.

2.5.6 Advanced therapies

Despite treatment with the aforementioned supportive therapies, some patients with ARDS will continue to deteriorate with the development of hypercapnoea and/or acidosis and severe refractory hypoxaemia. Clinicians can consider using advanced rescue therapies, that is to say adjunctive therapies that have not been conclusively proven effective for all patients but may be beneficial in individual with individual circumstances (*Table 2*). These therapies should be considered for patients with an advanced stage of severe, refractory ARDS and not for the management in typical cases.

Table 2: Advanced therapies for the treatment of ARDS

Treatment	Mechanism	Clinical setting for use	Potential risks
ECMO	Effective gas exchange, protective MV	Hypoxia, acidosis, first 7 days of MV with reversable cause	Bleeding, vascular access complications, thrombocytopaenia, stroke, only available at specialist centres.
High PEEP strategies	Recruitment of collapsed alveoli	Refractory hypoxaemia	Hypotension, barotrauma
Inhaled pulmonary vasodilators	Improve V/Q mismatching, reduce pulmonary pressures	Refractory hypoxaemia	Associated with AKI, development of tachyphylaxis
Corticosteroids	Decrease inflammation	Refractory hypoxaemia	Immunosuppression, myopathy, neuropathy, increased duration of viral shedding in influenza and SARS-CoV-1.
CVVH	Fluid removal and acid clearance, theoretical cytokine clearance	Refractory acidosis	Risk of vascular access bleeding

ECMO-Extracorporeal membrane oxygenation, PEEP-Positive end expiratory pressure, MV-Mechanical ventilation, AKI-Acute kidney injury, SARS-CoV-1- Severe acute respiratory syndrome coronavirus 1, CVVH- Continuous veno-venous haemofiltration. Modified from Meyer, Gattinoni and Calfee, 2021.

MV is clearly required in order to maintain gas exchange and homeostasis in the ARDS patient, but the paradoxical damage associated with prolonged treatment can set the recovery of the patient back if not compound an impending demise. What is required is a therapeutic modality by which the gas exchange demand can be met while concomitantly providing rest to the damaged lung to potentiate recovery.

2.6 Extracorporeal Membrane Oxygenation (ECMO)

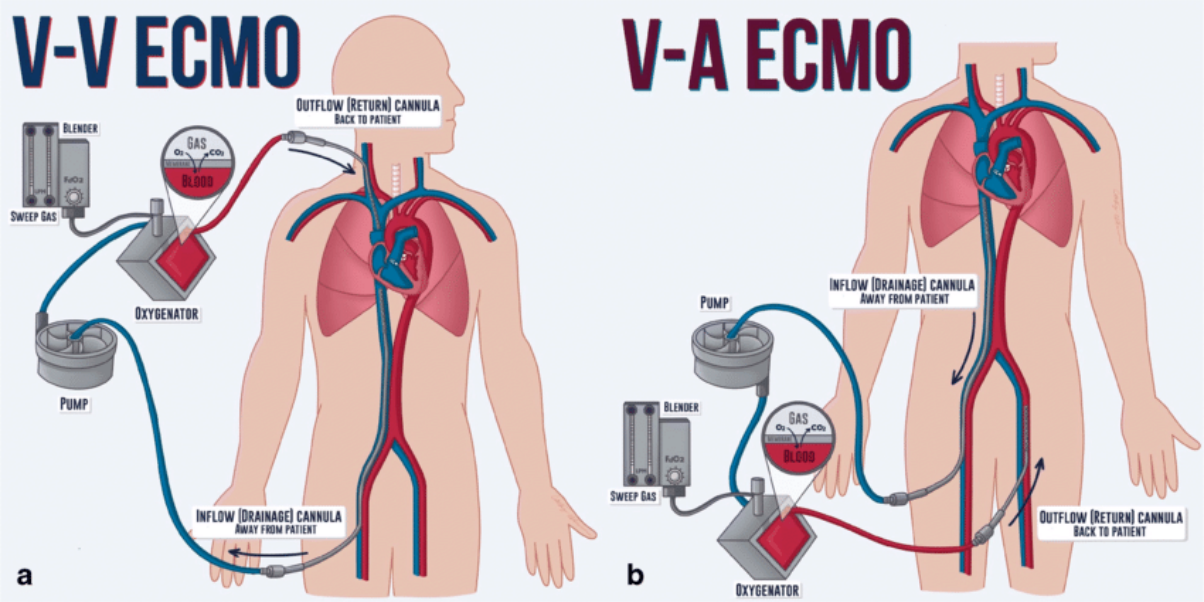
When IMV isn't effective at providing the gas exchange requirements of the pulmonary impaired patient, another way to support the respiratory process must be found. For many years, veno-venous ECMO (VV-ECMO) has been used in the most severely sick patient to provide advanced respiratory support. This relatively invasive method is generally the last resort life support option for patients in respiratory failure as seen with ARDS.

It works on the premise that as the gas exchange surface of the native lung is damaged and ineffective at being an intermediary at allowing oxygen to transfer from the external environment to the blood and vice versa for CO_2, a machine is used to cut out the middleman of the lungs/alveoli and supply oxygen direct to the blood and extract CO_2. VV-ECMO is used for respiratory support, but veno-arterial ECMO (VA-ECMO) can be used to support cardiorespiratory function in situations where the patients cardiac output is dysfunctional and must be maintained.

The system works by inserting cannula into large veins of the body such as the femoral vein or the internal jugular vein, draining the blood out into a pump which pumps the blood through an oxygenating device where the blood is oxygenated, and CO_2 removed while being warmed to normal temperatures. The blood then goes back to the patient through a cannula in another femoral vein or back through another lumen of the same cannula in the internal jugular vein, this is the case for VV-ECMO. For VA-ECMO, the same happens but the blood is taken out of the aforementioned veins and returned to an artery, usually the femoral artery. A common use of VA-ECMO is to provide cardiorespiratory support for

patients with cardiogenic shock, a state of low cardiac output that is insufficient to support the systemic perfusion requirements of the body.

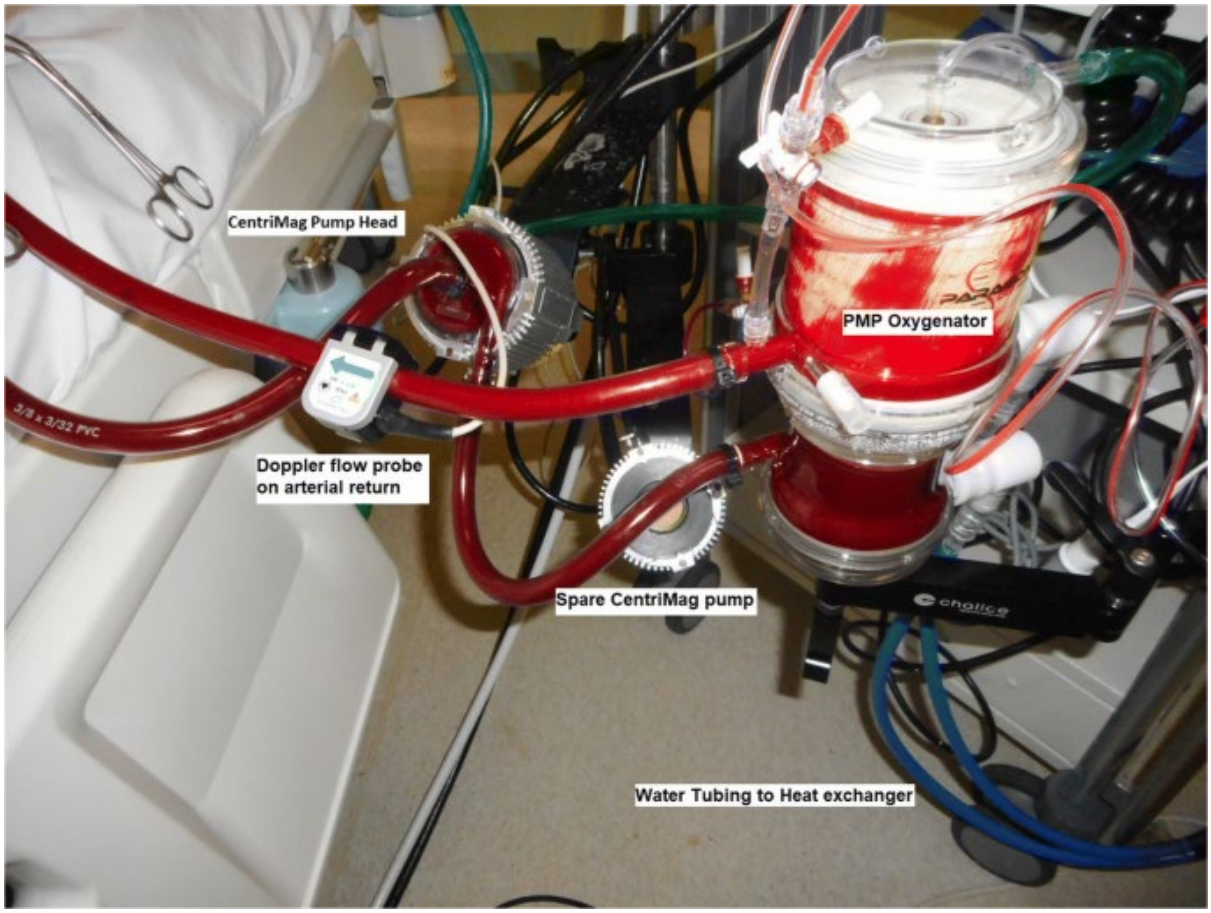
Figure 4: VV and VA ECMO Circulation



(a)Veno-venous (V-V) ECMO with a dual site cannulation. Drainage cannula inserted into the right femoral vein and return cannula in the right internal jugular vein. (b) Veno-arterial (V-A) ECMO, with a dual site cannulation, with the drainage cannula inserted into the right femoral vein, and the return cannula to the left femoral artery. Credit: Catherine Cichon, MD, MPH.

Taken from https://www.researchgate.net/figure/a-Veno-venous-V-V-ECMO-with-a-duel-site-cannulation-Drainage-cannula-inserted-into_fig2_350527049

Figure 5: ECMO circuit



(Mehta and Venkateswaran, 2020)

ECMO has been used for cardiorespiratory support since 1970 for support in infants undergoing cardiac surgery for congenital heart defects, and in adults from 1972 for post traumatic respiratory failure (Makdisi and Wang, 2015). Since then, this technology has progressed over the years to become an invaluable tool for adults and children with severe

cardiopulmonary dysfunction refractory to conventional treatments. However, not all clinicians have been proponents of this technology. Morris *et al.* failed to show an outcome advantage between ECMO and MV in a cohort of ARDS patients, thus not recommending ECMO as a support therapy for ARDS (Morris *et al.*, 1994), as did Akoumianaki *et al* who demonstrated no benefit at all, only complications such as severe bleeding (Akoumianaki *et al.*, 2021). ECMO for respiratory failure in the adult model was not commonplace until 2006 when the Conventional ventilatory support versus Extracorporeal membrane oxygenation for Severe Adult Respiratory failure (CESAR) trial was published. Through this trial Peek *et al.* demonstrated an improvement in the death rate and severe disability 6 months after randomization of patients with severe respiratory failure treated in an expert high-case-volume centre (Peek *et al.*, 2009)

2.6.1 The CESAR trial.

To this day, the CESAR trial is considered, and has been cited, as the definitive research that supports the use of VV-ECMO as a safe and efficacious treatment for the management of ARDS. The authors state that the CESAR trial study design was developed to be a pragmatic trial, in which the best standard practice (which at the time was MV) was compared with a "protocol that included ECMO". All patients included in the study were deemed to have potentially reversible respiratory failure, had not been on high pressure MV for more than 7 days and no indication of intracranial bleeding or any other contraindications to heparinisation. The primary hypothesis was that ECMO would increase survival without severe disability by 6 months after randomisation compared with conventional MV.

Over a period of 57 months, 766 eligible patients were referred to the study from 148 centres of whom 180 were enrolled (from 68 centres). Of the 90 in the ECMO treatment arm only 68 received ECMO support, 22 did not receive ECMO due to death, improved condition from conventional treatment and 1 contraindication to anticoagulation. These patients were still considered in the ECMO treatment arm as the 'pragmatic' nature of the study considered the holistic experience of the ECMO patient e.g., it considered the transportation of the patient to the ECMO centre as part of the ECMO treatment thus considered a death during transportation as a death attributable to this modality of intervention. This inclusion of transport risk into the design could be seen to be a strength of the study as the transport of a patient to an ECMO centre is a necessity, however, the inclusion of patients that recovered with conventional treatment alone after randomisation to the ECMO arm may be seen to be skewing the data as ECMO had no input into the recovery of the patient. All ECMO treatment was carried out at one single UK unit namely Glenfield Hospital Leicester, this monocentric treatment inhibits the extrapolation of results as other ECMO centres may have their own differences in treatment protocols thus the outcomes may be different. In the conventional arm there were 92 conventional treatment centres, here there was a lack of a standardised management protocols, this may have influenced the outcomes depending on the treatment centre.

In conclusion, the authors recommend transferring patients with severely but reversible respiratory failure that have a Murray score, a method of assessing acute lung injury >3 or a pH <7.20 on optimum conventional management of MV to a centre where ECMO-based management is available. On balance however, one could postulate that the CESAR trial supports ECMO as a valid treatment for patients with reversible respiratory failure, but with

incomplete follow up data and 24% of the patients in the ECMO therapy cohort not actually receiving ECMO, it could be considered that there may be insufficient evidence as to whether ECMO is better or worse than conventional MV therapy in adults with severe reversible respiratory disease (Giles J Peek *et al.*, 2009).

2.6.2 Other studies for ARDS

The ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial in 2018 acknowledged the limitations of the prior CESAR trial and set out to determine the effects of early initiation of VV-ECMO in patients with severe ARDS.

This was an international randomised trial, although conducted largely in France. The primary end point of interest was mortality at 60 days. The authors found that there was no significant benefit of the commencement of early VV-ECMO therapy for patients with severe ARDS compared with conventional MV. Unlike the CESAR trial, almost all patients randomised for ECMO treatment actually received that modality of treatment, however, the trial was stopped early (after 75% of intended recruitment) due to the pre-defined futility rules (unlikely to get a definitive result) *(Combes et al., 2018)*

In 2020 a systematic review conducted by Peek (CESAR trial author) and Combes (EOLIA trial author) and others, was carried out to assess the findings of randomised controlled trials that assessed the efficacy of VV-ECMO survival at 90 days (Combes *et al.*, 2020). Only 2 trials fulfilled the eligibility criteria of the review, namely the CESAR and EOLIA trials, this may be indicative of the lack of quality research in this area of medical treatment. The authors concluded that “the individual patient data of the CESAR and EOLIA trials showed strong evidence of a clinically meaningful benefit of early ECMO in severe ARDS patients” .

The authors further postulate that-

"another large study of ECMO appears unlikely in this setting and future research should focus on the identification of patients most likely to benefit from ECMO and optimisation of treatment strategies after ECMO initiation.

(Combes et al., 2020)

2.7 Patient selection

VV-ECMO may be seen to be an effective answer to severe refractory respiratory failure in the moribund patient, however, this modality of treatment is no panacea for all comers. Pre-CESAR trial experiences considered the use of VV-ECMO to be questionable at times due to the selection of prospective patients. It was not uncommon for irremediable patients that were far too ill to be rescued by any treatment to be put on ECMO, *in extremis* and ultimately succumb to their pathologies. This lack of triage and a 'one size fits all' approach to patient selection masked its utility as a viable treatment; a method to select patients that would benefit from ECMO was required.

The Extracorporeal Life Support Organisation (ELSO), an international non-profit consortium who curate a comprehensive registry of ECMO use worldwide, provide guidelines for the Initiation, use and management ECMO *(Figure 6).* This was derived from the collation of publications from a literature search (in English) in PubMed, rather than a formal, reproducible methodology.

Figure 6:Indications/Contraindications for Adult VV ECMO (Tonna et al., 2021)

Common indications for venovenous extracorporeal membrane oxygenation
One or more of the following:

1) Hypoxemic respiratory failure (PaO_2/FiO_2 < 80 mm Hg), after optimal medical management, including, in the absence of contraindications,
a trial of prone positioning.
2) Hypercapnic respiratory failure (pH < 7.25), despite optimal conventional mechanical ventilation (respiratory rate 35 bpm and plateau
pressure [P_{plat}] ≤ 30 cm H_2O).
3) Ventilatory support as a bridge to lung transplantation or primary graft dysfunction following lung transplant.
Specific clinical conditions:
• Acute respiratory distress syndrome (e.g., viral/bacterial pneumonia and aspiration)
• Acute eosinophilic pneumonia
• Diffuse alveolar haemorrhage or pulmonary haemorrhage
• Severe asthma
• Thoracic trauma (e.g., traumatic lung injury and severe pulmonary contusion)
• Severe inhalational injury
• Large bronchopleural fistula
• Peri-lung transplant (e.g., primary lung graft dysfunction and bridge to transplant)

Relative contraindications for venovenous extracorporeal membrane oxygenation
• Central nervous system haemorrhage
• Significant central nervous system injury
• Irreversible and incapacitating central nervous system pathology
• Systemic bleeding
• Contraindications to anticoagulation
• Immunosuppression
• Older age (increasing risk of death with increasing age, but no threshold is established)
• Mechanical ventilation for more than 7 days with P_{plat} > 30 cm H_2O and FiO_2 > 90%

PaO_2- partial pressure of arterial oxygen, FiO_2- fraction of inspired oxygen, P_{plat}-plateau pressure.

ELSO highlights that these are recommendations, which should be used with caution and are not intended to replace medical experiential judgement. This document further reinforces the sentiment of other authors in that ECMO should be utilized only for patients with reversible lung pathologies. The only absolute contra-indication to the implementation of ECMO is anticipated non-recovery without a plan for decannulation.

2.8 Mortality risk scores

A requirement for a more accurate, empirical method for the assessment of prospective ECMO patients was need by clinicians to scientifically enhance their anecdotal clinical experience. Predictive mortality scores were suggested by authors as a pre-requisite to the initiation of VV-ECMO therapy in order to predict the outcome of putting a patient on ECMO. Scoring systems where pre-treatment variables from a patient could be put into an algorithm and a score pertaining to survival after ECMO obtained were suggested by clinicians and over time, came to fruition.

The popular scores are described as follows.

2.8.1 Predicting death for severe ARDS on VV-ECMO score (PRESERVE)

This score predicts death at 6 month post intensive care (ICU) discharge for patients with ARDS after VV-ECMO. This is to be used for VV-ECMO only *(Figure 7).*

Figure 7 :PRESERVE score

Parameter.		Score
Age (years)	<45	0
	45-55	2
	>55	3
BMI	>30kg/m^2	-2
Immunocompromised		2
MV	>6 days	1
SOFA	>12	1
NO proning before		
ECMO		1
PEEP	<10cmH_2O	1
PIP	>35 cmH_2O	1

BMI= body mass index, SOFA=sequential organ failure assessment score, MV=mechanical ventilation, PEEP=positive end expiratory pressure, PIP=peek inspiratory pressure. Immunocompromised status included haematological malignancies, solid tumours, solid organ transplantation, high-dose or long-term corticosteroid and/or immunosuppressant use, or human immunodeficiency virus infection. Higher score indicates higher probability of death by 6 months post-ICU discharge; PRESERVE scores −1 and −2 converted to 0 for simplification. (Schmidt *et al.*, 2013).

Scores of 0-2 had a survival of 97%, scores of 3-4 had a survival of 79%, 5-6 was 54% and ≥7 was 16%

2.8.2 Respiratory ECMO for severe acute respiratory failure score (RESP)

The RESP score is calculated on 12 pre-ECMO clinical variables that have an association with hospital survival. This score is designed for use with VV-ECMO only *(Figure 8)*.

The variables are allocated a numerical score, like the PRESERVE method pertaining to diagnosis, MV, age, immunocompromisation status, central nervous system (CNS) dysfunction, neuromuscular blockade, nitric oxide use, bicarbonate use, cardiac arrest pre-ECMO and partial pressure of arterial carbon dioxide ($PaCO_2$). The total scores are calculated, and a class and prognosis allocated (Schmidt *et al.*, 2014a).

Figure 8: RESP score

Parameter	Score
Age, yr	
18 to 49	0
50 to 59	−2
⩾60	−3
Immunocompromised status*	−2
Mechanical ventilation prior to initiation of ECMO	
<48 h	3
48 h to 7 d	1
>7 d	0
Acute respiratory diagnosis group (select only one)	
Viral pneumonia	3
Bacterial pneumonia	3
Asthma	11
Trauma and burn	3
Aspiration pneumonitis	5
Other acute respiratory diagnoses	1
Nonrespiratory and chronic respiratory diagnoses	0
Central nervous system dysfunction†	−7
Acute associated (nonpulmonary) infection‡	−3
Neuromuscular blockade agents before ECMO	1
Nitric oxide use before ECMO	−1
Bicarbonate infusion before ECMO	−2
Cardiac arrest before ECMO	−2
Pa_{CO_2}, mm Hg	
<75	0
⩾75	−1
Peak inspiratory pressure, cm H_2O	
<42	0
⩾42	−1
Total score	−22 to 15

Hospital Survival by Risk Class		
Total RESP Score	**Risk Class**	**Survival**
⩾6	I	92%
3 to 5	II	76%
−1 to 2	III	57%
−5 to −2	IV	33%
⩽−6	V	18%

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; RESP = Respiratory ECMO Survival Prediction.
An online calculator is available at www.respscore.com.
*"Immunocompromised" is defined as hematological malignancies, solid tumor, solid organ transplantation, human immunodeficiency virus, and cirrhosis.
†"Central nervous system dysfunction" diagnosis combined neurotrauma, stroke, encephalopathy, cerebral embolism, and seizure and epileptic syndrome.
‡"Acute associated (nonpulmonary) infection" is defined as another bacterial, viral, parasitic, or fungal infection that did not involve the lung.

(Schmidt *et al.*, 2014)

2.8.3 Prediction of survival on ECMO therapy score (PRESET)

This score differs from the others in that it only uses 5 variables which are mean arterial pressure (MAP), blood lactate concentration, arterial pH, blood platelet concentration and hospital stay in days to generate prognostic outcomes. These variables from univariate analysis were identified as being independently associated with in-hospital mortality.

The final score is between 0-15 points where a score of 0-4 (category I) give a 26% mortality rate, a score of 5-9 (category II) a 68% mortality and a score of 10-15 (class III) a mortality of 93%. (Harnisch and Moerer, 2021). However, this score was based on a small derivation cohort of only 108 patients (Montero, Slutsky and Schmidt, 2018).

2.9 Utilization of prognostic scores

Prognostic scores for the selection of ECMO patients are now commonplace in the clinical environment, referring centres will often be asked for prospective patients RESP and/or PRESERVE scores in order for ECMO centres to assess and consider the modality of therapy to be used. The aforementioned scores are 3 of the more commonly used, there are others used such as ECMOnet, survival after veno-arterial ECMO (SAVE) , Apache II, Sequential organ failure assessment (SOFA) score, simplified acute physiology (SAPS) score. Of these scores only the RESP and PRESERVE scores were designed to be used to assess patients for VV-ECMO. The SAVE score should only be used for patients that require cardiac support and therefore require VA-ECMO, the SOFA, Apache II and SAPS scores are intensive care survival scores and do not take the provision of any form of ECMO into consideration.

