

Results of a study of some factors influencing mortality during lung replacement therapy for COVID-19

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Abstract

Introduction: On January 18, 2022, the Ministry of Health of Mongolia issued Order No. A/33, titled "On the new approval of temporary guidelines for the diagnosis and treatment of the novel coronavirus infection (COVID-19)." According to this order, extracorporeal membrane oxygenation (ECMO) therapy is recommended for managing severe cases of acute respiratory distress syndrome (ARDS). In August 2020, to enhance preparedness for potential outbreaks of a novel coronavirus, the First State Central Hospital (FSCH) made operational its first heart and lung replacement ECMO machine. Presently, a total of four such machines are operational across the nation. In our nation, the aforementioned treatment was effectively implemented for the first time during the epidemic at the National Center for Communicable Diseases (NCCD) in February 2021, facilitated by the ECMO treatment team associated with the First State Central Hospital (FSCH). Our study was based on the fact that VV-ECMO has been introduced in the medical care services of our country in the most severe cases of COVID-19, yet no significant work has been done to study its complications and mortality. The aim of the study is to investigate various risk factors influencing mortality in severe cases of COVID-19 and to assess the outcomes of VV-ECMO therapy in Mongolia.

Materials and Methods: The study was conducted using a hospital-based retrospective design. The study focused on 66 severe COVID-19 cases admitted to the Intensive Care Units of the National Center for Communicable Diseases (NCCD), First State Central Hospital (FSCH), and Military Central Hospital from February 2021 to July 2022. Data regarding 22 cases that underwent VV-ECMO therapy for respiratory failure with infection, along with 44 patients who met the criteria for VV-ECMO therapy but did not receive it, were retrieved from electronic medical records and intensive care checklists utilizing designated research forms. Statistical analysis of the research data was conducted using SPSS 25 software.

Results: The average age of the 66 cases included in our study was 53 ± 11.7 (ranging from 23 to 69) years, with 54.5% (36) being women and 45.5% (30) men. Among cases without VV-ECMO therapy, 4.5% (2) were treated and 95.5% (42) died. Of the cases receiving VV-ECMO therapy, 36.4% (8) were treated and 63.6% (14) died. In instances of VV-ECMO therapy, younger age ($p=0.001$), higher Murray score or lung injury score ($p=0.023$), and unvaccinated status ($p=0.002$) demonstrated statistically significant differences. Multivariate regression analysis revealed that VV-ECMO therapy (HR 0.307, 95% CI 0.131-0.722, $p=0.007$) significantly decreased the risk of death.

Conclusion:

1. In severe cases of COVID-19, ECMO therapy is predominantly administered to young individuals, patients with significant lung tissue damage, and those who are unvaccinated. The application of VV-ECMO therapy has reduced the risk of death by 70%.
2. In severe cases of COVID-19, the risk of death is increased by blood acidosis, kidney failure, and acute inflammatory complications. Conversely, the risk of death is reduced by adequate sleep, sedation, prone positioning, and muscle relaxation therapy.

Keywords: Mortality, Lung Replacement, Therapy, Covid-19

List of Abbreviations

- ARDS (АИДХШ) Acute respiratory distress syndrome
- MNUMS (АШУИНС) Mongolian National University of Medical Sciences
- BMI (БЖИ) Body mass index
- PRC (БНХАУ) People's Republic of China
- RT-PCR (БХ-ПГУ) Real-time polymerase chain reaction
- WHO (ДЭМБ) World Health Organization

- COVID-19 Novel coronavirus infection
- CT (КТГ) Computed tomography
- LDH (ЛДГ) Lactate dehydrogenase
- NLR (НЛХ) Neutrophil-to-lymphocyte ratio
- TSCH (УГТЭ) Third State Central Hospital
- FSCH (УНТЭ) First State Central Hospital
- LRT (УОЭ) Lung replacement therapy (VV-ECMO)
- NCCD (ХӨСҮТ) National Center for Communicable Diseases
- NCC (ХСҮТ) National Cancer Center
- MCH (ЦТЭ) Military Central Hospital
- ICU (ЭЭТ) Intensive care unit
- MoH (ЭМЯ) Ministry of Health
- ECMO Extracorporeal membrane oxygenation
- ELSO Extracorporeal Life Support Organization
- VV-ECMO Veno-venous extracorporeal membrane oxygenation