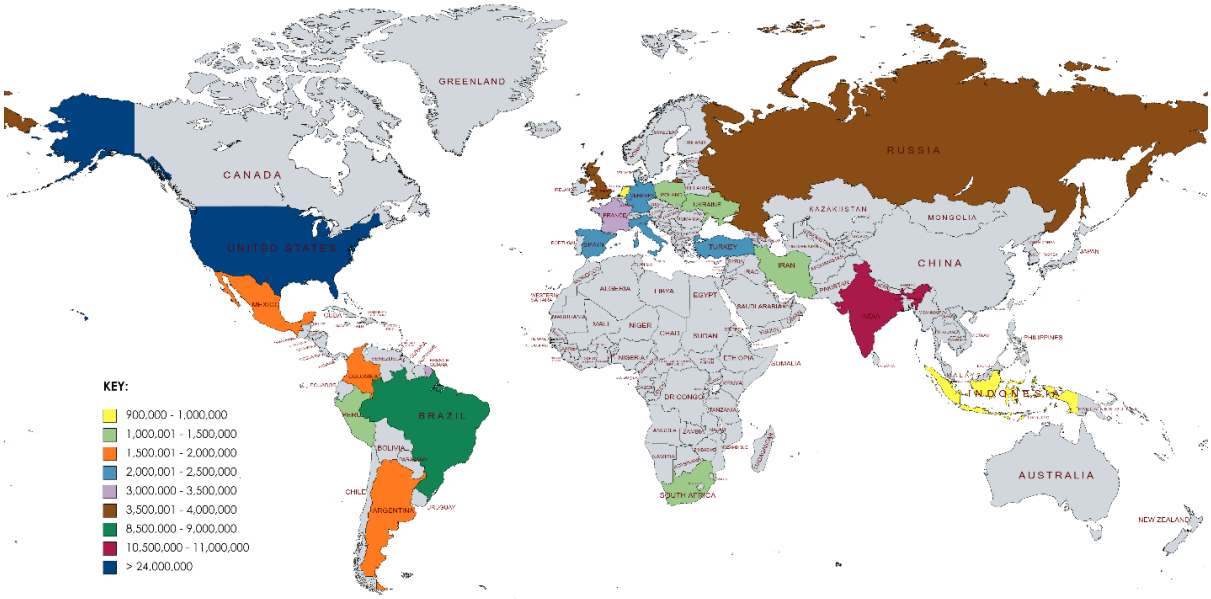
In a recent publication (*appendix 1*), the authors set out to assess the RESP and PRESERVE scores for their utility in the prediction of outcomes of VV-ECMO cohorts in the ITU setting. What was instantly evident during the data extraction phase of the systematic review was that it was commonplace for authors to use the incorrect tool (prediction score) for the situation. 2 of the 6 studies used in the qualitative synthesis used the incorrect end points for the scores i.e., used the scores that were designed to predict death at hospital discharge for death at 6 months post discharge and vice versa. Although the RESP and PRESERVE models were the ones of interest in the study, other models were also included, often, these prognostic models were used to assess VV-ECMO patients although their intended use was for VA-ECMO patients such as SAVE. So, this further highlighted the misuse or misunderstanding of prognostic score usage. The high level of heterogeneity in the studies made it difficult to report a definitive outcome as to which score had the best discriminatory ability. It was found that both the RESP and PRESERVE models performed with parity when assessed within the clinical context they were developed for (Majithia-Beet, Naemi and Issitt, 2022).

2.10 Covid-19 pandemic

On December 31st 1999, hospitals in Wuhan, a city of more than 14 million in the Hubai province of China, reported a cluster of idiopathic cases of pneumonia (Zangrillo *et al.*, 2020). These were found to be associated with people who had contact with the Huanan wholesale seafood market also in Wuhan (Holshue *et al.*, 2020), the Chinese authorities immediately notified the country office of the World Health Organisation (WHO). Later in early to mid-January, further cases started to appear in other provinces concomitant to the

population movements due to the annual new year holidays (Guo *et al.*, 2020). The causative agent was isolated and found to be a new novel Coronavirus, which was first sequenced and made public on January 10th 2020 (Carvalho, Krammer and Iwasaki, 2021). This Coronavirus was named (by the international committee on taxonomy of viruses) Severe Acute Respiratory Syndrome Covid 2 (SARS-Cov-2) which was the causative agent of the Coronavirus Disease (COVID-19). By March 11th 2020 the WHO had declared SARS-Cov-2 as a pandemic with confirmed cases in over 114 countries (Ochani *et al.*, 2021). As of June 2022, over 530,000 individuals worldwide had been diagnosed with COVID-19, culminating to over 6.3 million deaths by the end of the pandemic. A strategic preparedness response plan was drawn up in order to assist national stakeholders with their response.

Figure 9:Top 20 countries affected by COVID-19



(Ochani 2021).

The WHO's objectives were –

1. Supress transmission.
2. Provide optimized care for all patients and save lives.
3. Minimize the impact of the pandemic on health systems, social services and economic activity. (*Clinical Management of COVID-19:Living Guideline*, 2022)

2.11 Transmission

The purported transmission of the new virus was said to have originally been from bats and pangolins procured from the wet markets of Wuhan. However, critics of this hypothesis suggested a more contentious modality of spread which was due to containment failures at a nearby gain of function laboratory also in Wuhan (Li *et al.*, 2020). After the successful transmission to a human host the virus then spreads from human-to-human contact either through respiratory droplets and/or the faecal-oral route or by touching contaminated surfaces. SARS-CoV-2 can remain airborne for up to 3 hours increasing the risk of contamination (Patients *et al.*, 2020).

The spread and proliferation of the virus continued with new SARS-CoV-2 variants emerging and intensifying the global health threat. December 2020 saw the authorisation of COVID-19 vaccines produced by Pfizer (New York, USA), BioNTech (Mainz, Germany), Moderna (Massachusetts, USA) and Astra Zeneca (Cambridge, England) with the concomitant rollout across the globe (Carvalho, Krammer and Iwasaki, 2021). Viral shedding by asymptomatic hosts is a major contributor to the propagation of the virus, possibly representing between 25% to 50% of new infections. Viral shedding may start 1 to 2 days before the onset of symptoms and viral titres have been noted to be at their highest at the early stages of infection followed by a rapid decline (Sunjaya and Jenkins, 2020).

2.12 Clinical manifestations of Covid-19

The most common complaints identified in symptomatic individuals range from the more reported ailments such as fever, cough and dyspnoea to the less common of gastrointestinal (GI) symptoms such as diarrhoea, fatigue, and/or a loss or change in the sense of smell or taste (Ye *et al.*, 2020). Neurological disturbances have been reported such as headache, altered states of consciousness (brain fog) and acute cerebrovascular disease (Giacomelli, 2020). Cardiovascular system involvement is generally not considered to be a common complication of COVID-19, however, Aidan et al have reported a frequency of occurrence of 20% in all patients with confirmed COVID-19 and 43% of those in the ICU setting (Aidan *et al.*, 2020). The multiple cardiac injury mechanisms cited were hyper inflammation, pro-coagulant, pro-thrombotic states (Knight *et al.*, 2022), haemodynamic instability, sepsis related cardiomyopathy, and cytokine storm (Aidan *et al.*, 2020). Most thrombotic events were seen to be pulmonary embolisms (PE's) (F.A. Kloka, M.J.H.A. Kruipb, N.J.M. van der Meerc et al, 2020). Authors have tried to identify patient groups that are more pre-disposed to catching COVID-19, higher age groups ($\geq$ 65 years of age) have been shown to be more susceptible to developing a more severe COVID-19 infection due to the accompanying co-morbidities and also less responsive to the vaccine (Mahase, 2020), however, younger adults have been hospitalised with severe symptoms, albeit with much lower frequency (Ochani *et al.*, 2021). Children have been shown to be less likely to develop a symptomatic infection and are also less prone to severe disease, although data on symptoms and prognosis in children are rare (Ludvigsson, 2020). Data from Lighter and colleagues suggests that obesity may be an independent risk factor for the hospitalisation and heightened

severity of the disease (Jennifer Lighter, Michael Phillips, Sarah Hochman and Diane Johnson, 2020).

2.12.1 Hospitalisation

As the spread of COVID-19 continued, hospital wards and intensive care units (ICU) filled up with patients in need of treatment.

The clinical course of COVID-19 varies from asymptomatic to critical. Adults can be grouped into the following spectrum of severity-

2.12.2 Asymptomatic

UK Government guidelines suggested that one in three people who have COVID-19 are asymptomatic (*COVID-19: guidance and support - GOV.UK*, no date). These individuals may be pre-symptomatic.

2.12.3 Mild illness

Individuals have signs and symptoms including cough, sore throat, fever headache, malaise, nausea, vomiting, muscle pain, loss of taste and small (but do not have shortness of breath, dyspnoea or abnormal chest imaging).

2.12.4 Moderate illness

Individuals show evidence of lower respiratory disease during a clinical assessment with or without imaging and have an oxygen saturation (SpO_2) (when measured by pulse oximetry as opposed to SaO_2 which is measured by direct arterial blood sampling) $\geq$ 94% on room air and at sea level.

2.12.5 Severe illness

Individuals have an $SpO_2 \leq 93\%$ on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300mmHg, a respiratory rate (RR) >30 breaths/min or has lung infiltrates >50%.

2.12.6 Critical illness

Individuals have respiratory failure, septic shock and/or multi organ dysfunction leading to pneumonia and Acute Respiratory Distress Syndrome (ARDS) (Health, 2023).

2.13 Patient management and treatment

From the outset, supportive care was the main treatment for COVID-19 in the clinical setting.

2.13.1 Oxygen therapy

Moderate to severe illness was observed in patients admitted to wards which provided oxygen therapy as the main modality of treatment, and to ensure the respiratory status of the patient did not deteriorate (LaRosa, 2019). Low flow oxygen with a simple face mask was generally accepted as the first line of support, some authors suggested that this modality of oxygenation should be used when the saturation of oxygen in arterial blood (SaO_2) <88% (Nitesh, Kashyap and Surani, 2021). If further deterioration of oxygen

saturation occurred, the next line of oxygen therapy was the implementation of high flow nasal cannula (HFNC) in order to provide oxygen at very high flow rates (40-80 L/min). The gas could further be heated and humidified to simulate physiological conditions providing a greater level of comfort to the patient and also provide low levels of functional positive end expiratory pressure (PEEP) in the respiratory tract (Kumar *et al*. 2020). Non-invasive ventilation such as CPAP and BIPAP are the next level of respiratory augmentation. These are seen to decrease the work of breathing while applying PEEP. This method of respiratory support is generally supplied via a full face mask or a helmet mask, this also decreases the levels of aerosolization of the virus thus providing a greater degree of protection for staff (Ferioli *et al.*, 2020).

The oxygen therapies were further augmented with 'awake proning' (although this was much more difficult when patients were receiving oxygen via a helmet due to the size of the equipment). This technique is thought to improve the outcome in patients with or without COVID-19 by modulating lung mechanics. It is achieved by placing patients on their stomachs, this allows the posterior aspect of the lungs to expand fully, drain secretions and prevent ventilation/perfusion mismatch. This technique has mixed results in the awake patient, some authors showed a non-statistically significant reduction in supplemental requirements when a proning regimen was utilised in the COVID-19 Positive patient (Kharat *et al.*, 2021). Others showed an association of awake proning with improved outcomes in patients receiving non-invasive respiratory support (Hallifax *et al.*, 2020). Caputo, Strayer and Levitan showed early awake self-proning in this cohort of patients when admitted to the emergency room demonstrated improved oxygen saturations (Caputo, Strayer and Levitan, 2020).

Patients were closely monitored on the ward environment for further clinical deterioration and progressive respiratory failure which had been observed, most centres reported that about 25% of hospitalized COVID-19 positive patients required ICU admission for a more intensive therapy (Ramanathan *et al.*, 2020), (Hajjar *et al.*, 2021). The leading cause of ICU stay was respiratory failure refractory to oxygen therapy, creating the need for mechanical ventilation (MV) (Sadeghi *et al.*, 2020). MV is recognised as one of the main lifesaving treatments of the pandemic. It was noted that covid-19 positive patients that utilized IMV (thus had an ET tube in situ) limited the spread of the airborne virus to the clinical setting, but consideration should be taken that the act of intubation is in itself an aerosol generating procedure and should be carried out with the precautions required (Zuo *et al.*, 2020). The provision of this finite resource of ventilators worldwide became a concern as the pandemic continued. Between March and early August 2020, the UK government secured an additional 26,000 mechanical ventilators to use across the National Health Service (NHS) at a total cost of £569 million in fear that the already 7000 ventilators it had was woefully too few (Bailey *et al.*, 2020). Demand significantly outstripped the supply of this technology and provisions were put into place for third parties such as motor vehicle manufacturers to start mass producing ventilators (Lovett, 2020), (Brad Templeton, 2020). This technology was no 'silver bullet' for the treatment of COVID-19 ARDS, the recognised complications associated with MV can be seriously deleterious to an already compromised patient.

Acute hypoxemic respiratory failure was seen in 60%-70% of patients admitted to the ICU during the pandemic, admission criteria for ITU stays pre-COVID-19 was less stringent, but due to the lack of beds, specialist nursing care and mechanical ventilators, the need for MV was the main precursor to ITU admissions (Hajjar *et al.*, 2021). Monteiro et al found a

positive association between obesity and smoking history with the need for MV in COVID-19 patients intimating a susceptibility to a poorer prognosis (Monteiro *et al.*, 2020). Respiratory failure in many cases, lead to ARDS.

2.14 COVID-19 induced ARDS

Respiratory failure in the COVID-19 patient associated with an ITU stay commonly met the Berlin criteria for ARDS (Ferrando *et al.*, 2020). Nearly 75% of COVID-19 patients admitted to the ITU had ARDS (Tzotzos *et al.*, 2020), the ARDS occurs both from the direct viral effects and host cell derived substances. Activated cells of the immune system releases deleterious products such as neutrophil myeloperoxidases, eosinophil major basic proteins and an excessive productions of the pro inflammatory cytokines Interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α), known as the cytokine storm, which can cause aggravated tissue damage resulting in multi organ failure and death of the host (Aslan *et al.*, 2021). Authors have commented on a deviation from the Berlin criteria for patients with COVID-19 induced ARDS, it has been noted that these patients may have a high or near normal lung compliance (Li and Ma, 2020); however, others have not found this to be the case (Ferrando *et al.*, 2020).

2.15 ECMO for COVID-19

Parhar et al. posited that the successful implementation of an ECMO response to a viral pandemic as seen during the swine flu (H1N1) pandemic of 2009, suggested that this

modality of respiratory support may be highly efficacious when used against COVID-19 (Parhar *et al.*, 2020). Patients with H1N1 possessed similarities to those with COVID-19 in respect to their rapid deterioration requiring MV and development of refractory hypoxaemia necessitating the use of certain salvage therapies such as high frequency ventilation (HFV), neuromuscular paralysis, prone positioning and inhaled vasodilators (Mitchell *et al.*, 2010). The benefits were shown in Australia and New Zealand where a greater than 70% survival was seen in H1N1 patients treated with ECMO (Cooper and Hodgson, 2013). In Italy, a national referral network of selected ICU's was set up by the health authorities to provide advanced respiratory care including VV-ECMO. They showed a 71% survival rate at hospital discharge for patients presenting with H1N1 induced ARDS (Patroniti *et al.*, 2011)

Questionably, most publications regarding the efficacy of VV-ECMO for the treatment of the H1N1 virus are in the form of case reviews or very small series. The larger studies are usually of the single centre or single country setting, thus may have a limited external validity (Zangrillo *et al.*, 2013). However, the take home message of the majority of these papers is that the initiation of VV-ECMO facilitated the use of ultra-protective ventilation strategies which minimized alveolar damage , thus lead to recovery (Cho *et al.*, 2020).

The utilization of VV-ECMO during this time of viral outbreak along with the outcome of the CERSAR trial, cemented its place in the toolbox of therapies for reversible refractory respiratory failure. According to ELSO, 117,694 adults have received ECMO for all cause respiratory failure (in reporting centres) since its implementation in 1985 (*Extracorporeal Life Support Organization*, 2023, accessed 18/07/23), this number keeps on growing.

2.15.1 ELSO and the WHO response

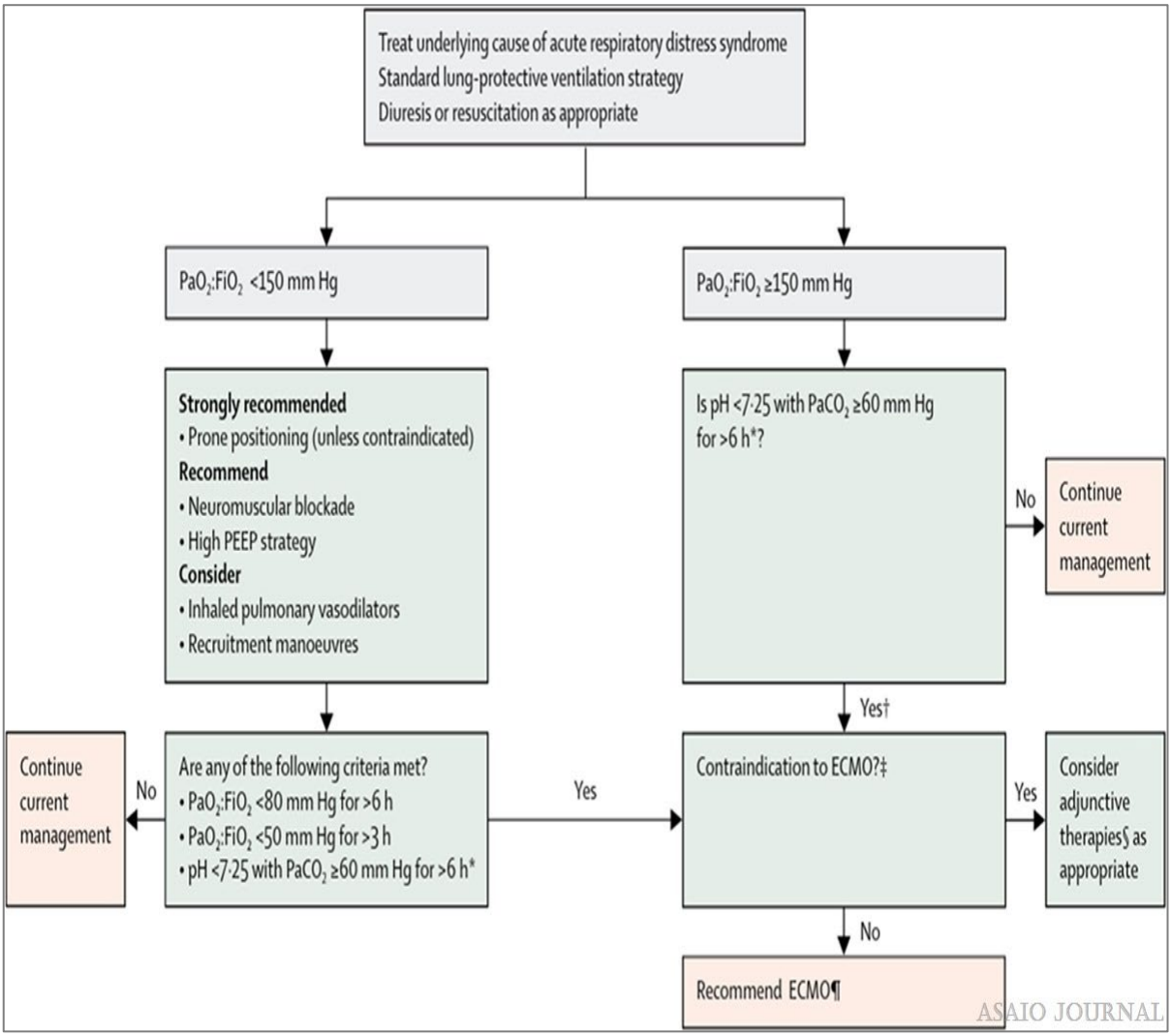
ELSO and the WHO suggested that COVID-19 patients suffering from acute cardiopulmonary impairment should be considered for ECMO therapy. The WHO further stipulated that this complex, labour-intensive, high risk intervention should be undertaken by specialist units with the appropriate ECMO volume and thus experience if MV proves to be ineffective (The Acute Respiratory Distress Syndrome Network, 2001).

2.15.2 ELSO guidance

ELSO published their initial guidance in an article in the American Journal for Artificial Internal Organs (ASAIO) journal in May 2020. They stipulated that it was of their opinion that VV-ECMO was a viable treatment for COVID-19 patients with reversible refractory respiratory failure and their document was a consensus guideline, intended for experienced ECMO centres. ELSO recommended that "new ECMO centres should not be implemented for the sole purpose of treating patients with COVID-19". For inexperienced centres "ECMO was not a therapy to be rushed to the front line when all resources are stretched during a pandemic", this was also the opinion of other authors (Rabie *et al.*, 2021). A list of experienced ECMO centres were provided on the ELSO web site, it was iterated that it was a reasonable assumption to concentrate patients with the greatest chance of survival/benefit from ECMO therapy in a hospital where an experienced ECMO team is available.

The indications for the use of ECMO, specifically for COVID-19 induced ARDS as stipulated by ELSO, was the same as for ARDS of other origins *(Figure 10).*

Figure 10: Algorithm for management of ARDS (Abrams *et al.*, 2018).



PEEP=positive end-expiratory pressure; PaO_2:HO_2= ratio of partial pressure of oxygen in arterial blood to the fractional concentration of oxygen in inspired air; ECMO= extracorporeal membrane oxygenation (in this instance VV-ECMO); $PaCO_2$= partial pressure of carbon dioxide in arterial blood.

2.15.3 Indications for use

Ultimately, the decision to start ECMO treatment would be a local one (hospital and clinician). ELSO suggested the decision to be based on case by case factors such as hospital/regional patient load, resources and staffing availabilities that were at times stretched. Then, if ECMO can be provided safety, then it should be offered to patients with a good prognosis. In an attempt to triage a limited resource, ELSO further stated that the use of ECMO in patients with a combination of advanced age, multiple co-morbidities or multiple organ failure should be rare. High priority patients were to be young with no or minor co-morbidities with specific reference to healthcare workers. The priorities should change, based on what can be done safely in the healthcare setting at the time.

2.15.4 Contraindications for use

The contentious indications for exclusion of patients were similar to those for all prospective ECMO patients, such as terminal disease, severe central nervous system (CNS) damage, do not resuscitate (DNR) orders and advanced directives refusing therapies. The exclusion criteria were fluid depending on resource availability in hospitals and regions. Because prognosis is worse for this cohort with time on MV, patients with a MV time greater than 7 days should be excluded. However, clinicians have questioned this finding; studies showing that a MV time >7 days has no effect on survival have suggested that ECMO applicability should be assessed and treatment should be based on an individual basis (Hermann *et al.*, 2022).

2.15.5 Cessation of ECMO

These guidelines were published at the start of the pandemic after very few reported runs of ECMO for COVID-19 had been achieved, therefore these suggestions were based on past experience of managing patients with ARDS of non-COVID-19 origin. In their guidelines, ELSO recognised that not all COVID-19 positive patients will improve while receiving ECMO therapy. As was standard with usual ECMO care, clinicians should be continuously monitoring patients to ascertain as to when ECMO no longer provides a realistic positive benefit to risk ratio, and when this occurs, return to conventional management, regardless of the duration that the patient has been supported by ECMO. This technology has never been intended to be a bridge to futility, especially in a time when the demand is significantly greater than the supply. The maximization of the benefit provided by ECMO to a population suffering from this pandemic was paramount, so a line had to be drawn as to when the termination of ECMO treatment should occur. ELSO posited a time of 21 days of observing no lung recovery as the definition of futility and therefore an indication to return the patient to conventional management. This was achieved by the cessation of ECMO support and decannulation of the patient.

2.16 ECMO treatment provision

As ECMO units around the world started to accept COVID-19 positive patients for treatment, initially a varying degree of success was seen.

A study from Germany showed that a cohort of 3397 patients supported with VV-ECMO at 213 federal German hospitals between the dates of March 2020 to May 2021 had a mortality rate of 68%. This mortality rate was markedly higher than mortality data reported from any other country at the time. The authors warned that the mortality of ECMO supported patients with COVID-19 related respiratory failure could be high if its use is not restricted to the patients who were most likely to benefit (Karagiannidis *et al.*, 2021).In a smaller study from China, retrospective data from 73 patients was collected from 21 hospitals in Hubei, ground zero of the outbreak, between the dates of January 2020 to March 2021. They reported a 63% 30 day mortality and an 80.8% 60 day mortality, again very high in comparison to patients treated with VV-ECMO for non-COVID-19 origin ARDS (Yang *et al.*, 2020). The Texas Medical Centre in Houston, Texas demonstrated better results with a mortality rate of 33% at hospital discharge (which extended to 1 year) for 35 patients that were treated between March and May 2020. At this time, ELSO, according to the ELSO registry, were citing a 90 day mortality rate of 40% (Akkanti, Erik E. Suarez, *et al.*, 2022).

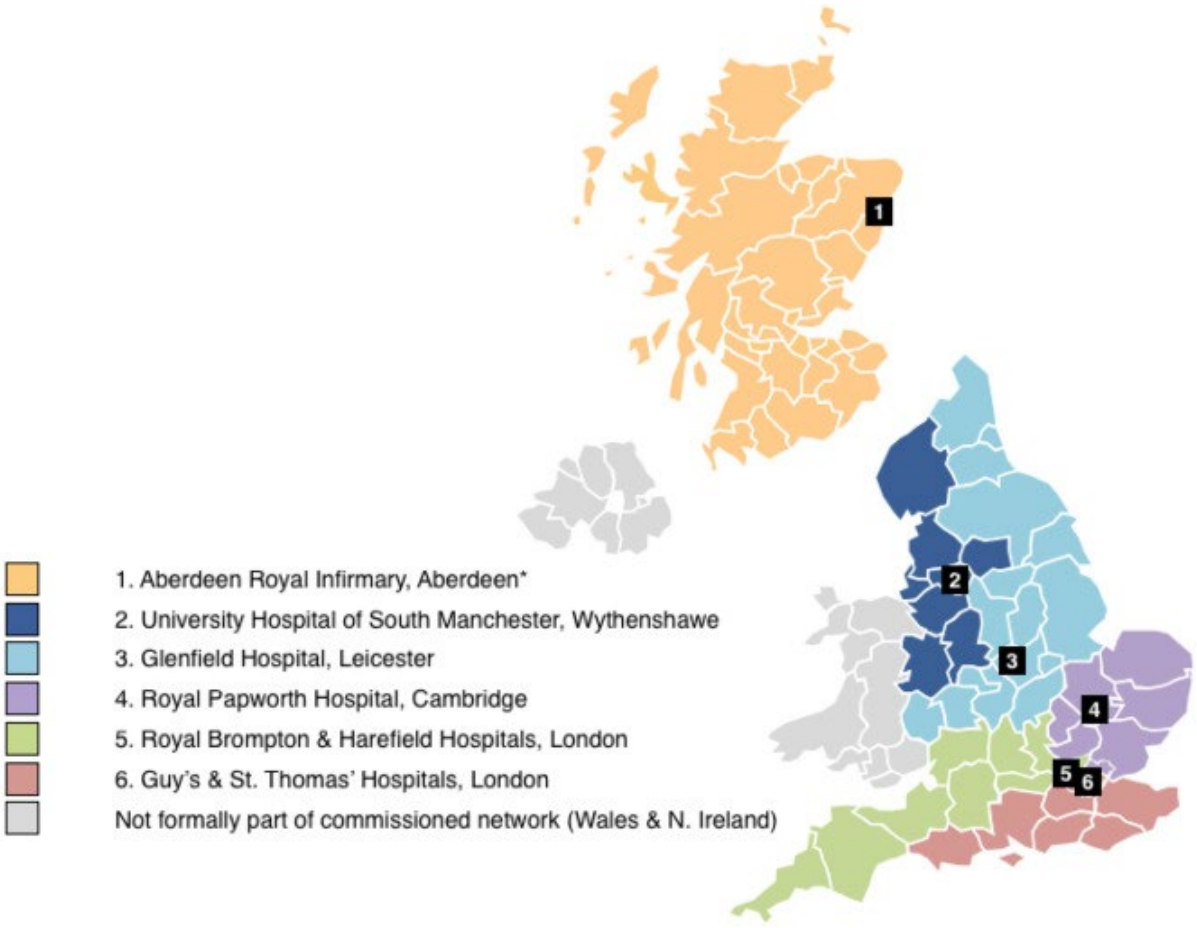
The selection and treatment of COVID-19 patients on ECMO by international ECMO centres was influenced by their already pre-established protocols, selection algorithms and pragmatic experiential opinions. In the early stages of the pandemic, clinicians and healthcare providers in the main, treated ARDS of COVID-19 origin the same as ARDS of non-COVID-19 origin. This intuitive approach could be deemed to be a reasonable strategy to treating a never before seen virus

2.17 ECMO provision in the UK

After the recommendation of ECMO as a viable treatment for COVID-19, hospitals began to triage prospective candidates that were perceived to benefit from VV-ECMO support in order to be sent to established ECMO centres.

In the UK, there were 6 substantive ECMO centres at the time of the pandemic. Figure 11 shows the catchment areas for the specific hospitals.

Figure 11: ECMO centres in the UK with catchment areas. (Warren *et al.*, 2020).



*Until May 2019, ECMO activity at Aberdeen Royal Infirmary were commissioned was funded by NHS Scotland as part of a portfolio of services commissioned on their behalf by NHS England, with Glenfield Hospital, Leicester, being the designated centre for referrals from Scotland.

Patients from Wales and Northern Ireland that required ECMO were treated on an *ad hoc* basis without formalized referral pathways by the substantive centres (Warren *et al.*, 2020). As ECMO centres reached capacity in no time, specific catchment areas no longer stipulated where patients were sent, the system defaulted to patients being sent to any available bed in the country. This occurrence was not uncommon, ECMO centres at the beginning of the pandemic procured extra ECMO technical equipment from non-established centres and from the industry in order to address the high influx of patients. Glenfield Hospital, a high capacity ECMO centre in Leicester, England were running ECMO provision at 300% pre-pandemic levels throughout the time of the pandemic, even this did not satisfy the needs of all referrals (Majithia-Beet, observational, 2023).

2.18 ECMO as a treatment for COVID-19

Irrespective of the initial outcomes of ECMO as a viable answer to life support for COVID-19, established ECMO facilities maintained a substantive service for its provision. Using ECMO in this cohort of patients remained controversial, The current understanding of COVID-19 pathophysiology at the time was limited. It was already established that ECMO was probably not a viable treatment for all COVID-19 patients with refractory respiratory failure and there were indications that ECMO may complicate the pathophysiological state (Huang *et al.*, 2021). Clinicians began performing analyses to identify factors that they anecdotally believed affected the survival of COVID-19 positive patients supported by VV-ECMO.

2.18.1 Age

An age-varying susceptibility to COVID-19 has been shown where children have been seen to be less susceptible to infection in comparison to adults when in contact with an infectious person (Davies *et al.*, 2020). By assessing age-specific mortality patterns O'Driscoll et al showed that infection fatality was the lowest in the 5-9 year old age group in children and there was a log-linear increase by age among individuals older than 30 years (O'Driscoll *et al.*, 2021). ECMO support for children with COVID-19 was very rare during the pandemic, the few publications as assessed by the systematic review by Watanabe *et al* showed favourable outcomes with low mortality rates for children on ECMO (Watanabe *et al.*, 2023). For adults, many authors showed that infected older patients supported by ECMO fared worse than the young. Lorusso *et al* showed a significantly poorer survival rate for 60-69 year olds (39.5%) and even poorer for ≥70 year olds (17.6%) (Lorusso *et al.*, 2022). Lee *et al* showed a significant difference between the ages of survivors (median age 49 range 42.5-63.0) and non-survivors (median age 69 range 65.3-73.5). Old age, here defined ≥65 was significantly associated with the prognosis of patients with COVID-19 on ECMO as defined by Cox multivariate survival analysis (OR=7.614 95% CI=1.066-54.393, p=0.043), however, this was on a small cohort of 39 patients (Lee *et al.*, 2022). Riera *et al.* In a larger study of 338 patients from 24 centres showed the age group of ≥65 years as also having a poorer prognosis (HR=4.106,95% CI=2.341-7.202, p<0.001) when referenced against the <50 years age group (Riera *et al.*, 2021). Pans *et al.* stipulated that in a univariate analysis, age does not predispose COVID-19 patients to a poorer prognosis on ECMO but incorrectly stated that being in a certain age group does. These age groups were not defined in the publication and the level of significance was purported to be <0.05 when the calculated p value was 0.05 (HR=2.45, 95% CI=0.97-6.18) (Pans *et al.*, 2022).

Very few publications showed that age did not have an effect on the outcome of treatment, In a relatively small study (n=54) Pauchet and Cabrol showed that age had no bearing (p=0.07) in the outcome of ECMO support for COVID-19 patients supported by ECMO (Pauchet and Cabrol, 2022) as did Biancari et al (Biancari *et al.*, 2021).

If we were to assess the COVID-19 induced ARDS cohort with the non-COVID-19 induced ARDS group we see that there is an indication that an advancing age is detrimental to survival, irrespective of the origin of ARDS. A retrospective study carried out in 2016 in China showed that an advancing age was a predictor of mortality in a non-COVID-19 ARDS group (Liu *et al.*, 2016) as does Baek et al. (Baek *et al.*, 2018) and Deatrick et al. who showed that age was an independent predictor of survival to discharge beginning at the age of 45, increasing incrementally (Deatrick *et al.*, 2020).

As is correctly stated by Raff *et al.* "there is a reproducible and robust association between increasing age and medical comorbidities and worse outcomes in COVID-19". It is highly believable that the older patient comes with greater clinical risks therefore will be more moribund when ECMO is implemented (Raff *et al.*, 2020).

When considering age as a predictor or influencer of poor outcome and even death on ECMO, one must also consider this to be a case of confounding by indication.

In a publication entitled "Veno-venous extracorporeal membrane oxygenation allocation in the COVID-19 pandemic" Merugappan *et al.* states in a table that an age of ≥65 is a relative contraindication for ECMO with COVID-19 and that the table is "Adapted from Extracorporeal Life Support Organization COVID-19 Interim Guidelines". It is the authors understanding that this is not the case, as previously stipulated ELSO stated that with

increasing age comes an increase in the probability of death, but no threshold has been established (Murugappan *et al.*, 2021).

2.18.2 Ethnicity

Early on in the pandemic, it was noticed that people from ethnic minorities groups had a higher risk of severe illness and death from COVID-19 than people of white ethnicity. Patients admitted to ICU or who die in hospital include a disproportionately large number of people from ethnic minorities (Platt and Warwick, 2020). The office for national statistics reported that "the mortality rate for people of black African or black Caribbean ethnicity in the first half of 2020 was two and a half times higher than for people of white ethnicity" (White and Ayoubkhani, 2020). These findings were reproduced in many publications worldwide. Several reasons were posited for this phenomenon, a higher prevalence of comorbidities that were associated with poor COVID-19 outcomes (such as type 2 diabetes among British South Asians), large multigenerational households, greater social deprivation (Lo *et al.*, 2021), differences in occupational risks and delayed access to healthcare were the main findings (Morales and Ali, 2021). Rodriguez *et al* stated in his 2021 paper, that the increase in mortality seen in the black and ethnic minority (BAME) community was due to their disproportionate representation among COVID-19 hospitalizations, as this did not differ after adjustment (Rodriguez *et al.*, 2021).

It would be reasonable to infer from the aforementioned data regarding ethnicity and survival that patients of a non-white ethnicity would not fare well with the adjunct therapy of VV-ECMO. However, many authors did not find ethnicity significantly affecting mortality.

Saeed *et al.* found that in a multivariable Cox model, ethnicity had no effect on time to death in a cohort of 292 patients in a multicentre (n=17) study (Saeed *et al.*, 2022). In a presentation, Yaqoob et al demonstrated a higher mortality of non-white ethnic minorities compared to white and Asian ethnicities receiving VV-ECMO therapy for COVID-19, although this was not significant and the study group was small (n=36) (Yaqoob *et al.*, 2022). Barbaro *et al*, in a larger cohort (n=1035) retrospective review utilizing data from the ELSO registry, found no significant difference between ethnicity and survival (Barbaro *et al.*, 2020).

2.18.3 Obesity

According to the WHO, the prevalence of obesity is steadily increasing worldwide; they define obesity as having a body mass index (BMI) greater than 30 kg/m^2 (Vaamonde and Álvarez-Món, 2020). Obesity is a known risk factor for respiratory infection (Kassir, 2020), it was acknowledged to be an independent risk factor in the 2009 H1N1 influenza pandemic for a poorer outcome (Cocoros *et al.*, 2014). Starting with a BMI of 23kg/m^2 Gao et al showed that there was a linear increase in risk of COVID-19 leading to hospitalization and death across the whole BMI range (Gao *et al.*, 2021). Sawadogo et al in his systematic review found similar results, that an increased adiposity is a significant risk factor for morbidity and mortality (Sawadogo *et al.*, 2022). An article in *Nature* commented on a positive correlation observed between the percentage of obese in adult populations and mortality due to COVID-19 across nations (Arulanandam, Beladi and Chakrabarti, 2023). However, in the non-COVID-19 patient, Akkinusi *et al* in a meta-analysis, found that although obesity was associated with an increase in morbidity, it was not proven to increase mortality rates in a large (n=62045) cohort of intensive care patients (Akinnusi, Pineda and

El Solh, 2008). Conversely, it has been indicated that obesity may have some sort of protective effect on patients in the hospital setting, this is known as the “obesity survival paradox”. Liu *et al* showed that obesity demonstrated a protective factor to ARDS mortality in a patient group undergoing cardiac surgery , even though obese patients were seen to develop ARDS more than the non-obese (Liu *et al.*, 2021). Similarly, Nie *et al* showed, in a meta-analysis, that obese patients were at a greater risk of pneumonia but have a lower mortality risk and succumb less than those who were normobaric (Nie *et al.*, 2014). In a large study of 78704 elective general surgery patients over the age of 65 years, El Moheb *et al* demonstrated a multi factorial benefit of obesity as the overweight and obese had a decreased risk of mortality, reintubation, pneumonia, Myocardial infarction (MI), stroke and less bleeding requiring transfusion, however, he could not comment on whether obesity would confer this protective effect on younger patients (El Moheb *et al.*, 2021).

There is a hesitancy in many ECMO centres to offer support for the obese population, this is in part due to morbid obesity posing a significant challenge to achieving indexed flows . Anatomical issues surrounding the obese anatomy can make it difficult to implement cannulation effectively also. Contrary to this, it has been shown that class III (BMI>40kg/m^2) obesity has a protective effect to patients on VV-ECMO (Kon *et al.*, 2015) and Lazzeri *et al* demonstrated that obesity was not associated with a worse outcome in a cohort of ARDS patients, and as such, should not be considered as a contraindication *per se* for VV-ECMO (Lazzeri *et al.*, 2017).

The poorer prognosis seen in non-supported COVID-19 positive obese patients also followed for infected patients supported by VV-ECMO. Javidfar *et al.* demonstrated an increased risk

of death associated with BMI, this risk was linear with no BMI threshold beyond which the risk for death increased (Javidfar *et al.*, 2023).

The majority of publications pertaining to obesity and survival in the COVID-19 patient indicated that BMI had no influence in outcome. Mongero *et al* showed no correlation between BMI and mortality on VV-ECMO (Mongero *et al.*, 2021) as did Balik *et al*. (M Balik *et al.*, 2022). In an attempt to ascertain whether the SARS-CoV-2 virus affected the mortality of the obese patient on VV-ECMO, Powell *et al.* in a single centre retrospective study demonstrated that COVID-19 positive patients with a BMI of >40 kg/m^2 have similar mortality rates compared to non-infected patient supported with VV-ECMO (Powell *et al.*, 2022).

2.18.4 Co-morbidities

It has been suggested that diabetes mellitus is one of the most common co-morbidities found In COVID-19 infected people. Fadini et al showed that diabetes may not increase the risk of infection from SARS-CoV-2 but contributes to the detrimental effects of the outcome (Fadini *et al.*, 2020). A Sicilian study found comparable results in that it was not a risk factor for the development of COVID-19 although was associated with a higher case mortality (Silverii *et al.*, 2021) as did the systematic review by Abdi et al. (Abdi *et al.*, 2020). This may not be surprising to find, as many chronic illnesses are predisposing factors for premature deaths in the sick (Erener, 2020). Kumar *et al.* found an astonishing twofold increase in death for patients with diabetes and COVID-19 (Kumar *et al.*, 2020). As indicated by Muniyappa and Gubbi, African Americans, Asians, Hispanics and Native Americans are highly prone to develop diabetes, this covariance between ethnicity and diabetes may cloud the findings as to what factor is at play in the lethality of the virus. This is also pertinent for

obesity and an advancing age, which both predispose an individual to type II diabetes (Muniyappa and Gubbi, 2020). These findings of the detrimental effects of diabetes on patients with COVID-19 stand also for patients supported by VV-ECMO (Seggelke *et al.*, 2021) however, specific publications addressing this phenomenon have yet to be published.

Age, obesity, ethnicity and diabetes mellitus are the more commonly noted factors described by authors, that have sought to identify predispositions to the infection by SARS-CoV-2 and for a premature death from COVID-19. To a lesser degree, other notable co-factors have been acknowledged less frequently as precursors to premature death on VV-ECMO such as renal dysfunction (Haroun *et al.*, 2022), non-proning on ECMO (Papazian *et al.*, 2022), Immunocompromised, Pre-ECMO cardiac arrest (Barbaro et al., 2020), major bleeding or thromboembolic events. However, a current general consensus is lacking. Herrmann *et al.* contrary to contemporary work, showed that diabetes mellitus did not contribute to a poorer prognosis to VV-ECMO support for COVID-19 (Herrmann *et al.*, 2022).

2.19 Mortality scores

A reliance on mortality scores as a method of identifying COVID-19 positive patients that could benefit from the modality of VV-ECMO was questionable. Supady, Bode and Duerschmied found that the use of the mortality scores SOFA, SAPS II, APACHE II, RESP, and PRESERVE for the prediction of mortality and outcome are not recommended for treatment decisions for patients with severe COVID-19 ARDS undergoing VV-ECMO support. The prognostic accuracy as defined by the area under receiver operating characteristic (AUROC)

curve was poor for these well-established ITU scores. These scores were not designed for use in the COVID-19 cohort of prospective ECMO patients and as such, were inefficacious (Supady, Bode and Duerschmied, 2021).

2.20 Aim of study

Clinicians needed to be able to allocate this finite resource (ECMO) in a utilitarian manner to maximise the total 'good' of a limited treatment. With such limited and conflicting data to guide clinical decisions pertaining to patient selection, a more definitive, empirical study with a greater selection of variables is needed to produce a more cogent process for identifying patients that would respond to this treatment with the best outcome. Therefore, key variables that are seen to predispose patients to poorer prognoses need to be identified in order to triage prospective ECMO patients more effectively.

It is the aim of this study to identify specific, contextual characteristics associated with outcome during and post ECMO therapy, in patients with COVID-19 induced ARDS.

2.20.1 Study objectives

The study objectives are as follows-

1. To investigate whether there are differences in characteristics of COVID-19 induced ARDS patients who survive VV-ECMO vs those who don't.
2. To identify pre and peri-ECMO measures that have an influence on the outcome of VV-ECMO in COVID-19 Induced ARDs patients.
3. To investigate whether there are differences in survival time between patients with certain risk factors.
4. To assess how changes in peri-ECMO and Pre-ECMO variables (risk factors) influence the risk of not surviving the ECMO treatment in COVID-19 induced ARDS patients.

Hypothesis

Specific measures and characteristics are associated with the survival of patients with ARDS of COVID-19 origin being treated by VV-ECMO.

2.20.2 Update

It should be noted that, at the time of conception of this study, there were very few comparable inquiries pertaining to patient selection for VV-ECMO to treat COVID-19 positive patients. This study was, at the time of postulation (*circa* September 2021), unique and this topic had not been formally addressed by academics and as such, there were very few publications to be found. At the time of writing (August 2023), studies had come to fruition over time and publications achieved. On the whole, these studies were underpowered (Pans *et al.*, 2022)(Beyls *et al.*, 2020) (Pauchet and Cabrol,

2022),concentrated on specific limited variables (Raff *et al.*, 2020)(M Balik *et al.*, 2022)(Laghlam *et al.*, 2022) or were case studies (Rinewalt *et al.*, 2020)(Zeng *et al.*, 2020).

This study stands apart from the aforementioned work by authors due to -

1. The 126 variables being assessed in the study makes it the most in-depth investigation to causes of mortality to date.
2. The cohort of 93 patients involved in the study enabled a thorough statistical analysis sufficiently powered to take place.
3. The monocentric nature of treatment negated the possible introduction of variables such as the variation in treatment between centres, the utilization of a larger pool of machinery used such as ECMO pumps, laboratory analytical equipment etc and the variation of clinical opinion between intensivists.

   It has not gone unrecognised that this single centre study limits the extrapolation of the findings to a global population, but this was not the intention at this juncture.

3 Methods

3.1 Study design and participants

A retrospective, observational study was performed on all presenting 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 ELSO guidelines (Tonna *et al.*, 2021) 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, this is to say that ventilation volumes and frequencies was reduced to lessen the barotrauma and aid in lung recovery.

3.2 Data

Routine clinical data generated during a Hospital/ITU stay were extracted from patients medical records, the extraction process was carried out by a sole investigator (author). These included demographic information, laboratory results, intensive care unit charts, ECMO management charts, haematology records and blood bank data, 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 the Glenfield

hospital or the referring hospital from which the patient was transferred and finished once cessation from ECMO support was complete due to death or recovery.

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. In total, 126 variables were collected and used during the study. These were-

Pre-ECMO

3.3 Demographics

3.3.1 Age

Patient age referred to the chronological age of the patient on the day that VV-ECMO therapy started. All patients were the same age when they were admitted to hospital to the implementation of ECMO, i.e., they didn't have a birthday in between. This was an adult study and as such all participants were >18 years of age.

3.3.2 Sex

The sex of the patient was taken to be that implied by phenotypical observation which also matched the individuals personal identification.

3.3.3 Wave of pandemic

2 waves of the COVID-19 pandemic were covered during the period of this study. The first patient from which data was collected was hospitalised on the 04/03/20, 47 more patients followed until a lull in the admissions was seen (until the 25/06/20). The next admission of patients began on the 18/09/2020 followed by 45 more patients with the final patient on the 17/03/21. These trends in admission were mirrored across the rest of the country and were considered to be wave 1 and wave 2 of the pandemic.

3.3.4 Ethnicity group

Patient ethnicity was considered to be a variable of interest. As previously mentioned, people from certain ethnic groups, namely BAME, demonstrated a greater risk of severe illness and death from COVID-19 so this was of interest. Membership of the BAME ethnic group was achieved by being Asian (Indian, Pakistani, Filipino), Asian British, Black (African), Black British.

3.3.5 Weight, BMI and Obesity category

The patients weight was ascertained upon admission to hospital. Irrespective to weight change during hospital stay this was the value used to generate a BMI value and therefore an obesity category.

The obesity category was calculated as follows-

Normal weight = BMI<25Kg/m^2

Overweight = BMI=25-28Kg/m^2

Obese = BMI=29-39Kg/m^2

Extremely Obese = BMI>39Kg/m^2

These classifications are based on WHO guidelines (2022).

3.3.6 Diabetes

A positive diabetic status was considered to be a type I or type II diabetes mellitus diagnosis prior to or during hospital admission.

3.3.7 Smoker

Smokers were actively smoking up until hospital admission as confirmed by the patient or relative.

3.3.8 Referral Region

Although Glenfield hospital has its own geographical catchment area for patients requiring ECMO, due to the nature of the pandemic it was possible for patients to be sent to the study centre from anywhere in the British isles; the region from which they came was recorded. Patients came from 9 areas spread throughout the UK and Ireland, centres that were more pro ECMO for the treatment for COVID-19 featured more significantly in the numbers.

3.3.9 Cannulated at the referring hospital

This variable indicated whether the patient was cannulated and ECMO commenced at the referring hospital, or they were taken conventionally by road/air to the study centre where ECMO therapy was commenced.

3.3.10 Vascular access

This indicates the modality of venous access for the cannulation of ECMO. As only VV-ECMO was used, venous access was required only.

3.3.11 Infections

Some patients presented to hospital with an active infection. Infections found to be associated with respiratory suppression that could aggravate ARDS are Legionella and pneumococcus. Methicillin Resistant Staphylococcus Aureus (MRSA) is strongly associated with airway infections and community/hospital acquired pneumonia (Defres, Marwick and Nathwani, 2009) and because of its prevalence in the community was included as a variable of interest. Human Immunodeficiency Virus (HIV) is not a common condition, but as one patient was HIV positive it was necessary to include this observation due to the morbidity of the condition and detrimental effect it would have on the treatment.

3.3.12 Immunocompromisation

Patients considered to be in an immunocompromised state by the referring hospital were indicated. However, this does not include the perceived increased risk of infection concomitant with corticosteroid therapy.

3.3.13 Cardiac arrest

These patients had experienced a cardiac arrest between the times of hospital admission and the start of ECMO.

3.3.14 Time to ECMO

This variable was a measurement in days between hospital admission and cannulation for ECMO.

3.3.15 ABO blood group

This indicates the patient's blood type pertaining to the ABO system. Patients were either A, B, O or AB.

3.3.16 Rhesus

This indicates the patient's blood carried the rhesus factor, if this was apparent the patient was considered to be rhesus positive, if not the patient was rhesus negative.

3.4 Pulmonary function

All pulmonary function data pertains to the ventilator settings on the hospital ward/ITU prior to instigation of ECMO. These are the settings of the MV support that the patient was receiving while in a steady state rather than transient to other therapy.

Below is an explanation of the terminology associated with MV in order to better understand the principles behind the technology.

For reference, normal values can be seen in Table 4.

3.4.1 Duration of MV before cannulation

This is the time period between intubation for MV and cannulation for ECMO in days.

3.4.2 Mechanical ventilation mode

The modes of MV used on the ward/ITU prior to cannulation were recorded. These modes were Continuous positive airway pressure (CPAP), Bilevel positive airway pressure (BIPAP), Synchronized intermittent mandatory ventilation (SIMV), Pressure controlled (PC), Airway pressure release ventilation (APRV), Volume control-assisted control (VCAC), Pressure regulated volume control (PRVC), Continuous mandatory ventilation (CMV), Pressure control ventilation volume guaranteed (PCV-VG) and manual hand bagging.

3.4.3 FiO_2 on MV

This is the fraction of inspired oxygen on mechanical ventilation, the percentage of oxygen inspired in each breath while being ventilated.

3.4.4 Respiratory rate on MV

This is the number of inspirations per minute delivered to the patient by the ventilator or taken by themselves (depending on the MV mode)

3.4.5 Tidal volume

The volume of gas moved into and out of the lungs in one respiratory cycle.

3.4.6 Peak inspiratory pressure (PIP) on MV

This is the peak pressure within the breathing circuit measured at the end of the inspiration portion of the respiratory cycle. This increases as airway resistance increases, causes can be increased secretions, decreased lung compliance (increased stiffening of the lungs as seen in ARDS) and pneumothorax to mention just a few.

3.4.7 Positive end expiratory pressure (PEEP) on MV

This is the positive pressure that remains in the patients airways at the end of the respiratory cycle after exhalation. This protects the alveoli against collapse and therefore recruits more surface area of the lung for gas exchange. The alveoli of patients with ARDS produce less surfactant, a liquid that maintains alveoli integrity and stops them collapsing on exhalation. PEEP is effective for these patients as the alveoli are held open at the end of expiration and therefore maintains their functional form.

3.4.8 Lung compliance

This can be expressed as 'the change in lung volume divided by the change in pressure', essentially, it is the lungs ability to stretch and expand. A decreased lung compliance makes it harder for the lungs to expand, they are stiffer. A lack of surfactant, atelectasis/ARDS and obesity are a few conditions that causes a decreased lung compliance.

3.4.9 PaO_2/FiO_2 ratio

This is the ratio of oxygen partial pressure to the fraction of inspired oxygen. This is a tool to assess lung function, especially for those patients on MV. This tool plays a major role in the diagnosis of ARDS. The lower the ratio, the more severe the lung damage *(Table 3).*

Table 3: PaO_2/FiO_2 ratio pertaining to ARDS severity

ARDS Severity	PaO_2/FiO_2	Mortality
Mild	200 – 300	27%
Moderate	100 – 200	32%
Severe	< 100	45%

(Chandrasekhar, no date)

Table 4: Normal values of pulmonary functions.

Pulmonary Function	Normal Values
FiO_2 on MV	25%-30%
Respiratory rate	12 BPM
Tidal volume	5-10 mL/Kg
Peak inspiratory pressure	20 cmH_2O
Positive end expiratory pressure	4-6 cmH_2O
Compliance	0.1-0.4 L/cmH_2O
PaO_2/FiO_2 ratio	300-400

FiO_2=Fraction of inspired oxygen, MV=Mechanical ventilation, PaO_2= Partial pressure of arterial oxygen, H_2O= Water, BPM= Breaths per minute

3.4.10 Patient on nitric oxide

This indicates whether the patient has received nitric oxide therapy from the period of hospitalisation to ECMO cannulation. Nitric oxide is a potent pulmonary vasculature dilator

used to treat hypoxic respiratory failure and/or pulmonary hypertension. It is given via a ventilator in order to improve blood oxygen levels.

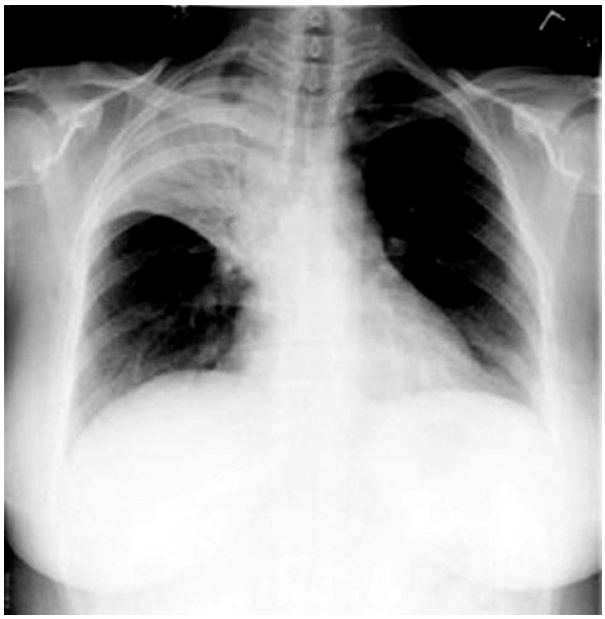
3.4.11 Patient proning

This indicates that the patient has undergone a proning regimen between the times of hospital admission and ECMO cannulation. Proning has been shown to improve lung recruitment during periods of hypoxia due to ARDS and excessive pulmonary fluid/secretions.

3.4.12 Lung consolidation

This condition is when the air in the smaller airways of the lungs is replaced with fluid or solid material such as puss or tissue cells. ARDS and pneumonia cause the creation of an inflammatory exudate which creates this consolidation; this can cause a reduction in the expansion of the chest wall during breathing and a lower PaO_2 than expected. The severity of this consolidation can be quantified using X-ray and/or CT assessment and affected areas show up as white and dense. As the chest is divided into 4 quadrants (right upper, left upper, right lower and left lower) the amount of consolidation can be referred to by the number of quadrants that are affected i.e., 1 quadrant would be where there is significant consolidation occurring in 1 quadrant of the chest *(Figure 12).* The more severe and widespread the consolidation, the more quadrants are affected.

Figure 12: 1 quadrant consolidation (right upper quadrant)



X-rays shows consolidation of right upper quadrant.(Chandrasekhar, no date)

3.4.13 Pneumothorax

This indicates whether the patient had developed a pneumothorax before starting ECMO treatment. A pneumothorax is a collection of air outside the lung but within the pleural cavity and can be caused by emphysema, chronic obstructive pulmonary disease (COPD) and barotrauma from MV.

3.4.14 Chest drains in situ

This indicates if the patient had any chest drains inserted prior to the commencement of VV-ECMO.

3.4.15 No. of chest drains

This indicates how many, if any, chest drains the patient has before going onto ECMO. A chest drain is a piece of tubing that is placed into the chest in order to facilitate the removal of fluid or air. Fluid and/or air (pneumothorax) in the pleural cavity stops the lungs from working properly. Between 0 to 2 chest drains were inserted.

3.4.16 Total duration of MV

This is the total amount of time that the patient was receiving MV therapy from hospitalisation to weaning from the ventilator.

3.5 Pre-ECMO drug therapy

Data for pre-ECMO drugs received by the patient between hospitalisation and ECMO cannulation were collected from bedside ward/ITU charts. The drugs deemed pertinent to this study were neuromuscular blockers, catecholamines, glucocorticoids, anti-virals, biologicals and disease modifying drugs.

3.5.1 Neuromuscular blockade

Neuromuscular blockade is a technique used to cause paralysis of skeletal muscle and is commonly used for patients requiring some modes of MV that have a reduced lung compliance in order to ventilate the lungs more effectively. It is achieved by the

administration of neuromuscular blocking drugs such as Vecuronium, Atracurium and Rocuronium.

3.5.2 Noradrenaline

Noradrenaline is a catecholamine and found in the body as both a neurotransmitter and a hormone. It is used in the hospital setting intra-venously (IV) to cause vasoconstriction in order to raise the systemic blood pressure.

3.5.3 Adrenaline

Adrenaline is a hormone made endogenously in the adrenal glands. It is used IV in hospitals to increase a patient's heart rate, respiratory rate, cause bronchodilation, its effect is dose dependent and is generally used in cardiac arrest and anaphylactic shock.

3.5.4 Dexamethasone

This drug is a corticosteroid and is commonly used as an anti-inflammatory agent. It blocks the immune response to inflammation which helps to prevent the auto-immune damage to the lungs often see in COVID-19 patients (Su *et al.*, 2020).

3.5.5 Tocilizumab

Tocilizumab is a monoclonal antibody that inhibits interleukin-6 (IL-6) receptor. IL-6 is a cytokine released in high levels in people who are critically ill with COVID-19. It is used to treat arthritis and cytokine release syndrome.

3.5.6 Remdesivir

This is an anti-viral drug whose mode of action is the inhibition of RNA transcription. This inhibits viral proliferation which makes it suitable for use to treat critically ill COVID-19 patients (Rezagholizadeh *et al.*, 2021).

3.5.7 Hydroxychloroquine

Hydroxychloroquine is a disease modifying drug with anti-malarial actions that is used to treat rheumatoid arthritis, systemic lupus erythematosus (SLE) and other inflammatory diseases. As of March 2023 the WHO does not recommend the use of Hydroxychloroquine for the treatment of COVID-19 ('coronavirus-disease-(covid-19)-hydroxychloroquine @ www.who.int', 2023)

3.5.8 Tamiflu

Tamiflu is an anti-viral drug generally used to treat symptoms caused by the flu virus. It was used during the H1N1 (off label) outbreak to treat adults and children to prevent life threatening pneumonia.

3.6 Renal / liver function

All renal/liver function variable data was generated after hospital admission and before ECMO cannulation. Data came from patient bedside charts, hospital notes and blood laboratory results.

3.6.1 Renal impairment

Any patient with an acute kidney injury (AKI) variable greater than 0 was considered to have renal impairment.

3.6.2 AKI

AKI can be defined by an abrupt decrease in kidney function due to many aetiologies. Even a minor acute reduction in kidney function can have an adverse prognosis for the hospitalised patient. The degree of AKI can be staged due to a deviation of serum creatinine values from a baseline value or urine output.

Table 5: AKI staging

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline or ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline or increase in serum creatinine to ≥4.0 mg/dl (≥353.6 μmol/l) or initiation of renal replacement therapy or in patients <18 years, decrease in eGFR to <35ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 hours or anurea for ≥12 hours

eGFR= Estimated glomerular filtration rate.(It *et al.*, 2012)

3.6.3 Patient on haemofiltration

This indicates whether the patient has received continuous veno-venous haemofiltration (CVVH) therapy between hospitalisation and ECMO cannulation. CVVH is a temporary treatment for patients with acute renal failure to provide renal support or to remove excess fluid from the body. Approximately 5%-10% of patients with AKI require CVVH (Tandukar and Palevsky, 2019) and it is a common complication of critically ill patients.

All renal and liver function markers were taken within 12 hours of ECMO cannulation. Normal values can be seen on Table 6.

3.6.4 Creatinine

Creatinine is a waste product found in the blood that comes from the muscles. Elevated levels of creatinine are an indication of sub optimal renal function, as it is the kidneys that clear it from the blood.

3.6.5 Urea

Urea is the major constituent of urine and is the main means for elimination of nitrogen derived from the deamination of proteins. It is excreted by the kidneys and higher than normal levels in the blood can be an indication of renal dysfunction.

3.6.6 Amylase

Amylase is a digestive enzyme responsible for breaking down carbohydrates in the digestive system. Abnormal serum amylase levels can be an indication of pancreatic, renal and/or hepatic dysfunction.

3.6.7 Bilirubin

Bilirubin is a yellowish pigment made during the breakdown of red blood cells, It is a waste product and as such is eliminated by the liver. Abnormally high levels can be an indication of hepatic dysfunction or infection

3.6.8 Alkaline Phosphatase (ALP)

ALP is an enzyme found in many parts of the body but primarily found in the liver, bones, kidneys and intestines. An ALP test measures the amount in the blood, abnormal levels can be a sign of conditions such as liver disease, bone disorders, and chronic kidney disease.

3.6.9 Alanine transaminase (ALT)

ALT is an enzyme found mostly in the liver. When hepatocytes are damaged they release ALT into the blood, high serum levels of ALT are an indication of liver damage/disease.

3.6.10 Albumin

An albumin blood test checks the levels of albumin circulating in the blood. The most common cause for a low serum albumin is chronic liver failure, other causes are kidney disease or an inflammatory disease.

Table 6: Normal values of renal / hepatic markers.

Renal / Hepatic marker	Normal Values
Creatinine (micromol/L)	53-115
Urea (mmol/L)	2.6-9.2
Amylase (iu/L)	40-140
Bilirubin (micromol/L)	<21
Alkaline phosphatase (ALP) (iu/L)	44-147
Alanine transaminase (ALT) (iu/L)	7-40
Albumin (g/L)	35-50

3.7 Pre-ECMO blood results

Blood results were obtained within 12 hours pre-cannulation at the referring or study hospital. All blood tests were derived from an arterial sample.

Normal blood results can be seen on Table 7.

3.7.1 pH

This is a measurement of acidity/alkalinity of the blood. In respiratory failure the pH has a tendency to become lower (more acidic) due to excess CO_2 in the blood.

3.7.2 PaO_2

This is the partial pressure of arterial oxygen and reflects the amount of oxygen gas dissolved in the arterial blood. This gives an indication of how effective the lungs are at extracting oxygen.

In respiratory failure the lungs are not able to maintain satisfactory physiological levels of PaO_2 and/or PCO_2. Respiratory failure can be classified into type I and II-

- Type I – Hypoxaemic, This type of respiratory failure is defined by a PaO_2 of <60mmHg (8.0kPa) with a normal/subnormal PCO_2. This occurs due to damage of the lung tissue from anomalies such as pulmonary oedema, pneumonia, ARDS, COVID-19 and chronic pulmonary fibrosis.
- Type II, Hypercapnic, This type of respiratory failure is defined by a PCO_2 >50mmHg (6.7 kPa) and commonly occurs with hypoxia. The most common cause is chronic obstructive pulmonary disease (COPD).

3.7.3 SaO_2

This is the saturation of oxygen of arterial blood. It indicates the percentage of available binding sites on haemoglobin that are bound with oxygen in arterial blood. This should not

be confused with SpO_2 which is obtained through the exogenous method of pulse oximetry and as such is a surrogate marker for SaO_2. SaO_2 can only be measured by sampling arterial blood. A value lower than 90% is considered low and would require supplemental oxygen if the subject was spontaneously breathing room air. As the patients in the study were supported by MV at the time of blood sampling, the SaO_2 was a product of their artificial respiratory support and lung pathology.

3.7.4 Bicarbonate (HCO_3)

Bicarbonate is a by-product of the bodies metabolic processes. In normal physiological processes the blood would transport the bicarbonate to the lungs where it would be exhaled as CO_2 or excreted through the kidneys. Therefore, it is reasonable to posit that respiratory or renal failure would bring about abnormal bicarbonate readings.

3.7.5 Lactate

Lactate is a metabolic substrate; an increase in lactate production is indicative of impaired tissue oxygenation either from decreased oxygen delivery or a disorder in oxygen use. Common causes of increased lactate are shock, cardiac arrest, severe lung disease, respiratory failure, pulmonary oedema and liver dysfunction.

3.7.6 Haemoglobin (Hb)

Haemoglobin is a measurement of the amount of haemoglobin, the oxygen carrying protein, in the blood. Low levels of haemoglobin indicate anaemia and this value helps guidance on blood transfusions. Low levels of haemoglobin in the blood can be an indication of bleeding, kidney disease, increased haemolysis and inflammation to name a few.

3.7.7 Haematocrit (HCT)

Haematocrit is similar to Hb in that it can indicate anaemia and pathologies of the blood, but unlike Hb it is a measurement of the percentage of red blood cells in the blood rather than the amount of haemoglobin.

3.7.8 Platelets

Platelets are cell fragments in the blood that are responsible, in part, for the coagulation process. The blood test value is known as the platelet count and measures the number of platelets in 1 microlitre of blood. A low platelet count can be due to infections or autoimmune diseases and is commonly seen in patients undergoing mechanical circulatory support such as ECMO due to the traumatic nature of the ECMO circuit and disseminated intravascular coagulation (DIC) (Chandler, 2021). Low platelet counts predispose patients to a greater chance of bleeding and therefore blood loss.

3.7.9 Fibrinogen

Fibrinogen is a glycoprotein made in the liver and is the main structural component in blood clots. Sub-optimal levels of fibrinogen are associated with an increased chance of bleeding; causes of this are liver disorders and DIC.

3.7.10 C-Reactive protein

C-Reactive protein (CRP) is made in the liver and circulates in the blood at low levels. Levels increase when inflammation is present in the body and is released as an acute phase response.

3.7.11 D-Dimers

D-Dimers are protein fragments found in the blood that result from broken down blood clot. These are generally only found in very small concentrations in the body unless the body is creating and breaking down significant amounts of blood clots. An elevated concentration of D-dimers can indicate DIC, pulmonary embolism (PE), deep venous thrombosis (DVT) and infection.

3.7.12 International Normalised Ratio (INR)

This blood test is based on the results of a prothrombin (PT) test. Prothrombin is a protein made in the liver and is one of several clotting factors found in the blood, PT test times show how long it takes for prothrombin to activate to thrombin, therefore is indicative of clotting time. The ratio of what the PT time is in respect to what the normal PT is expected to be is the INR. The normal INR value is 1, substances such as anticoagulants or pathologies such as DIC will result in an abnormally elevated INR time. As some patients pre-ECMO receive the drug heparin in order to negate any intravascular clotting, INR values may be indicative of this anticoagulation therapy rather than an underlying pathology (Bulletin, International and Ratio, 2004).

3.7.13 Prothrombin time (PT)

As explained above, PT is an indication of the coagulation status of the blood, an elevated PT is associated with an increased risk of bleeding. Because of this observation, clinicians sometimes use the PT of patients in conjunction with other triggers to transfuse fresh frozen plasma (FFP), a component of fractionated whole blood, to patients with abnormally low PT's (Desborough and Stanworth, 2013).

3.7.14 Activated partial thromboplastin time (APTT)

This test measures the time to fibrin formation of a clot in a platelet poor sample of blood. Again, this test is altered by therapeutic anticoagulants.

3.7.15 White cell count (WCC)

White blood cells (leukocytes) are the bodies cellular component of the immune system. They are comprised of –

Neutrophils

Lymphocytes

Monocytes

Eosinophils

Basophils

The WCC measures the total number of white cells in 1 microlitre of blood. An elevated WCC can indicate autoimmune or inflammatory diseases and bacterial and viral infections. Disorders relating to a low WCC include diseases of the immune system such as HIV, and diseases of the liver and the spleen.

3.7.16 Glucose

Blood glucose mainly comes from the nutrition received throughout the day and thus fluctuates as a response. Individuals with type I or II diabetes have difficulty controlling the

levels without medication due to the absence of insulin or the inefficacy of the action of said hormone.

3.7.17 Calcium

Calcium is one of the more common minerals in the body, responsible for muscle contraction, blood coagulation and nervous conduction. An abnormal serum calcium test result can indicate kidney, liver or thyroid dysfunction.

3.7.18 Potassium

This electrolyte is responsible for fluid balance and nerve and muscle conduction in the body. It is important that homeostatic levels are maintained for the cardiovascular and nervous system to work effectively. Hypokalaemia can be caused by chronic kidney disease, low serum magnesium and antibiotic therapy. Hyperkalaemia can be just as dangerous as a low blood potassium and is caused by uncontrolled diabetes mellitus, severe bleeding and dehydration causing cardiac arrythmias, muscle paralysis and a decreased brain function.

3.7.19 Sodium

Sodium is an electrolyte chiefly responsible for fluid balance and it also plays an important function at a cellular level antagonistically with potassium.

3.7.20 Troponin-I

Troponin-I is a constituent of cardiac muscle tissue. It is part of the troponin protein complex which binds to actin to hold the actin-tropomyosin complex in place. Troponin-I prevents myosin from binding to the protein actin when muscles are relaxed. Elevated levels of troponin-I are a good indication of myocardial infarction (MI) and cardiac injury, concentrations in excess of 0.40ng/mL indicate an MI, the amount of serum troponin-I is proportional to the myocardial damage. Unlike troponin-T which is also found in skeletal tissue, troponin-I is unique to heart tissue.

Table 7: Blood results

Measurement	**Normal Values**
pH	7.35-7.45
PCO_2 (kPa)	4.7-6.0
PaO_2 (kPa)	10.5-13.5
SaO_2 (%)	94-100
HCO_3 (mEq/L)	22-26
Lactate (mmol/L)	<2
Hb (g/L)	115-180
HCT (l/L)	34-46
Platelets (10x9/L)	150-450
Fibrinogen (g/L)	1.5-4.5
C-Reactive Protein (mg/L)	<3.0
D-Dimers (mg/L FEU)	0-500
INR	1.0
PT (sec)	9.5-12.5
APPT (sec)	25-35
White Cell Count (10x9/L)	4-11
Glucose (mmol/L)	3.9-5.6
Calcium (mg/dL)	2.2-2.6
Potassium (mmol/L)	3.5-5.2
Sodium (mmol/L)	135-145
Troponin-I (ng/L)	0-0.04

PCO_2=partial pressure of carbondioxide, $PaCO_2$=partial pressure of oxygen in arterial blood, SaO_2=saturation of oxygen in arterial blood, HCO_3=bicarbonate, Hb-haemoglobin, HCT=haematocrit, INR=international normalised ratio, PT=prothrombin time, APTT=activated partial thromboplastin time.

Blood pressure measurements were taken from ITU charts and were the last recorded

before transfer cannulation (<30 mins).

3.7.21 Systolic blood pressure

Systolic blood pressure is the pressure generated by the heart when it contracts. This was

measured in the arteries.

3.7.22 Diastolic blood pressure

Diastolic pressure is the pressure in the arteries in between heart beats.

3.7.23 Mean blood pressure

This is the average blood pressure throughout one cardiac cycle of systole and diastole. This

can be calculated by-

Diastolic Pressure + 1/3 (systolic pressure-diastolic pressure)

3.8 Prediction scores

Severity scales are an important tool for the clinician in order to empirically predict patient

outcome. They generally work by the inputting of specific physiological variables into an

algorithm in order to generate a score (a number assigned to outcome severity), and a probability grade (a value assigned to the probability of hospital death). The ideal model should be well validated, discriminated and calibrated.

Common ITU and ECMO scores were collected from referral documents and collated.

3.8.1 Murray score

This is a clinical tool to estimate the severity of acute lung injury *(Table8)*.

Table 8: Murray Score

Criteria	0	1	2	3	4
PaO_2/FiO_2 on 100% O_2	≥40kPa	30-40 kPa	23-30 kPa	13-23 kPa	<13 kPa
CXR quadrants	Normal	1	2	3	4
PEEP (cmH_2O)	≤5	6-8	9-11	12-14	≥15
Compliance (ml/cmH_2O)	≥80	60-79	40-59	20-39	≤19

PaO_2=partial pressure of arterial oxygen, FiO_2=fraction of inspired oxygen, CXR=chest X-ray, PEEP=positive end expiratory pressure.

The Murray score is judged on 4 criteria. Each criterion receives a score from 0 to 4 according to the condition severity. These numbers are summed and divided by 4 to create a Murray score. A score greater than 2.5 indicates ARDS, a score of between 1-2.5 indicates

mild to moderate lung injury (Patel *et al.*, 2019). Referral criteria for VV-ECMO can vary slightly depending on the centre; thus Guys and St Thomas' Hospital, London (*extracorporeal-membrane-oxygenation-ecmo @ www.guysandstthomas.nhs.uk*, no date) The Royal Brompton, London (*ecmo-referrals-and-transfer-pathway @ www.rbht.nhs.uk*, no date) and the Mater Misericordiae, Ireland (Failure and Ecmo, 2018) all use a score of 3 or greater as a trigger to consider VV-ECMO.

3.8.2 Sequential Organ Failure Score (SOFA)

SOFA is a scoring system that assesses the performance of several organ systems in the body and assigns a score based on the function of those organs *(Table 9).*

Table 9:SOFA score

Organ System, **Measurement**	**SOFA Score**				
	0	1	2	3	4
Respiration PaO_2/FiO_2, mmHg	Normal	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation Platelets $x10^3/mm^3$	Normal	<150	<100	<50	<20
Liver Bilirubin, mg/dL (µmol/l)	Normal	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (<204)
Cardiovascular Hypotension	Normal	MAP<70 mmHg	Dopamine ≤5 or dobutamine (any dose)**	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System Glasgow Coma Score	Normal	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL (µmol/l) or Urine output	Normal	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or <500 mL/day	>5.0 (>440) or <200 mL/day

PaO_2= partial pressure of arterial oxygen, FiO_2= fraction of inspired oxygen

(Vincent *et al.*, 1996)

Six specific scores, one for each organ systems (respiratory, cardiovascular, renal hepatic, and neurological) contribute to the final score. Each organ system is allocated a score from 0 (normal) to 4 (least normal) giving a final SOFA score of between 0 and 24.

3.8.3 Respiratory ECMO Survival Prediction (RESP) score

The RESP score is used to predict in hospital survival after VV-ECMO therapy for acute respiratory failure. It is calculated based on 12 pre-ECMO clinical variables *(Table 11)* that have been shown to have an independent association with hospital survival (Schmidt *et al.*, 2014a).

These are-

- Age
- Immunocompromised status
- MV before ECMO
- Diagnosis
- History of Central Nervous System (CNS) dysfunction
- Acute associated non-pulmonary infection
- Neuromuscular blockage before ECMO
- Nitric Oxide before ECMO
- Bicarbonate infusion before ECMO
- Cardiac arrest before ECMO
- $PaCO_2 \geq 75$mmHg ($\geq$ 10kPa)
- PIP$\geq$ 42 cmH_2O ($\geq$4.1 kPa)

The calculations create a RESP score from which a risk class and an in-hospital survival percentage are derived.

Table 10: Interpretation of RESP score

RESP Score	Risk class	In-hospital survival
≥6	I	92%
3-5	II	76%
-1 to 2	III	57%
-5 to -2	IV	33%
≤-6	V	18%

(ClinCaseQuest, 2023)

Table 11: RESP scoring system

Age, years	18–49	0
	50–59	−2
	≥60	−3
Immunocompromised status at time of ECMO *Any malignancy, solid organ transplant, HIV, or cirrhosis*	No	0
	Yes	−2
Mechanically ventilated before ECMO initiated	>7 days	0
	48 hours to 7 days	+1
	<48 hours	+3
Diagnosis	Viral pneumonia	+3
	Bacterial pneumonia	+3
	Asthma	+11
	Trauma or burn	+3
	Aspiration pneumonitis	+5
	Another acute respiratory diagnosis	+1
	Nonrespiratory or chronic respiratory diagnosis	0
History of central nervous system dysfunction *Neurotrauma, stroke, encephalopathy, cerebral embolism, or seizure/epilepsy*	No	0
	Yes	−7
Acute associated nonpulmonary infection *Any other bacterial, viral, parasitic, or fungal infection not involving the lung*	No	0
	Yes	−3
Neuromuscular blockade before ECMO	No	0
	Yes	+1
Nitric oxide before ECMO	No	0
	Yes	−1
Bicarbonate infusion before ECMO	No	0
	Yes	−2
Cardiac arrest before ECMO	No	0
	Yes	−2
$PaCO_2$ ≥75 mmHg (≥10 kPa)	No	0
	Yes	−1
Peak inspiratory pressure ≥42 cm H_2O (≥4.1 kPa)	No	0
	Yes	−1

(ClinCaseQuest, 2023).

3.8.4 Predicting death for severe ARDS on VV-ECMO (PRESERVE) score

The PRESERVE score is similar to the RESP score although it is designed to predict survival at 6 months post hospital discharge *(Table 12).* Calculations are very similar in that values are assigned to physiological parameters and when put through an algorithm a score is generated, this score is linked to a risk class and survival rate *(Table 13)*.

Table 12: PRESERVE algorithm

Age, years	<45	**0**
	45-55	**2**
	>55	**3**
BMI > 30 kg/m²		**-2**
immunocompromised		**2**
SOFA > 12		**1**
mechanical ventilation > 6 days		**1**
no prone positioning before ECMO		**1**
PEEP < 10 cm H_2O		**2**
plateau pressure >30 cm H_2O		**2**
Total Score		**-2 to 12**

BMI=body mass index, SOFA=sequential organ failure assessment, ECMO=extracorporeal membrane oxygenation, PEEP=positive end expiratory pressure.

Table 13: PRESERVE score

6 Month Survival by Risk Class		
Risk Class	Survival Rate	**Score**
I	97%	**-2 to 2**
II	79%	**3 to 4**
III	54%	**5 to 6**
IV	16%	**7 to 12**

(Petran *et al.*, 2020)

3.8.5 Horowitz index for ARDS

This is used for assessing lung function in patients, particularly those on MV, it is useful for determining the extent of lung damage. This is also known as the PaO_2/FiO_2 ratio and has been discussed previously, it is represented here as the Horowitz index to provide a comparison between the severity of ARDS and mentioned previously as the PaO_2/FiO_2 ratio to investigate the actual scores.

3.9 Peri-ECMO data

Peri-ECMO data was collect after the implementation of VV-ECMO and before cessation.

3.9.1 Circuit change

For reasons including hardware failure or intra-circuit coagulation, the ECMO study patients circuits may need to be changed for a new set up during a run of treatment. Although this is relatively rare, it does occur from time to time. The change out procedure is carried out the same way as for all change outs and components are changed out for identical makes and models.

3.9.2 Oxygenator change

Like the circuit change, the oxygenator component of the ECMO circuit may need to be changed if a failure is detected and/or blood clots collect in the device. In this situation, only the oxygenator is changed while preserving all other components of the circuit. The changeout procedure is identical for all changeouts and the faulty components are exchanged for like components.

3.9.3 Trial off

The decision to discontinue ECMO support for patients that are deemed to have recovered enough to support their ventilatory needs is first preceded with a trial off period. ECMO support is stopped by continuing with the extracorporeal circulation through the ECMO circuit but discontinuing the oxygenation and CO_2 removal. If the patients lungs have recovered sufficiently to sustain life then the ECMO circuit is disconnected; if not the patient can be put back on ECMO support simply by re-establishing the oxygen supply. It may be necessary to repeat this process of trialling off multiple times depending on whether the patient at this juncture can tolerate the lack of support. The trial off variable represents the amount of trial off periods the patient has had before they are either successfully taken off ECMO or they succumbed to their illness.

3.9.4 Combined trial off time

By combining the times of which the patient was off ECMO during the trial off periods we get the trial off time variable.

3.9.5 Time on ECMO

This is the total duration that the patient was supported by ECMO. It includes the time trialled off and any other cessation of circulation on ECMO until the decision was made to end support.

3.9.6 Cardiac arrest Peri-ECMO

These patients had experienced a cardiac arrest between the times of the start of ECMO and the cessation of ECMO.

3.9.7 Prone Peri-ECMO

As like the 'patient proned' demographic variable, this indicates that the patient has undergone a proning regimen during the time of ECMO therapy.

3.9.8 Haemofiltration peri-ECMO

This indicates whether the patient has received continuous veno-venous haemofiltration (CVVH) therapy while being supported by ECMO. The modality and protocol of filtration is the same as that utilized as the 'Patient on haemofiltration' variable.

3.10 Blood transfusion

During VV-ECMO support, patients were transfused, when required, with non-autologous components of fractionated whole blood from the hospitals blood bank.

The volume of product in each unit differed slightly for like product, i.e., the volume of fluid in a unit of RBC would be close but not exact to the volume in all bags of RBC's, this volume was specific for blood component types. The volumes of product/unit were-

Albumin- 500mls (5%) (volume of 500mls used for indexing calculations)

RBC-280 +/- 60 mls (volume of 280mls used for indexing calculations)

platelets- 350-400mls ($\geq 240x10^9$ platelets/ml) (volume of 375 used for indexing calculations)

FFP – 200mls -360mls (volume of 280mls used for indexing calculations)

Cryoprecipitate- 200mls-280mls (volume of 240mls used for indexing calculations)

(Committee, 2023)

3.10.1 Units of Albumin/RBC/FFP/platelets/cryoprecipitate transfused

This indicates the number of units (bags of varying volume) the patient received during their period of ECMO support.

3.10.2 Volume of Albumin/RBC/FFP/platelets/cryoprecipitate transfused

This is the volume of the blood product the patient received while on ECMO support

3.10.3 Albumin/RBC/FFP/platelets/cryoprecipitate to body weight ratio

This is the volume of blood product (mls) divided by the patient's body weight (kg) to give an indexed ratio based on the size of the patient.

3.10.4 Albumen/RBC/FFP/platelets/cryoprecipitate volume to time on ECMO index

This is the volume (mls) of blood product given to the patient divided by the time (days) on ECMO. This was used in order to take into account the length of time the patient stays on ECMO, as it is reasonable to assume that the longer the patient remains on ECMO, the more blood transfusions they are likely to get due to the longer treatment time.

3.10.5 Albumin/RBC/FFP/platelets/cryoprecipitate volume to weight to time on ECMO index

This is comparable to the above variable but also including indexing for the patients weight (kg).

A follow up was conducted 6 months after hospital discharge for all survivors to ascertain the status of the patient.

3.11 VV-ECMO 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 *(Figure 4).*

3.12 Data management

Data was extracted from the aforementioned sources and entered onto an Excel (Microsoft, Washington, USA) spreadsheet by the author.

3.13 Screening and cleaning data

After importation of data into the statistical package, a process of screening and cleaning occurred to identify and correct any errors made in the collection process. The following steps were undertaken

1. Check each variable scores for feasibility of range- i.e., the values were within the range of the possible scores.
2. Check for coding errors- make sure the corresponding categories match the coding value i.e., 1= male, 2=female, there should be no other value other than 1 and 2.
3. Check the number of valid and missing cases to ensure the data was not inputted into the wrong cells.

3.14 Statistical analysis

This data was imported into the data editor sheet of the SPSS statistical package by IBM (New York, USA) in order to be analysed.

3.14.1 Continuous variables

All continuous variables were described by their median and interquartile range (IQR) if non-normally distributed, or arithmetic mean and standard deviation (SD) if normally distributed. 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. Shapiro-Wilk was chosen over Kolmogorov-Smirnov due the sample sizes in the study (Mishra *et al.*, 2019).

Differences between groups in normally distributed continuous data were evaluated using the Students Independent T-test with a Levenes test significance >0.5 to assume equal variance. Non-normally distributed continuous data used the 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.

Power calculations were generated using the G Power software version 3.1.9.7. A sufficiently powered sample size was found to be n=70.

3.14.2 Categorical variables

Categorical variables were described by their counts and percentages. Differences between groups was 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 three categories, and small=0.06, medium=0.17 and large=0.29 for four or more categories.

3.14.3 Survival analysis

Cox Univariate survival analysis was used to identify and assess the contributing factors from the study variables to the study end point (time to event) 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 to death for the effect of variables on patients . For example, a median time to death was obtained for patients receiving Nitric Oxide in comparison to those that did not receive Nitric Oxide and those that had renal failure vs those that did not have renal failure.

A graphical representation was used to show the cumulative survival probability for different variables. A steeper slope indicated a worse survival prognosis. The point of censoring on the curve (a vertical mark) indicated that a patient had either died or been removed from ECMO alive. The curve ended at 0 cumulative survival when all patients had either died or been removed from ECMO alive.

Cox multivariable survival analysis was used to control for confounding variables. Variables that had a univariate $p<0.2$ were assessed as possible confounders.

There were a total of 21 pre-ECMO and 28 peri-ECMO variables that had a significance of <0.2. Using all of these variables in a multivariate model ran the risk of overfitting as the '1 in 10 rule' would have been exceeded (Van Stralen *et al.*, 2010). In order to negate this effect, 3 criteria were used to include variables in the model. There were-

1. The variable needs to be associated with the exposure, from experience (e.g., renal failure is known to increase with age).
2. The exposure needs to be associated with the outcome (have a significance <0.2)
3. The variable should not be an intermediate in the causal pathway.

(appendix 2).

Multicollinearity was assessed using a Variance Inflation Factor (VIF) value >10 indicating significant multicollinearity.

Statistical tests were conducted assuming a 0.05 significance level.

4 Results

4.1 Demographics

A total of 93 patients from wave 1 and 2 of the COVID-19 pandemic were treated during the study period (Table I4). The study group had a median (range) 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 respectively). The survival rate for patients treated with ECMO was 52.7% (n=49).

There was no significant differences between survivor and non-survivor groups regarding the demographic variables. Also, time to death and prognosis for these variables were not significant.

Findings of interest were that the survival of both sexes were similar (male=52.2% vs female=54.2%) as was age (survivors=46 (35) vs non-survivors=46 (38)).

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

Table 14: Patient demographics

Variable	All n=93		Survived	n=49 (52.7%)	Median	Mean	Died	n=44 (47.3%)	Median (Range)	Mean (SD)	Diffrence between groups	Cox univariate survival analysis		Kaplan-Meier Survival Analysis	
	Count	%	Count	%	(Range)	(SD)	Count	%			P Value	HR (95% CI)	P Value	Median Time to Death	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)	
Weight (Kg)	96.42 (20.68)[a]					97.114 (20.168)				96.095(21.42	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

Variable	All n=93		Survived	n=49 (52.7%)	Median	Mean	Died	n=44 (47.3%)	Median (Range)	Mean (SD)	Diffrence between groups	Cox univariate survival analysis		Kaplan-Meier Survival Analysis	
	Count	%	Count	%	(Range)	(SD)	Count	%			P Value	HR (95% CI)	P Value	Median Time to D	P Value[g]
Referal Region											0.097[d]				
North East	5	5.4	1	20			4	80				Ref			
North West	1	1.1	1	100			0	0				0.000(0.000-0.000)	0.996		
Yorkshire & Humber	8	8.6	3	37.5			5	62.5				0.364 (0.088-1.500)	0.162		
East midlands	32	34.4	13	40.6			19	59.4				0.729 (0.243-2.185)	0.573		
West Midlands	29	31.2	16	55.2			13	44.8				0.718 (0.231-2.228)	0.566		
East of England	2	2.2	2	100			0	0				00....(0.000-0.000)	0.987		
London	7	7.5	5	71.4			2	28.6				0.770 (0.138-4.279)	0.765		
South East	3	3.2	3	100			0	0				0.000(0.000-0.000)	0.985		
Wales	2	2.2	1	50			1	50				1.068 (0.116-9.801)	0.953		
Ireland	4	4.3	4	100			0	0				0.000(0.000-0.000)	0.988		
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,

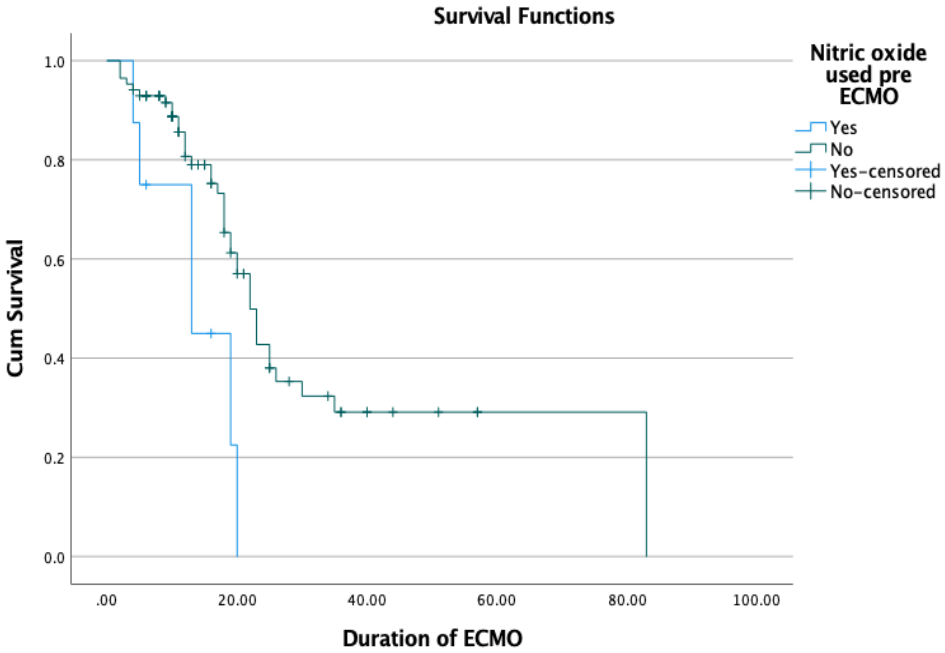
Obesity Cat-Normal Weight= <25Kg/m^2, Over Weight= >24Kg/m^2, Obese=29-39Kg/m^2, Extremely Obese=>39Kg/m^2. Based on WHO guidelines (2022)

P<0.05 indicates statistical significance

4.2 Pulmonary function

Survivors were seen to have higher peak inspiratory pressure (PIP) values before the initiation of ECMO (Md=31.5, U=794.5, z=-2.05, p=0.040, r=0.2) than non-survivors (Md=30.0) (objective 2). The percentage of patients receiving nitric oxide was not significantly different (*p*=0.143) in patients who survived (n=49) compared to those who didn't (n=44), however, it was associated with a poorer prognosis (HR=3.047, CI=1.247-7.447, *p*=0.015) with shorter survival times (13 days (3.161-22.839) vs 22 days (19.116-24.884))(figure 12) (objective 3). 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=1.300-488.694; *p*=0.033) albeit with wide confidence intervals (*appendix 2*).

Figure 13: Kaplan-Meier table for Nitric Oxide



Duration of ECMO=days

Table 15: 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		
FiO_2 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 (cmH_2O)	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 (cmH_2O)	10.5 (4.0)[b]				10.00 (17)			12.00 (12)	0.671[c]	1.013 (0.920-1.116)	0.788		

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]
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_2 ratio, 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	1	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, FiO_2=Fraction of inspired oxygen, 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

4.3 Drug therapy

It can be seen that the majority of patients that underwent ECMO therapy had received neuromuscular blockade (89%) and were supported with noradrenaline (73%). However, the drug regimen received by patients pre-ECMO was shown to have no significant effect on the outcome of interest, namely survival.

Table 16: Pre-ECMO drug therapy

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]
Neuromuscular blockade	89	95.7	47	52.8		42	47.2		1.000[e]	0.405(0.095-1.723)	0.221	22.000 (19.265-24.735)	0.200
Noradrenaline	73	78.5	39	79.6		10	20.4		0.985[d]	1.179(0.565-2.461)	0.662	20.000 (16.727-23.273)	0.654
Adrenaline	2	2.2	1	50		1	50		1.000[e]	1.398(0.190-10.258)	0.742	20.000 (-)	0.736
Dexamethasone	49	52.7	21	42.9		28	57.1		0.484[d]	0.854(0.462-1.579)	0.614	23.000 (18.967-27.033)	0.607
Tocilizumab	18	19.4	11	61.1		7	38.9		0.593[d]	0.767(0.341-1.725)	0.521	25.000 (18.047-31.953)	0.511
Remdesivere	15	16.1	6	40		9	60		0.428[d]	1.778(0.849-3.725)	0.127	19.000 (9.968-28.032)	0.114
Hydroxychloroquin	3	3.2	0	0		3	100		0.102[e]	2.809(0.845-9.238)	0.089	17.000 (7.398-26.607)	0.071
Tamiflu	1	1.1	0	0		1	100		0.473[e]	0.601(0.218-11.778)	0.644	20.000 (-)	0.633

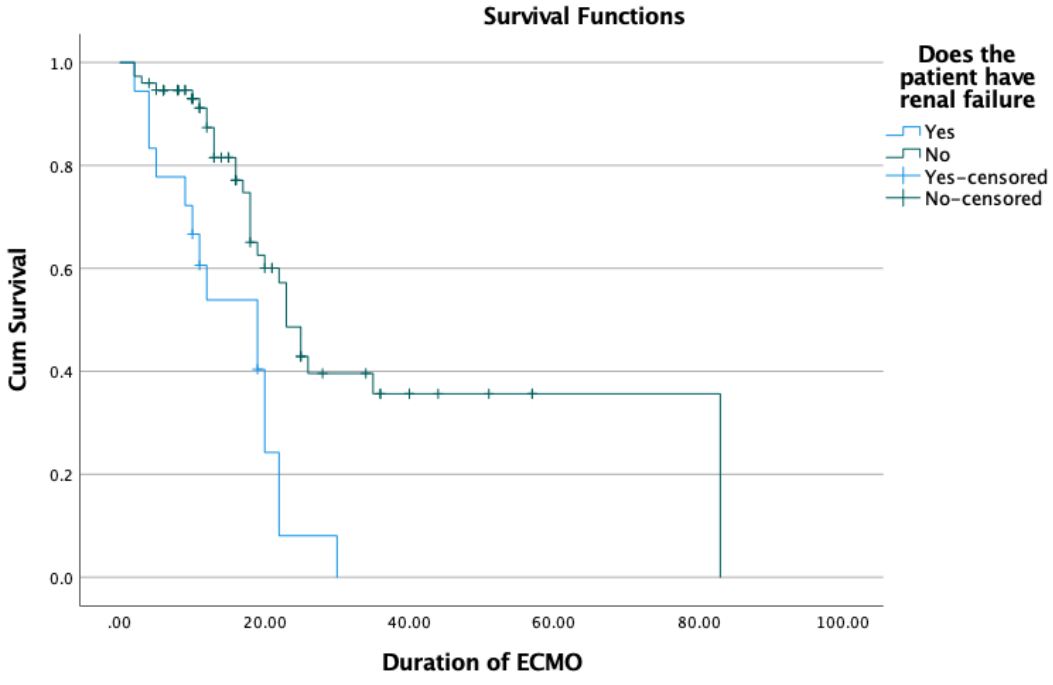
[a]=mean (SD), [b]=median (IQR), [c]=Mann-Whitney U test, [d]=Chi-square test, [e]=Fisher exact test, [f]=Independent T-test, [g]=*p* value based on Log Rank test

P<0.05 indicates statistical significance

4.4 Renal/liver function

The percentage of patients with renal failure as defined by an AKI staging score of ≥1 was significantly higher in the non-survivor group (X^2(1,n= 93) =11.618, p=0.002, phi=-0.35) (objective 2).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 (*appendix 2*)when controlling for age (HR=2.969, CI=1.551-5.683, *p*=0.001) (objective 4). The median time to death as assessed by the Kaplan-Meier analysis was 19 days (9.466-28.543, *p*=<0.01) compared to 23 days (19.795-26.205) for patients without AKI (objective 3).

Figure 14:Kaplan-Meier table for renal failure

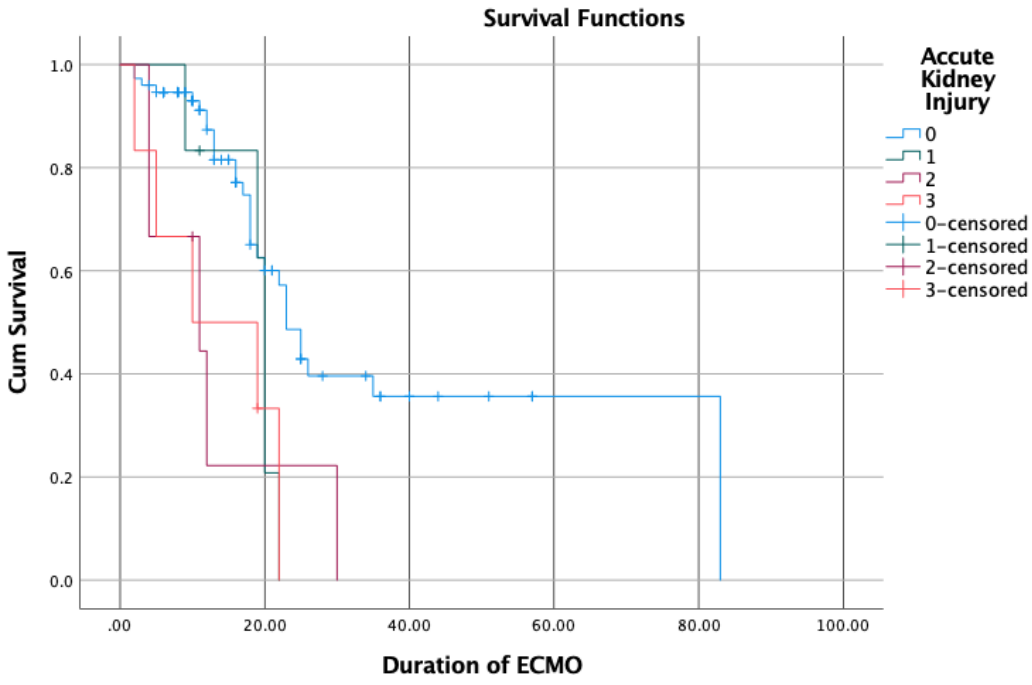


Duration of ECMO in days.

When assessing AKI categories individually (X^2(3,n=93)=11.618, p=0.001, C=0.4) 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 (*appendix 2*).

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) (objective 3).

Figure 15: Kaplan-Meier table of AKI staging



Duration of ECMO in days

Blood urea values were found to be significantly higher (Md=9.9, U=1343.0, z=2.039, p=0.041, r=0.2) 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 (X^2 (1,n=93)= 10.538, p=0.01, C=0.4). 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) (*appendix 2*) (objective 4). A significantly reduced median time to death of 19 days (17.192-20.808, *p*=0.003) was seen for those that received peri-ECMO CVVH vs 25 days (21.418-28.582, *p*=0.004) for those that did not (*Table 22*) (objective 3).

Table 17: 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	16.7		15	83.3		**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	9	9.7	2	22.2		7	77.8		0.079[e]	1.927(0.851-4.365)	0.116	20.000 (0-40.444)	0.102
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		
Albumen (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,

Renal impairment= AKI>0

4.5 ECMO data

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 better prognosis than those that did not require one (HR=0.255, CI=0.089-0.731, *p*=0.011) (objective 2). 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 (X^2(8,n=93)=16.600,p=0.035, C-0.4) 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 that 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 (Md=12, U=639.0, z=-3.534, p<0.001, r=0.4) 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).

There was no Cox survival analysis for the 'time on ECMO' variable as the time component of the analysis was also the covariate to be calculated.

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 (M=84.730,

SD=15.600; t(79)=2.270, 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 18: 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^{291})	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**		
Pre-ECMO Systolic 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		
Pre-ECMO 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		
Pre-ECMO 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

4.6 Blood product transfusion and blood type

The peri-ECMO transfusion of fractionated blood components was assessed in the survival and non-survival groups. Normalisation of patient weight and duration of ECMO was undertaken for blood component volume transfused in order to take into consideration the size of the patient on the volume of blood products received and the duration of time spent on ECMO support. It was found that the normalised volumes 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 normalised transfusion volume of Fresh Frozen Plasma (FFP) (MD-0(10), U=1320.0, Z=2.387, P=0.009, r=0.3) (HR=1.559,CI=1.246-1.952, *p*<0.001) and Platelets (Md=0(0.1), U=1313.5, z=2.037, p=0.010, r=0.2) (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 *(Table 19).*

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 ('Blood group basics - NHS Blood Donation', no date), O (42%) was the most common followed by A (33%), B (13%) and lastly AB (5%). 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 (objective 1). 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 (*table 20*) 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) *(Figure 16).*

Figure 16:Kaplan-Meier table of ABO blood groups

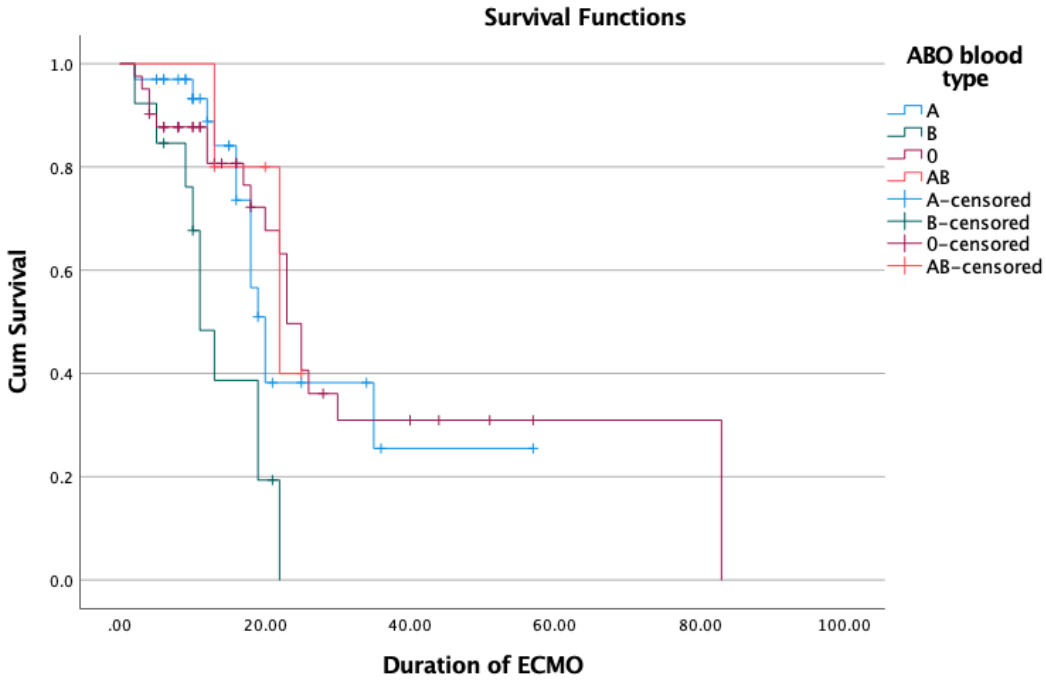


Table 19: Blood data

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]
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)	
Units of albumen transfused (n)	0 (1.50)[b]				0 (7)			0 (10)	0.312[c]	0.888(0.762-1.034)	0.127		
Volume of albumen transfused (mls)	0 (750.0)[b]				0 (3500)			0 (5000)	0.312[c]	1.000(0.999-1.000)	0.127		
Albumen to body weight index (mls/kg)	0 (8.53)[b]				0 (45.45)			0 (65.5)	0.265[c]	0.981(0.956-1.007)	0.156		
Albumen vol to time on ECMO index	0 (49.1)[b]				0 (125.0)			0 (1000.0)	0.275[c]	**1.003(1.001-1.005)**	**0.002**		
Albumen vol/ Weight/ Time on ECMO Index	0 (0.52)[b]				0 (1.89)			0 (11.11)	0.216[c]	**1.395(1.157-1.681)**	**<0.001**		
Units of RBC transfused (n)	6 (9.50)[b]				5 (45)			8.5 (30)	**0.039[c]**	**0.961(0.926-0.998)**	**0.039**		
Volume of RBC transfused (mls)	1650.0 (2475.0)[b]				1375 (12375)			2337.5 (8250)	**0.045[c]**	**1.00(1.00-1.00)**	**0.028**		
RBC to body weight index (mls/kg)	17.68 (19.69)[b]				13.614 (89.380)			25.639 (150.00)	0.051[c]	0.988(0.976-1.001)	0.070		
RBC vol to time on ECMO index	120.614 (151.06)[b]				110.0 (395.31)			131.761(1237.5)	0.062[c]	**1.004(1.002-1.005)**	**<0.001**		
RBC vol/ Weight/ Time on ECMO Index	1.302 (1.56)[b]				1.217 (4.04)			1.526 (15.28)	0.09[c]	**1.266(1.147-1.397)**	**<0.001**		

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]
Units of FFP transfused (n)	0 (1.0)[b]				0 (5)			0 (10)	**0.017**[c]	1.024(0.910-1.151)	0.695		
Volume of FFP transfused (mls)	0 (225.0)[b]				0 (1125)			0 (2250)	**0.017**[c]	1.000(1.000-1.001	0.695		
FFP to body weight index (mls/kg)	0 (2.64)[b]				0 (14.06)			0 (28.64)	**0.014**[c]	1.025(0.978-1.074)	0.308		
FFP vol to time on ECMO index	0 (9.0)[b]				0 (70.31)			0 (450.0)	**0.010**[c]	**1.010(1.005-1.015)**	**<0.001**		
FFP vol/ Weight/ Time on ECMO Index	0 (0.90)[b]				0 (0.68)			0 (10.0)	**0.009**[c]	**1.559(1.246-1.952)**	**<0.001**		
Units of platelets transfused (n)	0 (3.0)[b]				0 (9)			1 (16)	**0.042**[c]	0.999(0.912-1.095)	0.998		
Volume of platelets transfused (mls)	0 (750.0)[b]				0 (2250)			250 (4000)	**0.042**[c]	1.000(1.000-1.000)	0.988		
platelets to body weight index (mls/kg)	0 (7.28)[b]				0 (19.48)			2.300 (48.19)	**0.035**[c]	1.004(0.973-1.035)	0.822		
Platelet vol to time on ECMO index	0 (34.9)[b]				0 (125.0)			11.384 (250.0)	**0.011**[c]	**1.007(1.002-1.012)**	**0.009**		
Platelet vol/ Weight/ Time on ECMO Index	0 (0.34)[b]				0 (1.0)			0.123 (3.18)	**0.010**[c]	**1.797(1.161-2.783)**	**0.009**		
Units of cryoprecipitate transfused (n)	0 (1.50)[b]				0 (9)			0 (10)	0.118[c]	0.931(0.821-1.057)	0.270		
Volume of cryopreciopitate transfused (mls)	0 (30.0)[b]				0 (180)			0 (200)	0.118[c]	0.996(0.990-1.003)	0.270		
Cryoprecipitate to body weight index (mls/kg)	0 (0.321)[b]				0 (1.75)			0 (2.25)	0.103[c]	0.823(0.454-1.492)	0.521		
Cryoprecipitate vol to time on ECMO index	0 (1.40)[b]				0 (13.33)			0 (20.0)	0.063[c]	**1.113(1.021-1.214)**	**0.015**		
Cryoprecipitate vol/ Weight/ Time on ECMO Index	0 (0.1)[b]				0 (0.12)			0 (0.25)	0.057[c]	**23509.940(51.968-10635757.2)**	**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

FFP=Fresh frozen plasma, RBC=Red blood cell

P<0.05 indicates statistical significance

Table 20: ABO comparison and multivariable model

ABO Blood Group	Cox univariate survival analysis		Cox Multivariable survival analysis	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
A	Ref		Ref	
B	**3.103(1.335-7.212)**	**0.008**	**3.083 (1.326-7.164)**	**0.009**
O	0.860(0.418-1.768)	0.681	0.785 (0.383-1.611)	0.509
AB	0.723(0.162-3.224)	0.671	0.504 (0.064-3.958)	0.515
A	1.387(0.311-6.182)	0.668	1.357 (0.302-6.089)	0.690
B	4.274(0.927-19.710)	0.063	4.202 (0.909-19.420)	0.066
O	1.126(0.259-4.900)	0.874	1.037 (0.235-4.579)	0.962
AB	Ref		Ref	
A	1.217(0.591-2.508)	0.594	1.274 (0.621-2.614)	0.509
B	**3.745(1.649-8.505)**	**0.020**	**3.927 (1.728-8.926)**	**0.001**
O	Ref		Ref	
AB	0.807(0.185-3.515)	0.775	0.642 (0.082-5.003)	0.672
A	**0.325(0.140-0.775)**	**0.009**	**0.322 (0.138-0.748)**	**0.008**
B	Ref		Ref	
O	**0.267(0.118-0.606)**	**0.002**	**0.275(0.112-0.590)**	**0.001**
AB	**0.215(0.047-0.992)**	**0.049**	0.237(0.051-1.097)	0.065

P<0.05 indicates statistical significance

Multivariable regression analysis adjusted for ethnicity (BAME)

4.7 Pre ECMO blood results

Pre-ECMO blood gas results were analysed using the most recent results before the implementation of ECMO (all within 12 hours of cannulation). Blood pressure measurements were the last taken before ECMO cannulation (within 30 mins). Non-survivors were seen to be more acidotic (Md=7.275, U=761.00, z=-2.441, p=0.015, r=0.3) (HR=0.023 CI=0.002-0.210, $p<0.001$) and have lower bicarbonate (HCO_3) concentrations (M=25.302, SD=5.871, t(91)=2.004, p=0.045, two tailed) than survivors (pH Md=7.330) (HCO_3 M=27.512, SD=4.748). Non-survivors also had lower arterial saturations (SaO_2) (Md=88.0, U=779.5, z=-2.164, p=0.030, r=0.2) and higher International Normalised Ratios (INR) (Md=1.1, U=501.5, z=2.918, p=0.004, r=0.4) (HR=2.571, CI=1.438-4.598, p=0.001) than survivors (SaO_2 Md=91.00) (INR Md=1.00)(objective 1). 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 21).*

Table 21: Pre-ECMO blood result

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, PO2=Partial pressure of oxygen

PT=Prothrombin time, SaO_2=Saturation of arterial oxygen

P<0.05 indicates statistical significance

4.8 Pre-ECMO Risk Stratification Scores

Prior to the referral of prospective patients for ECMO, referring centres calculated potential 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 *(Table 23).*

Table 22: Peri-ECMO data

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]
Cardiac arrest peri	2	2.2	0	0		2	100		0.221[e]	3.682(0.869-15.603)	0.077	10.000 (-)	0.054
Prone peri	3	3.2	1	33.3		2	66.7		0.601[e]	2.565(0.609-10.802)	0.199	19.000 (-)	0.176
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**

[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 23: Pre-ECMO risk stratification score

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]
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 Scale Percentage									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 (-)	

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]
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 Scale									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 for ARDS									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

Analysis by wave

The statistical analysis by wave was carried out (analysing all variables of patients in wave 1 and also for wave 2 of the pandemic individually) but due to the small numbers of the cohorts (wave 1 n=44 and wave 2 n=49) the statistical analysis, when compared to the combined study of both groups, was seen to have a large effect on the statistical analysis of the data as stipulated by the “law of small numbers” (Button *et al.*, 2013). Due to these discrepancies, this analysis was not included in this treatise.

5 Discussion

To date, there have been publications addressing the application of VV-ECMO as a viable, cost effective bridge to recovery for patients with COVID-19 induced ARDS (Yang *et al.*, 2021),(Daniela *et al.*, 2021),. Most have been case reports which generally centred on the application of ECMO for patients presenting with COVID-19 induced respiratory failure in a non-ECMO centre. These findings should be taken with caution, case reports are considered to be at the bottom of the hierarchical pyramid of evidence based practice in medical literature. Non-quantitative in nature, this type of research design is a good approach to generate a hypothesis or concept for future studies; however, one must follow this up with more robust research methodologies such as randomised controlled trials or cohort studies in order to make more scientifically sound empirical statements (Alsaywid and Abdulhaq, 2019).

The viability of data generated from a hospital that does not normally provide ECMO therapy pre-pandemic is also questionable. The provision of ECMO treatment is a very technical, labour/equipment intensive method of advanced respiratory care. It is highly discouraged for a non-ECMO unit to provide an ECMO treatment as it sees fit, the lack of experience, support, knowledge and logistics can incur a greater risk of morbidity and death in comparison to a commissioned unit.

ELSO stipulated in its interim guidelines for the management of ECMO during the pandemic that-

"Due to the intensive hospital resource utilization, substantial staff training, and multidisciplinary needs associated with starting an ECMO program, ELSO recommends against starting new ECMO centres for the sole purpose of treating patients with COVID-19. As mentioned in a recent article by ELSO leaders in JAMA, for inexperienced centres, "ECMO is not a therapy to be rushed to the front lines when all resources are stretched during a pandemic". A list of experienced ECMO centres is provided on the ELSO website. During the COVID-19 surge, it is reasonable to concentrate those patients with the greatest chance of benefit from receiving ECMO in a hospital where an experienced ECMO team is available".

(Bartlett *et al.*, 2020)

However, it was evident that non-experienced centres were seen to be providing ECMO support, reporting their experiences with ECMO therapy for COVID-19 positive patients with refractory respiratory failure. In a retrospective, multicentre international, observational study Rabie *et al.* reported a survival rate of 45% in 5 newly established ECMO centres. The reason for this acceptable outcome was purported to be due to the appropriate supervision of regional experts. It was also noted that the rate of prone positioning prior to ECMO was low (52%), and as such it cannot be excluded whether the patients would have responded to this treatment therefore negating the need for ECMO (Rabie *et al.*, 2021). Conversely, Friedrichson *et al.* showed a significantly poor outcome for patients treated with ECMO in

Germany. A large cohort of 4279 patients treated with ECMO in all hospitals in Germany were included in this cohort study. It was found that the mortality rate was extremely high (VA-ECMO=72% and VV-ECMO=65.9%) and as such the recommendations were made that ECMO for COVID-19 patients should only be conducted in high volume centres i.e. centres that had ample experience of managing ECMO support (Friedrichson *et al.*, 2022).

Many of these studies used very small cohorts in their statistical analysis, under powering the findings (Rinewalt *et al.*, 2020), (Akkanti, Erik E Suarez, *et al.*, 2022), (Zeng *et al.*, 2020), (Pans *et al.*, 2022). A low sample size study, low effects or both, negatively affects the chances that a nominally statistically significant result actually reflects the true effect thus skewing the findings of these publications (Button *et al.*, 2013).

5.1 Findings

The findings of this study were able to fill a knowledge gap in the present academic understanding of COVID-19 induced ARDS and its treatment with VV-ECMO.

From assessing the data, we identified a cohort of patients that had a poorer outcome and a shorter time to death after VV-ECMO support had been implemented.

5.1.1 Pre-ECMO variables

Clinically, it was highly important to identify prospective VV-ECMO patients that would respond effectively to the treatment in order for a successful triage. The importance of

being able to highlight pre-ECMO variables that contributed to the outcome were of high importance. These can be seen below.

Pre-ECMO variables

5.1.2 Blood results

In this study, patients that had a poorer outcome on VV-ECMO support displayed a pre-ECMO acidaemia with a low HCO_3, SaO_2 and mean systemic arterial blood pressure and a higher PIP. These are all concomitant with ARDS and mainly the sepsis associated with this condition. Stapleton in a 2005 paper stated that sepsis was the major cause of death in the ARDS patient (Stapleton, R. Wang, B. Hudson,L, 2005) while only 16% of deaths were due to insupportable respiratory failure (DiFonzo and Bordia, 1998).

5.1.3 pH

This acidaemia finding was mirrored by Chong et al in a 2022 systematic review looking at 728 patients from 16 eligible studies (Chong, Saha and Medarov, 2022).pH was seen to be lower in non-survivors (mean 7.33 survivors vs 7.26 non-survivors $p<0.001$) and were comparable to our findings of 7.330 in survivors and 7.275 in non-survivors. Dreier *et al.* also demonstrated a poorer outcome for patients with a lower pH (survivors 7.33 vs non-survivors 7.18 $p<0.001$) (Dreier *et al.*, 2021); however, this was a relatively small study (n=16). Biancari *et al.* also found that a decreased arterial pH before the implementation of ECMO was significantly associated with early mortality (Biancari *et al.*, 2021). This detrimental attribute of a low arterial pH was a common finding amongst authors and very few showed no correlation with pH and outcome (Pans *et al.*, 2022).

5.1.4 PCO_2

In this study, higher PCO_2 levels were seen to contribute to a poorer prognosis. This observation is part of the ARDS picture with other studies showing that hypercapnoea is a marker of poor prognosis in patients with ARDS (Nin, Angulo and Briva, 2018). Both groups were severely hypercapnic (>6.7 kPa) with a non-significant higher PCO_2 in the non-survivor group, again, a similar finding as the Pans study differing only by lower PCO_2 results (in the Pans study) (Pans *et al.*, 2022).

5.1.5 HCO_3

High HCO_3 concentrations (>27.0 mEq/L) in the blood of COVID-19 positive patients have been shown to be associated with clinical worsening within 90 days (HR=2.98 95% CI=1.04-8.53, p=0.042) as has low HCO_3 concentrations (<21.0 mEq/L) (HR=3.80 95% CI=1.46-9.89, p=0.006) in a twin centre study of 60 patients. The low HCO_3 group showed a 300% increased probability of death (HR=4.01 95% CI=1.29-12.4, p=0.016) within 90 days compared to the normal concentration category (Sada *et al.*, 2022). This studies high concentration category was comparable to the mean concentration of survivors in this study whereas the non-survivors HCO_3 was within the normal reference range of Sadas study. Although this study did not show an effect on prognosis by HCO_3 levels, the survivors had a significantly higher concentration than the non-survivors. Low HCO_3 levels with a metabolic acidosis (thus a low pH) are associated with multiple organ damage and are sometimes seen in COVID-19 patients. The low concentration in the non-survivor group was low in relation to the survivor group, however, a HCO_3 concentration of 25 mEq/L is considered to be normal for the general population (Castro, 2022). Sadas study did not include patients being

supported by ECMO and thus the findings can only be loosely correlated to this study's findings.

5.1.6 Lactate

The difference in serum lactate levels between survivors (1.5 mmol/L) and non-survivors (1.8 mmol/L) was not significantly different (p=0.155), although there was a poorer prognosis for patients with a higher level. The mechanism of lactate production is generally from tissue hypoperfusion and hypoxia which in turn causes a 'lactic acidosis', this could account for the lowered pH. Lactic acidosis is commonly associated with sepsis, septic shock and respiratory failure all of which were common findings in both cohorts of this study. A study by Diaz *et al*. did not show blood lactate levels to be associated with a poorer outcome (HR=1.16 95% CI=0.98-1036, p=0.080) in COVID-19 positive VV-ECMO patients (Diaz *et al.*, 2021) neither did Biancari *et al.* (Biancari *et al.*, 2021), or Saeed *et al.* (Saeed *et al.*, 2022). However, Trejnowska et al. showed that in a retrospective multicentre cohort study of 158 patients, that survivors had a lower lactate level (1.51) than non-survivors (1.93, p=0.008) (Trejnowska *et al.*, 2022).

Our findings of higher lactate levels in non-survivors could be due to the patients in this study being sicker and more moribund than in other studies that reported no difference. It should be noted that the time to ECMO in both survivors and non-survivors was 7 days, showed no significant different in means and had no effect on prognosis. One could postulate that a longer time in respiratory failure before ECMO treatment (longer time to ECMO period) could plausibly cause the lactate levels to be elevated, but this did not differ between groups.

5.1.7 SaO_2

The survivors, pre-ECMO, presented with significantly higher SaO_2 levels (91%) than non-survivors. Non-survivors had a median SaO_2 of 88.0% which is known clinically as hypoxaemia (<90%), this was caused by the acute respiratory failure from the SARS-CoV-2 virus. Specific to COVID-19, there is a disparity between hypoxaemia and the functioning of the respiratory system. Normally, hypoxaemic patients present with dyspnoea and tachypnoea, the bodies way to try to restore normal blood oxygen levels. In COVID-19, patients have shown a distinct disparity between the degree of hypoxaemia and the normal functioning of the respiratory system. Commonly, patients experience hypoxaemia but have relatively normal ventilatory mechanics giving this condition its name of “Happy Hypoxia”. It is believed that COVID-19 has an idiosyncratic response on receptors involved with the chemosensitivity of oxygen which brings about the blunted physiological response to the insult (Tobin, Laghi and Jubran, 2020).

The risk of this silent hypoxia is that infected patients will be unaware that they are experiencing hypoxaemia and will not seek medical treatment due to the lack of symptoms. By the time the patient becomes symptomatic, the SaO_2 could be extremely low, which would account for the low median SaO_2 of 89% in the total cohort and would be a relevant factor in the decision making process for the clinician to implement VV-ECMO. As the non-survivor group had a significantly lower pre-ECMO SaO_2 than the survivors we can therefore reasonably deduce that the degree of lung injury and severity of ARDS was significantly greater. This would account for the greater of incidence of death. It would be reasonable to expect other markers of respiratory dysfunction, such as the PaO_2/FiO_2 ratio and PO_2, to be

indicators of outcome; although they were below normal values that did not contribute to the demise of the non-survivor group.

These findings were not reproduced in current literature. Lebreton et al. found no significant difference between the SaO_2 in survivors and non-survivors although mirrored our findings regarding a lower pH in non-survivors (Lebreton *et al.*, 2021). Shuanglei *et al.* found that PaO_2 and the PaO_2/FiO_2 ratio was seen to be lower in non-survivors (Lai *et al.*, 2021) but did not mention SaO_2 ; we did not find these variables to contribute to the demise of the non-survivors.

Pulmonary Function

5.1.8 PIP

PIP was shown to significantly differ between groups, being lower in the non-survivor group (30 vs 31.5, p=0.040). PIP increases with airway resistance from factors including increased secretions and an increased lung compliance, both of which are indicative of ARDS. A PIP of between 30-40 is indicative of respiratory failure so both of the groups in the study only showed minimal signs. A high PIP over time can be responsible for ventilator-induced barotrauma and it would be intuitive to perceive that the survivors would have a lower PIP than the non-survivors, however, they presented with a higher PIP. The difference was minimal, only 1.5 cmH_2O between the two groups with a similar range. Pans *et al.* showed no significant effect on outcome in his 2022 study, however, both groups had lower PIP values than we saw (survivors=27.16, non-survivors=23.91) in this study. Similarities were that the survivor group had a higher PIP and did not fit the respiratory failure criteria but

the findings were not significant (*p*=0.33) and the PIP was measured immediately after placement on ECMO rather than pre-ECMO (Pans *et al.*, 2022).

5.1.9 Nitric Oxide

Used therapeutically as a pulmonary vasodilator to increase pulmonary blood flow, nitric oxide was seen to worsen the prognosis of patients receiving it pre-ECMO. Three time as many patients in the non-survivor group received nitric oxide therapy pre-ECMO than in the survivor group, although this was not significant. As indicated by Cox and Kaplan-Meier survival analysis, patients that received nitric oxide had a 300% greater chance of death with a median time to death of 13 days (Log rank *p*=0.009).

It would be contentious to conclude that the treatment of nitric oxide therapy had a direct effect on the patient outcome of this study. It would be more likely that the bias of confounding by indication was responsible for the relatively poorer prognosis of the non-survivor group. In order to receive nitric oxide these patients would have been far sicker than others which would predispose them to a greater chance of death. In a non-ECMO cohort of COVID-19 positive patients, inhaled nitric oxide (iNO) was seen to improve outcome and delay respiratory deterioration in COVID-19 induced moderate to severe ARDS (Lotz *et al.*, 2021), and nitric oxide has been purported to inhibit SARS-CoV-2 replication, reduce inflammatory cell mediated lung injury and attenuate cytokine release making this an ideal therapy to limit the impact of this virus (Kobayashi and Murata, 2020). However, nitric oxide has been shown to increase the incidence of renal dysfunction in an ARDS cohort (Ruan *et al.*, 2015).

5.1.10 Lung Consolidation

All patients in the study presented with some degree of lung consolidation as would be expected for prospective ECMO patients with severe ARDS. A greater proportion of patients had an increasing severity of consolidation with few having 1 quadrant (n=1), more having 2 (n=9), even more with 3 (n=10) and the majority with 4 (n=73).

Although there was no difference between the groups, it was shown, statistically, that 4 quadrant consolidation improved the prognosis of recovery (HR=0.117, 95% CI=0.015-0.921, *p*=0.042) using 1 quadrant as the reference value conferring a protective effect.

This counter intuitive observation may be a statistical anomaly due to the very high numbers of patients with 4 quadrant consolidation in comparison to all other categories. Based on this skewing of data it would be remiss to postulate that patients with a greater degree of lung injury would have a greater chance of survival than those with minimal injury when treated with VV-ECMO.

5.1.11 Total duration of MV

It can be seen that the survivors spent more time on MV (23 days) in comparison to the non-survivors (21 days). This is due to the demise of the non-survivors being more rapid than the survivor cohort, however, the difference between groups was not statistically significant. This observation may have been responsible for the protective effect seen in the survival analysis which showed that every day supported by MV conferred a 10% increase in survival.

Research on this variable is sparse and comparable studies regarding MV have concentrated on the duration of MV before the implementation of ECMO. The time between intubation and ECMO has been shown to affect the outcome of treatment in ARDS patients, the longer the period the poorer the outcome (Hermann *et al.*, 2022). Giraud et al. concluded that implementing VV-ECMO for COVID-19 patients that have been treated with MV >7 days was a futile exercise (Giraud *et al.*, 2021). Drier also found that MV before the implementation of ECMO to be longer (19 days) in non-survivors than survivors (5 days, p=0.002) (Dreier *et al.*, 2021).

This study did not replicate these findings. All patients in this study had a MV time before ECMO of <9 days, so minimal by comparison to other studies.

5.1.12 Renal and Liver Function

Pre-ECMO renal function was seen to significantly affect therapy outcome. 19% of patients in the study had a degree of renal impairment of which 83.3% died (p=0.002), having pre-ECMO renal impairment increased the chance of death by 300% (p=<0.0001) with a median time to death of 19 days (p<0.001). When breaking down this observation to severity of renal dysfunction we saw that only when patients reach an AKI score of 2 and above do we see a detrimental effect on the prognosis. Unintuitively, we showed that patients with an AKI score of 2 had a worse prognosis than those with an AKI score of 3, one would expect a poorer prognosis with increasing severity. However, Kaplan-Meier showed a median time to death for an AKI of 2 to be 11 days and 3 to be 10 days indicating a more rapid demise for an increasing degree of renal dysfunction.

An elevated urea in all patients was seen, with the non-survivor group being significantly higher, the aetiology of which could possibly have been renal impairment, although, one cannot be certain without further investigation. This observation did not contribute to the prognosis of the group.

The use of pre-ECMO haemofiltration was relatively low (10%) for the patients with renal impairment (19%). The use of haemofiltration at this juncture was seen to have no effect on outcome. When compared to the usage of CVVH peri ECMO, we saw an increased threefold usage (32%), a significant increase in mortality and a poorer prognosis with a median time to death of 19 days. The reason for usage of CVVH both pre and peri ECMO was not noted in the patient documents as this technique may be used to clear metabolites or reduce blood volume due to renal failure or over transfusion.

As expected, renal function was seen to play a large part in the efficacy of ECMO, many authors have reported similar findings to this study. Chong, Saha and Medarov stated that the use of renal replacement therapy (RRT) is a predictor of death for COVID-19 patients on VV-ECMO (Chong, Saha and Medarov, 2021). Salazar *et al.* showed a very poor prognosis (HR=5.78, 95% CI=2.39-13.94, $p<0.01$) for patients receiving this therapy in conjunction with ECMO (Salazar *et al.*, 2022) as did Lorusso *et al.* (HR=1.85, 95% CI=1.44-2.37*, no p indicated*) (Lorusso *et al.*, 2022). The aforementioned studies did not stipulate whether the use of CVVH was pre or peri ECMO so a direct comparison may not be made, but still, these highly significant observations make the knowledge of renal function for prospective ARDS VV-ECMO patients of high importance, not only for a COVID-19 cohort but ARDS of all genesis (Devasagayaraj, Cavarocchi and Hirose, 2018), (Lan *et al.*, 2010).

Variables pertaining to pre-ECMO hepatic function were found to play no part in the outcome of treatment. Acute liver injury (ALI) has been seen to be a recognised complication of COVID-19 in ICU patients (Effie Polyzogopoulou, Pinelopi Amoiridou, Theodore P Abraham, 2022). None of the studies at the time of writing have addressed hepatic function in the COVID-19 positive ECMO patient.

5.1.13 Mean blood pressure

A common symptom of ARDS is hypotension (Tignanelli *et al.*, 2019). The MAP of non-survivors was seen to be significantly lower than that of survivors but had no prognostic effect on outcome. This was not seen in research by Haroun et al. (Haroun *et al.*, 2022). Systolic and diastolic pressures were not significantly different between the groups.

5.1.14 INR

The pre-ECMO INR of the non-survivors was seen to be significantly higher with a poorer prognosis than the survivor group. It was not uncommon practice to prescribe anticoagulant therapy to COVID-19 positive patients, especially on ICU. The incidence of venous thromboembolisms (VTE) in COVID-19 patients was seen to be more common than in the general populous and are an independent predictor of poor outcome (Behnood B *et al.*, 2020). It is believed that this comes from the increased hypercoagulability due to the immune response to the virus (Bradbury and McQuilten, 2022).

None of the patients that were accepted for ECMO had a noticeable haemorrhage before cannulation, neither did they bleed more excessively upon cannulation. The rationale for anticoagulation at each referring unit was individual centric, sometimes with a different regimen for each referring clinician, making this difficult to monitor. Upon commencement of ECMO, each patient would receive an anti-coagulation drug into the circuit in order to

negate emboli production due to the action of the non-biological circuit with the patient's blood.

5.1.15 Survival Scores

There was no statistical difference between the two groups for the Murray score, SOFA score, PRESERVE score or the Horowitz index. This shows that these prognostic aids should be used with caution in this cohort. As previously commented upon, frequently these prognostic models are used incorrectly by clinicians, Majithia-Beet, Naemi and Issitt found that both the RESP and PRESERVE scores were being used for the wrong modality of ECMO (i.e., VV instead of VA and vice versa) in studies (Majithia-beet, Naemi and Issitt, 2022). SOFA, RESP and PRESERVE were considered not to be useful in the decision to implement VV-ECMO in COVID-19 patients by Supady *et al.* (Supady *et al.*, 2021). Gannon *et al.* in his study using data from more than 7000 patients also found that the RESP score performed poorly on patients with COVID-19 (Gannon *et al.*, 2022).

We found that having a RESP score of 4 conferred a better prognostic outcome but all of the other points on the RESP score were not significant. Also, it was demonstrated that the higher the RESP class, the shorter the median time to death (*Table 23*).

Table 24: Time to death of RESP class

RESP Class	Median Time to Death (days)
1	23
2	22
3	16

Time to death according to Kaplan-Meier, Log Rank *p*=0.012

The RESP in hospital survival score only showed a significant positive prognosis for the 76% category, but also showed that the time to death decreased upon increasing % in hospital survival score (*p*=0.012) (*Table 23*).

Table 25: Time to death of RESP in hospital survival

RESP in Hospital Survival (%)	Median Time to Death (days)
57	16
76	22
92	23

Time to death according to Kaplan-Meier, Log Rank *p*=0.012

This comparable finding is indicative of the same data produced from the RESP test being presented as both in-hospital survival and RESP Class, essentially 2 different ways.

We showed that the RESP score did display a degree of discriminative ability in this COVID-19 cohort. The higher the RESP class, the shorter the survival time also seen as the lower the % in hospital survival, the shorter the survival time.

Other authors also found that RESP was of some predictive value. Pellegrini *et al.* and Schmidt *et al.* found that RESP was seen to have an effective discriminative ability (p=0.016)

to triage prospective VV-ECMO patients (Pellegrini *et al.*, 2021), (Schmidt *et al.*, 2014a); however, this research was on non-COVID ARDS patients and therefore the results may not have been reproducible on this cohort.

Figure 17: Interaction of Pre-ECMO Variables

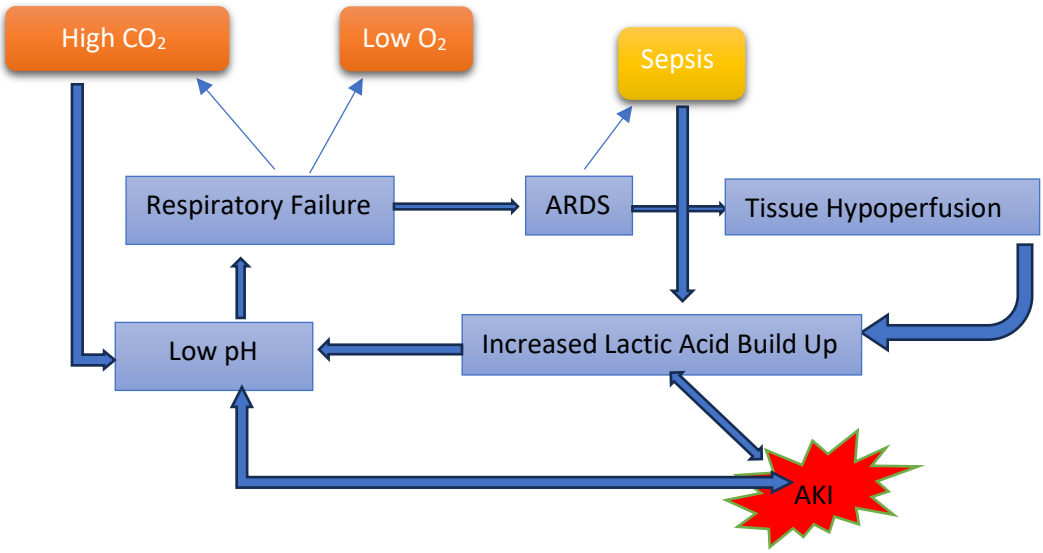


Figure 17 shows the interactions and implications of some of the PRE-ECMO variables. This positive feedback loop highlights the multifactorial respiratory failure picture of the ARDS patient.

5.1.16 Peri-ECMO variables

An outcome of interest was to identify peri-ECMO independent risk factors for death in the study group. Although this won't allow us to assess the viability of patients during treatment triage, the findings will aid us as an indication of the deterioration of patients on VV-ECMO. This early warning can serve as a trigger to modify treatment to pre-empt a known possible outcome.

Blood transfusion

Over the course of ECMO therapy it is not uncommon for patients to receive blood transfusions. ECMO in itself can be a catalyst for an increase in bleeding and depletion of clotting factors and platelets. The high sheer forces in the circuit in conjunction with the non-biological-initiated immune response from the tubing and components can create the need for significant transfusions of blood components (Chandler, 2021).

5.1.17 RBC

The most common component transfused was packed red cells, a significantly increased median average was seen to be given to the non-survivor group, although when indexed for time and also time and weight we saw no difference. A better prognosis was seen for the non-indexed variable, but when time spent on ECMO, and patient size was taken into consideration we saw that a poorer prognosis was actually the case. Indexing the values

with time and patient size will give a more accurate comparison of transfusion requirements for reasons of direct comparison. It is reasonable to state that the larger the patient, the greater the volume of transfusion that will be required, also the longer the time spent on ECMO (therefore the longer the patient is subjected to the stimulus of the haemorrhagic diathesis) the more transfusions will be required. As the input for these variables is from the same data, a degree of comparability will be seen.

5.1.18 Albumin

There were no difference between the groups for the albumin transfused, however, it was seen that there was a 40% increase in chance of death in the vol/weight/time variable.

5.1.19 FFP

There was significant difference between groups in all variables of FFP transfusion with a large range difference between the 2 groups in the vol/weight/time variable and also a poorer prognosis.

5.1.20 Platelets

There was significant difference between groups in all variables of Platelet transfusion. it was seen that there was an 80% increase in chance of death in the vol/weight/time variable.

5.1.21 Cryoprecipitate

No difference between groups was observed although a poorer prognostic outcome was seen in the vol to time indexed variable. The vol/weight/time variable showed an excessively large hazard ratio, this may have been due to the very small amount of this product being used for ECMO patients in this study.

It can be seen from the data that the transfusion of any blood product can be seen as an indication of poor prognosis peri-ECMO (Doyle *et al.*, 2020). The transfusion of platelets can be seen to be a more important indicator of poor prognosis than the other blood products. The requirement of platelets can be an indication of major bleeding or a disseminated intravascular coagulation type of condition, specific to COVID-19 patients (Asakura and Ogawa, 2021), (Levi and Iba, 2021), (Merrill *et al.*, 2020). An increase in the transfusion requirements of any blood product should be seen as a prospective indicator of patient deterioration.

The increased blood product transfusion volumes seen in the non-survivor group are indicative of the concomitant coagulopathies associated with COVID-19 (Hayakawa *et al.*, 2021). Further studies would be beneficial to ascertain whether the blood transfusion requirements in non-COVID-19 ARDS are comparable to those seen in COVID-19 positive patients with ARDS on VV-ECMO.

5.1.22 ABO blood type

The distribution of ABO blood groups between patients in this study were typical for the variability of different ethnicities in this country. There were more type B in the non-survivor group (77%) and type A in the survivor group (61%) although there was no significant difference found between the groups.

Further scrutiny using survival analysis highlighted that type B had a poorer prognosis when using type A as the reference group, the other 2 blood groups showed no significance. From this finding it was decided to use all ABO group types as reference for further information

(*Table 20*). It was seen that type B had a significantly poorer prognosis than all other types for univariate analysis apart from when type AB was used as the reference group. As previously stipulated, ABO blood types vary among ethnic groups with certain blood types being more common in specific ethnicities, therefore It was decided to perform a multivariable analysis controlling for ethnicity (Liu *et al.*, 2017). Ethnicity was seen to have no effect in the prognostic findings when comparing univariate and multivariable results other than when using type B as reference, type AB was not significant in the multivariable model.

Marked significant differences were seen when assessing median time to death, type B had a significantly shorter time to death than all other types.

Table 26: Time to Death of ABO Blood Types

ABO Blood Type	Median Time to Death (days)
A	20
B	11
O	23
AB	22

Time to death according to Kaplan-Meier, Log Rank *p*=0.005

This raises the question of 'does the ABO blood type predispose an individual to a poorer outcome'?

Abegaz , in his paper in 2021 postulated that ABO blood type may influence the risk of different diseases by different known and unknown mechanisms. He stated that non-O

blood types are more susceptible than others to certain diseases (Abegaz, 2021). Vasan *et al*. provided evidence that there was a consistent association between non-O blood types and VTE's (Vasan *et al.*, 2016), Parente *et al.* found a link between blood type A and ischaemic heart disease (IHD) (Parente *et al.*, 2020) as did Chen (Chen *et al.*, 2016). Su *et al.* stated that ABO blood group appeared to be a prognostic factor in respiratory tract infections with non-O type being more susceptible (Su *et al.*, 2022), this compares with many observations during the COVID-19 pandemic. Authors reported on the association of ABO phenotypes with respect to infection with the SARS-CoV-2 virus and how certain blood types were more susceptible. Blood type O was claimed to have a protective effect against infection and types O and B were more likely to become symptomatic in the presence of a viraemia (Kotila *et al.*, 2021). This resistance was confirmed by many other authors (Latz *et al.*, 2020), (Golinelli *et al.*, 2020), (Ray *et al.*, 2021), (Sertbas, 2021). Very few authors have reported the prognostic value of the ABO blood type, Hultstrom et al. found an association between type A and an increased risk of requiring ICU care (HR=2.01, 95% CI=1.23-3.28, no *p* reported) and 30 day mortality (HR=3.16, 95% CI=1.28-7.77, no *p* reported), whereas Zietz, Zucker and Tatonetti found that blood type A and B was at a decreased risk of death relative to type O (Zietz, Zucker and Tatonetti, 2020).

Clearly there was a general consensus regarding the virulency of the SARS-CoV-2 virus and ABO blood type but not the lethality.

We have shown a positive correlation between blood type B and a poor prognosis for COVID-19 positive patients on VV-ECMO, more work needs to be undertaken in order to bring about a greater understanding of this phenomenon as the implications for using this finding for triaging purposes could be highly contentious or at worse, ethically questionable.

5.1.23 Circuit changes

Sometimes, due to factors such as excessive blood clots in the components of the ECMO circuit or component failure (mainly oxygenator), ECMO circuits may have to be changed out for a new set up during the course of support.

We saw that the survivor group had more changeouts than the non-survivors during their ECMO runs. Twice as many survivors had 1 change out than the non-survivors and 4 times as many survivors had 2 changeouts, however this was not significant. We can see that the survivors (13 days) did not spend longer on ECMO than the non-survivors (17 days), again, this difference was not significant, therefore we cannot attribute the greater number of changeouts being due to the longer duration the patient spent on ECMO, working on the premise that the circuit would have more time to fail the longer it was being utilised.

A better prognosis was seen in patients that had one circuit change out when referenced against no changeouts, however, in the multivariable model (appendix 2) controlling for duration of ECMO, no benefits were seen.

5.1.24 Trial Off

A significant association was seen between survival and the number of trial off periods. In all of the trial off categories (1 to 8) It was found that patients that survived had more trials off than the non-survivors and that over twice as many non-survivors didn't have a trial off period. Patients that had 1 and 3 trials off during the course of their treatment had a better prognosis. The multivariable analysis showed only a better prognosis for the 1 trial off category when controlling for duration of ECMO (*appendix 2*). This is an understandable

observation in the light that patients that were perceived to be 'recoverable' were given extra runs of ECMO whereas patients that were considered to be beyond the point of recovery may not have been. A difficult aspect of ECMO treatment logistically and ethically is the identification of the point in time where further treatment becomes futile and ECMO becomes a palliative bridge to death, this is where outcome 2 can aid patient management by assessing the prospective outcome (Rutz Voumard *et al.*, 2023).

The combined trial off time variable further acknowledged these findings, survivors had a significantly longer combined trial off time than non-survivors indicating more tolerance to autogenous respiratory function indicating an ability to thrive. This longer combined trial off time also indicated a better prognosis.

5.1.25 Non-reproducible results

It was interesting and unsurprising to find commonality between our observations, and those of other authors, confirming our results indicated that there was a predictable defined pathway to the demise of patients supported by VV-ECMO for COVID-19 induced ARDS.

However, some common findings from other research were not seen in our study, these were-

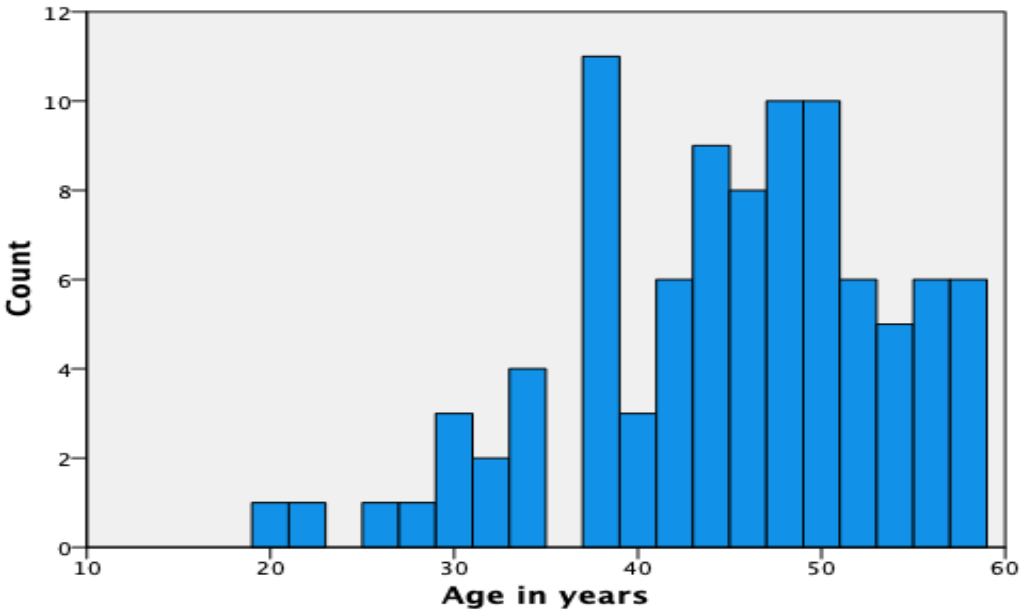
Age

It was commonly accepted that there was in increased incidence of infection by COVID-19 with an increase in age (Takeuchi *et al.*, 2022). It would be highly plausible to relate this predisposition to the failure of an aging immune system and the inability to protect against the virus (Weyand and Goronzy, 2016).

Age has been highly correlated with ECMO prognosis in cohorts of ARDS patients in the pre-pandemic era (Schmidt *et al.*, 2014a)(Baek *et al.*, 2018). Lee *et al.* showed in a COVID-19 positive cohort, that patients supported by VV-ECMO in an age group greater than 65 years had a significantly higher prognosis than younger patients (Lee *et al.*, 2022). Hermann *et al.* showed age to be an independent risk factor for non-survival in a subset of patients aged between 41-70 years of age (OR=2.48, 95% CI=1.32-4.17) and also for patients aged between 71-80 years of age (OR=6.81, 95% CI=2.13-26.90) compared to 19-40 year olds (Herrmann *et al.*, 2022).

By comparing our study demographic to those that showed age to be influential on outcome, we can see that patients in other studies were older.

Figure 18: Distribution of ages in the study



Our patients were younger than those in the aforementioned studies, our youngest being 20 and our oldest 58 years of age. The median age in both survivor (46 range=35) and non-survivor (46 range=38) groups were highly comparable. We cannot compare the variable of age to the previously mentioned findings, what we can say with certainty is that-

"Between the ages of 20 years and 58 years, age does not affect the outcome of VV-ECMO for ARDS patients of COVID-19 origin"

BMI

Obesity has been seen to diminish almost every aspect of health leading to chronic illnesses and a diminished quality of life (Djalalinia *et al.*, 2015).

On the basis of this, it would be understandable if we would see these patients succumb to treatment for COVID-19 on VV-ECMO. However, this was not the case. Our study showed no correlation of the BMI of a patient with the outcome of treatment. Our study groups consisted mainly of obese patients (n=38) so this demographic was not underrepresented in the study.

Other research also showed that there was no association between obesity and survival of COVID-19 positive patients on VV-ECMO (M. Balik *et al.*, 2022), (Farooq *et al.*, 2022). Some studies had reported a protective effect of obesity on survival (Prasad *et al.*, 2023), (Daviet *et al.*, 2021).

Many relate this protective effect of obesity to the 'obesity survival paradox'. This is a recognised phenomenon whereby obesity, presented as a high BMI, in hospital patients, seems to confer a degree of protection associated with an improvement in survival. This proposal is counterintuitive to common general beliefs, as obesity is generally associated with co-morbid chronic illnesses and psychological abnormalities. These have been shown to increase the incidences of complications of critical illnesses. It has also been commented that subjects with a low BMI had a greater incidence of succumbing to chronic illnesses and had an overall higher mortality.

Some authors attribute this phenomena to statistical strategies such as collider bias rather than a direct factor of obesity itself (Cole *et al.*, 2010), (Griffith *et al.*, 2020), (Banack and Kaufman, 2013). This observation clearly requires further research to posit a more definitive understanding.

Ethnicity

Racial and ethnic minorities were seen to exhibit a higher rate of SARS-CoV-2 virus infections, hospitalizations and death in the USA and UK (Lo *et al.*, 2021), cultural, socio-economical and behavioural differences amongst ethnic groups was purported to influence the spread of COVID-19 from the outset of the pandemic (Pan *et al.*, 2020). Rodriguez et al. commented on the observation that hospital mortality from COVID-19 did not differ between race/ethnicity, but black and Hispanic patients were seen to have a greater burden of mortality due to their disproportionate representation of hospitalisations. We included an almost equal representation between white (50.5%) and BAME (49.5%) patients in our study group, there was no indication of one ethnic group succumbing to COVID-19 more than the others. Outcomes were comparable, neither ethnicity carried a better or worse prognosis, there has been no further investigations into ethnicity and outcomes of ECMO during the COVID-19 pandemic or otherwise making a comparison of our findings not possible.

Through the collection and collation of the data generated as part of the patient treatment and care from hospitalisation to discharge, we were able to identify factors that were seen

to influence patient outcome and prognosis. We showed these to be from both pre-ECMO and peri-ECMO data.

5.2 COVID-19 pandemic as a test bed

The patient data used in this study was collected during the time of the COVID-19 pandemic. There was a real need to effectively triage prospective patients for treatment with VV-ECMO. Equipment for ECMO support as well as sufficiently trained staff to manage the circuits were in short supply in comparison to the overwhelming number of patients with refractory respiratory failure. It would be reasonable to postulate that the ARDS seen in this cohort of COVID-19 positive patients was initiated by the SARS-CoV-2 virus and therefore we can state that our findings were specific to ARDS of COVID-19 origin. But it could be a reasonable assumption that if this ARDS seen in these patients was no different to that of any other ARDS origin, we could apply these findings to all ARDS patients.

Lu *et al.* stated that ARDS of COVID-19 origin had its own unique pathophysiological features, naming microthrombus production, endothelial injury and pulmonary capillary hyperplasia as differences to ARDS of other origins (Lu *et al.*, 2022). Bernauer, Alerbrand and Heurich also found similar differences (Bernauer, Alebrand and Heurich, 2023). Other authors have warned against a rigid adherence to the clinical guidelines for the management of ARDS that were derived from pre-pandemic studies, again, citing pulmonary vascular injury and immunothrombosis as the differences (Selickman *et al.*, 2022). However, Bain et al. highlighted the differences between the two, but suggested no deviation in treatment from the current evidence-based management of pre-pandemic ARDS and suggested the need for further studies (Bain *et al.*, 2021). Goligher, Ranieri and

Slutsky recommended a similar approach, in that all ARDS patients irrespective of origin should receive the same ventilation strategies (Goligher, Ranieri and Slutsky, 2021).

The mixed sentiment between authors regarding the parity between ARDS of COVID-19 origin and ARDS of non-COVID-19 origin remains inconclusive. Whilst there is a common agreement that the pathophysiological effects differ between the two, there is still no consensus on how best to manage the pathology and as such, we cannot say with confidence that the findings in this study can be extrapolated to be pertinent for patients with non-COVID-19 ARDS.

5.3 Ethical implications

The origins of this study arose from an inability to provide advanced respiratory support in the form of VV-ECMO for all patients that were deemed to be viable candidates based on pre- COVID-19 criteria. At this time nationally, hospitals were inundated with patients that were prospective VV-ECMO candidates but due to the large influx over a relatively small period of time, it was not possible to treat all-comers. As a result of this, patients were dispatched to hospitals with available ECMO beds, irrespective of geographical distribution or received an alternative therapy.

The aim of this study was to identify specific contextual characteristics pre and peri treatment, associated with outcome during and post ECMO therapy which was accomplished. The rationale behind this endeavour was for the utilitarian application of VV-ECMO.

5.3.1 Utilitarianism

Jeremy Bentham (1748-1832) the English philosopher and social reformer was the father of utilitarianism, he postulated that " actions should be judged right or wrong with relation to the extent they increase or decrease human wellbeing (utility)" When making a choice or deciding between options, utilitarianism holds that the most ethical choice, and therefore the choice to be pursued, is the one that brings about the greater good for the greater number.

The utilitarian application of ECMO was recommended by ELSO for the treatment of COVID-19 in a 2020 guidance document. They stated that-

> *"Younger patients with minor or no co-morbidities are the highest priority while resources are limited. Health care workers are a high priority"*

ELSO here, very early on in the pandemic when very little empirical data was available, clearly were aiming for conserving ECMO, in the first instances, for demographic groups that were believed to have a better prospective outcome than others, and thus possessing the most utility. The inclusion of healthcare workers in this recommendation would be due to the actual utility brought about by the value of their work in the healthcare setting.

Our study highlights the variables that were seen to influence the outcome of COVID-19 patients supported by VV-ECMO, therefore it would be reasonable to say that the provision

of VV-ECMO would bring about the greatest utility when used for this cohort of patients. However, this may bring about other moral implications in patient selection.

Morality versus utilitarianism

We showed that patients with an ABO blood group of B had a poorer prognosis and a shorter time to death when compared to other phenotypes. As previously stated, certain blood groups are more prevalent in specific racial and ethnic groups, blood group B is more common in Asians (25%) and black (19%) ethnicities than white (11%) (American Red Cross, 2023). If we were to triage patients based on their ABO blood group according to the findings of this study, we would be withholding ECMO therapy for more Asian and Black patients than white patients. This may be seen as ethically questionable, irrespective of scientific consensus and needs to be considered when applying these findings.

5.3.2 Distributive justice

Distributive justice, proposed by John Rawles in his seminal work 'A Theory of Justice', concerns the fair allocation of resources of any kind among the diverse members of a community. He states that every person should have or have access to approximately the same level of goods and services, focusing on equal social and economic outcomes. Justification of this concept is on the grounds that all people are morally equal and the best way to promote this idea is through the equal provision of material goods and services. If the tenets of distributive justice were followed in the allocation of ECMO for COVID-19 positive patients, or any patients for that matter, it would not be morally correct to triage

based on the possession of the highlighted variables that influenced the possible outcome to the treatment in question.

The dichotomy between utilitarianism and distributive justice in the allocation of a finite medical treatment needs to be highlighted in the implementation of a triage process. There is *prima facie* evidence for a utilitarian approach, in a time where treatment is finite and not available for all. Saving the most lives as a metric for the successful application of a limited treatment can be seen as a viable method of treatment allocation. However, when the variables that correlate to a poor outcome of treatment are not autogenous but actually congenital or hereditary, distributive justice may be a more equitable approach. Clinicians need to be aware of this philosophical dilemma when justifying treatment.

6 Conclusion

Since ECMO was considered a viable modality of life support for refractory respiratory failure associated with ARDS, academics and clinicians alike have sought to identify a cohort of patients that would be more likely to benefit from this treatment. Members of the EOLIA trial group in 2018 put forward a criteria to be used as guidance for determining patient selection based on which patient would benefit from ECMO support (Combes *et al.*, 2020). This criteria was derived from a study that collected data on a small amount of pre-ECMO variables, significantly less than the current work.

This study set out to address the question of whether it was possible to identify the contextual characteristics that are associated with the survival of patients that were triaged to receive VV-ECMO support for ARDS in order to potentiate the utility of this method of life support. Because of the timing of commencement of data collection, this cohort of patients presented with ARDS of COVID-19 origin

The study objectives were-

1. To investigate the differences in characteristics of Covid-19 induced ARDS patients who survive VV-ECMO vs those who don't.
2. To identify pre and peri-ECMO measures that have an influence on the outcome of VV-ECMO in Covid-19 Induced ARDs patients.
3. To investigate the differences in survival time between patients with certain risk factors.

4. To assess how changes in peri-ECMO and Pre-ECMO variables (risk factors) influence the risk of not surviving the ECMO treatment in Covid-19 induced ARDS patients.

Having identified these characteristics it was postulated that

- Triaging would be more effective.
- A finite resource would be allocated to those who had a better chance of survival.
- A greater utility in treatment would be seen.
- Treatment vs outcome would be more cost effective.

These objectives were met, and the hypothesis confirmed. This study not only assessed the largest number of variables to date of any study, but also these variables were all standard charted and recorded data points that were used by the hospital for all patients, therefore there was no “cherry picking” of variables that could be seen to influence statistical analysis.

The timing of the study was also fortuitous. It only took one year to treat 93 patients with ARDS due to the large influx of patients brought about by the pandemic. To access this number of patients with ARDS pre-pandemic would have taken 8 years at the study centre. Over this extended time period, techniques and experience-based opinion can change drastically due to advances in medical opinion. If this cohort was used for the study, discrepancies could have been introduced. Over the relatively short one year period taken to collect the data, the probability of patients being treated differently would have been very small therefore we can compare ‘like for like’.

The key findings of this study were that we were able to identify a set of pre-prognostic variables that were shown to pre-dispose patients supported by VV-ECMO for ARDS of COVID-19 origin to a poorer outcome than those without these characteristics (*Table 27*).

Table 27: Pre and peri-prognostic variables

Pre-Prognostic	**Peri-Prognostic**
pH	Blood transfusion
PCO_2	Circuit changes
HCO_3	Trial off periods
Lactate	Trial off times
SaO_2	Haemofiltration
PIP	
Nitric Oxide	
Lung Consolidation	
Total duration of MV	
Renal impairment	
AKI	
Urea	
Mean arterial BP	
INR	
RESP score	
ABO Blood Group	

PCO_2=partial pressure of carbondioxide, HCO_3=bicarbonate, SaO_2=saturation of arterial oxygen, PIP=peek inspiratory pressure, AKI=acute kidney injury, BP=blood pressure, INR=international normalised ratio, RESP=respiratory ECMO survival.

These 16 significant study variables possessed commonalities with each other. These variables painted a picture of metabolic derangement with a tendency of renal dysfunction which was seen in patients that had a poorer outcome. The take home message from this finding would be that the triage decision for the implementation of VV-ECMO should be made prior to this derangement, as indicated by the presence of these markers. Once the process has begun, a more detrimental prognosis may be seen.

The ABO blood group association with a poorer prognosis is an interesting and potentially contentious finding. This phenomenon could account for a perceived discriminatory effect if used during triage, although it is easily identified pre-treatment. Clinicians must use this finding at their discretion.

A liberal approach to patient selection should be avoided to mitigate tying up essential equipment that is in short supply. ECMO is a unique treatment in comparison to all other forms of life support, it can keep a patient alive long after all other modalities of life support would have failed. The implications of this are that once a patient is being supported by ECMO, they can remain clinically alive for a prolonged period of time regardless of whether recovery is possible or not. This bridge to futility can be seen if patients are triaged that are not viable candidates for ECMO support; this is why the pre-ECMO triage process is of the utmost importance. To withdraw ECMO life support from patients that are not recovering, but remaining alive solely due to the action of the ECMO circuit is both ethically and morally difficult. This difficulty is also apparent for the patient's relatives, removing life support as there is no hope for the patient recovering from their condition may seem barbaric and unjustifiable to someone with a vested emotional attachment to the patient. It is important for many stakeholders that key indicators of prognosis were found by this study thereby removing the scenario of futility and false hope for patients and relatives alike.

The majority of prognostic scores that we assessed were shown to be unreliable for highlighting prospective patients for VV-ECMO support. As previously stated, they were not designed or calibrated for use with ARDS of COVID-19 origin so their accuracy cannot be relied upon. The RESP score was the only prognostic marker that showed any discriminatory ability in the study. As previously stated, the author had shown the RESP score to be the

more accurate of the scores in his recent publication when assessing non-COVID respiratory failure patients (Majithia-beet, Naemi and Issitt, 2022). If prognostic scores (RESP) are to be used for triage in this cohort of patients, they must be utilised with caution in the knowledge that they were not designed for ARDS of COVID-19 origin.

The triage process itself should be a multi-clinician event, whereby the decision to implement ECMO support is brought about by a team decision rather than an individual input. Strength in numbers and the combined cumulative experience of multiple clinicians makes this approach more robust and reproducible. However, it must be recognised that the experiential ability of clinicians must not go overlooked and whilst we have identified factors that may play a role in the outcome of this cohort of patients, individual clinical decision based on experience should be exercised.

The presence of these pre-prognostic indicators may be influential in the generation of the peri-prognostic conditions, therefore acting on these indicators may be necessary to halt the pathological process seen during ECMO support. We identified 5 peri-prognostic indicators that were associated with a poor outcome, the need for increased blood transfusion in the non-survivor can be seen as a surrogate marker for the deterioration of the patient and as such, an indication of imminent demise. Clinicians may be able to use this as a trigger for the modification of treatment and/or an indication of demise. Circuit changes and trial off times/periods can also be used as an indication of treatment outcome. It is plausible that the increased use of peri-ECMO haemofiltration in the non-survivor group was a continuation of the pre-ECMO renal failure. If the renal failure is selected against during triage, this peri-prognostic indicator may not become apparent.

6.1 Limitations of study

As with all studies there were limitations that require addressing. It cannot go unremarked that this study was retrospective in nature, and it must be recognised that a randomised controlled prospective trial would be a more effective study design.

The monocentric nature of the study may impact upon the generalisability of the findings. The relatively small pool of clinicians found in the centre may not be indicative of a more widespread group.

Although the number of patients involved in this study were relatively large in comparison to other research, from a statistical point of view it would have been more beneficial to have a larger study size.

As mentioned, the reason for the use of haemofiltration was not recorded in the patients documentation therefore it was not possible to ascertain the rational for its use. We cannot rule out that it was used for the reduction of blood volume due to over transfusion rather than an indication of renal failure/impaired renal function. This is one of the problems associated with a retrospective study rather than one prospective in nature.

6.2 Future studies

The inability to generalise between ARDS of COVID-19 origin and non-COVID-19 origin can be seen to be of importance. Future studies to compare the same study variables within

these 2 cohorts to ascertain whether there is any statistical differences would be of value in order to extrapolate the findings.

The influence on outcome of the ABO blood group B is of interest. This has not been observed and addressed by other authors to date. It would be beneficial to see if there was any interaction between ABO blood group and outcome for non-COVID-19 patients receiving VV-ECMO support. This finding may or may not be peculiar to COVID-19.

In summary, 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, a liberal approach to patient selection for the COVID-19 patient should be avoided at this time. Commonly used clinical predictive 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, fulminant respiratory failure and renal failure in order to reap the benefits from ECMO in the support of COVID-19 induced ARDS. By monitoring patients for peri-prognostic triggers, an indication of treatment outcome may be identified.

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8 Appendices

8.1 Appendix 1.

Review

Perfusion

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Efficacy of outcome prediction of the respiratory ECMO survival prediction score and the predicting death for severe ARDS on VV-ECMO score for patients with acute respiratory distress syndrome on extracorporeal membrane oxygenation

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Abstract
Background: Extracorporeal Membrane Oxygenation (ECMO) therapy for respiratory failure is an increasingly popular modality of support. Patient selection is an important aspect of outcome success. This review assesses the efficacy of the popular prognostic tools Respiratory ECMO Survival Prediction Score (RESP) and Predicting Death for Severe ARDS on VV-ECMO score (PRESERVE) for ECMO patient selection.
Methods: A literature search was performed. Six publications were found to match the specified selection criteria. These publications were assessed and compared using the area under the receiver operating characteristic (AUROC) curve statistical method to ascertain the discriminatory ability of the models to predict treatment outcome.
Results: Six articles were included in this review from 306 screened, of which all were retrospective cohort studies. Data was generated over a period of 3–9 years from 13 referring hospitals. Studies consisted of 467 male and 221 female (30 unknown) participants in total with a high heterogeneity. The PRESERVE prognostic model was found to have a higher AUROC score than the RESP model, however both models were found to be sub-optimal in their discriminatory ability. A high chance of bias was seen across all included studies.
Conclusion: It was the findings of this review, indicated by analysis using the AUROC measures, that the prognostic model PRESERVE performed better than RESP for predicting post ECMO therapy outcomes, for patients presenting with Acute Respiratory Distress Syndrome within their respective validated time frames, i.e., RESP at Intensive care unit (ICU) discharge and PRESERVE at 6 months post ICU discharge. However, It was recognized that comparator groups were small thereby introducing bias into the study. Further prospective, randomized studies would be necessary to effectively assess the utility of these predictive survival scores.

Keywords
Acute respiratory distress syndrome, extracorporeal circulation, extracorporeal membrane oxygenation, predication score, PRESERVE, RESP, survival

Introduction

Acute Respiratory Distress Syndrome (ARDS) accounts for around 10% of Intensive care unit (ICU) admissions carrying a mortality of around 45%[1] This pathology manifests in the form of acute respiratory failure with pulmonary oedema, leading to tissue hypoxia and sometimes hypercapnia. The supportive measures for the management of ARDS include attention to fluid

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8.2 Appendix 2.

Multivariable analysis.

Variable	HR (95% CI)	*p* value	Controled Variable
Infections			Immunocompromised
None	REF		
Legionella	0.000(0.000-)	0.994	
Pneumococcus	0.000(0.000-)	0.979	
MRSA	0.000(0.000-)	0.994	
HIV	4.731(0.624-35.888)	0.133	
Time to ECMO (days)	0.974(0.894-1.062)	0.551	Referal region
Mechanical ventilation mode			Referal region, Lung consolidation
CPAP	REF		
Hand Bagged	0.000(0.000-)	0.997	
BIPAP	0.743(0.092-6.036)	0.781	
SIMV	0.874(0.107-7.134)	0.9	
PC	0.000(0.000-)	0.997	
APRV	0.637(0.072-5.646)	0.686	
VCAC	0.000(0.000-)	0.995	
PRVC	1.897(0.079-45.331)	0.693	
CMV	0.000(0.000-)	0.991	
PCV	**25.204(1.300-488.694)**	**0.033**	
Renal impairment	**2.969(1.551-5.683)**	**0.001**	Age
AKI			Age
0	REF		
1	2.353(0.884-6.262)	0.087	
2	**3.520(1.338-9.257)**	**0.011**	
3	**3.253(1.227-8.625)**	**0.018**	
Patient on Haemofiltration (Pre)	1.833(0.779-4.313)	0.165	
Systoilc Blood pressure (mmHg)	0.989(0.977-1.002)	0.092	Age
ABO type			BAME
A	**0.322(0.138-0.784)**	**0.008**	
B	REF		
O	**0.275(0.112-0.590)**	**0.001**	
AB	0.237(0.051-1.097)	0.065	
No. of circuit changes			
0	REF		Duration of ECMO
1	1.042(0.320-3.394	0.945	
2	0.004(0.000-7.223X10^{167})	0.978	
No. of trial off			Duration of ECMO
0	REF		
1	**0.211(0.063-0.701)**	**0.011**	
2	0.644(0.061-7.190)	0.736	
3	0.165(0.010-2.787)	0.211	
4	0.035(0.001-1.436)	0.077	
5	0.012(0.000-2.301)	0.099	
6	0.467(0.001-399.219)	0.825	
7	0.096(0.001-13.839)	0.355	
8	0.041(0.000-25.350)	0.330	
Patient on haemofiltration (Peri)	**2.445(1.325-4.510)**	**0.004**	Age