1. Introduction

1.1. Rationale of the Study

Pneumonia of unknown cause in Wuhan, Hubei Province, People's Republic of China, was first reported by the WHO Country Office in China on 31 December 2019. On 12 January 2020, WHO confirmed that a novel coronavirus causes respiratory disease. On 11 March of that year, WHO declared COVID-19, caused by the SARS-CoV-2 virus, a pandemic. On 20 March 2020, the novel coronavirus infection (COVID-19) (ICD-10 U07.1) caused by SARS-CoV-2 was registered in Mongolia for the first time [1]. According to WHO, as of October 2023 there had been 696,731,063 COVID-19 cases in total, 668,654,659 recoveries and 6,927,438 deaths. The United States, India and France led the world in numbers of cases and deaths. Mongolia, with its small population, ranked 72nd by number of COVID-19 cases. As of 11 March 2024, Mongolia had recorded 1,010,459 COVID-19 cases, 1,008,991 recoveries and 2,284 deaths [2]. The main complication of SARS-CoV-2 is acute respiratory distress syndrome (ARDS), which leads to death [3]. As COVID-19 spread worldwide and medical care recommendations were being updated, in April 2020 the Extracorporeal Life Support Organization (ELSO) updated its guideline on extracorporeal membrane oxygenation (ECMO). On 18 January 2022, the Ministry of Health of Mongolia reissued, with amendments, Minister of Health Order No. A/33 "On the revised approval of the temporary guideline for the diagnosis and treatment of the novel coronavirus infection (COVID-19)", which recommended ECMO for the treatment of ARDS [4]. ECMO technology was first developed in the late 1960s by a team led by Robert H. Bartlett, MD; its main purpose was a machine providing long-term bypass to support the lungs or heart [5]. ECMO was first used in veno-venous (VV-ECMO), or lung replacement, mode in 1971 for severe lung injury after a motorcycle accident, and it came into wide use worldwide for respiratory failure during the 2009 H1N1 influenza pandemic [6]. During the COVID-19 pandemic, many countries newly introduced lung replacement therapy and began using it on a large scale, and many studies have been done on its outcomes in COVID-19 [7]. In the review by Pietro Bertini, ICU mortality with lung replacement therapy was 39%; in the study by Shiquan Huang et al. it was 63%,

and in the study by Armin. 56%. In Mongolia, to ensure preparedness during the COVID-19 pandemic, the first heart-lung replacement ECMO machine was made ready for use at the First State Central Hospital (FSCH) in August 2020, and there are currently 4 machines operating nationwide. A single-use set for this therapy costs about 30 million MNT, making it a high-cost treatment. Thirty sets were made ready during the pandemic, and to date heart-lung replacement therapy has been performed in 28 cases nationwide. The ECMO machine works in a mode similar to the heart-lung machine used in open-heart surgery: it oxygenates the patient's blood outside the body, allowing the heart and lungs to rest. ECMO is used in VV-ECMO (lung replacement) and VA-ECMO (heart-lung replacement) modes. When a patient is connected to the ECMO machine, blood flows through dedicated membrane tubing into an artificial lung that oxygenates it and removes carbon dioxide; the blood is then warmed to body temperature and pumped back into the body. In Mongolia, this therapy was first performed successfully during the pandemic in February 2021 at the National Center for Communicable Diseases (NCCD) by a professional team led by L. Munkh-Ochir, ICU physician at FSCH, and Ts. Chinbayar, head of the NCCD intensive care unit [8]. VV-ECMO, or lung replacement therapy (LRT), has been introduced into our country's medical care for critical COVID-19, but no substantial work has studied its complications and mortality. This was the rationale for our study [9].

1.2. Aim of the Study

To study some risk factors influencing mortality in critical COVID-19 among Mongolian patients, comparing a group that received lung replacement therapy with a group that did not.

1.2.1. Objectives of the Study

1. To assess the clinical status of critically ill COVID-19 patients who did and did not receive lung replacement therapy, and to compare their complications.
2. To study some risk factors influencing mortality in critical COVID-19.

1.2.2. Hypotheses

1. In critical COVID-19, lung replacement therapy reduces mortality and can save lives.
2. In critical COVID-19, multiple organ failure dominated by kidney failure and acidosis is a risk factor for mortality.

1.2.3. Novelty of the Study

At a time when lung replacement therapy is being established in Mongolia's medical care for critical pneumonia and acute respiratory distress syndrome, this is the first baseline study of the situation in these life-threatening conditions.

1.2.4. Practical Significance of the Study

The study has practical significance because it identifies the complications that arise during treatment, and some risk factors for mortality, in cases of critical COVID-19 complicated by ARDS and respiratory failure that were

treated with lung replacement therapy.

1.3. Chapter One. Literature Review

1.3.1. Clinical Stages and Life-Threatening Complications of COVID-19

The novel coronavirus infection is COVID-19 (ICD-10 U07.1), an infectious disease caused by the SARS-CoV-2 virus. Coronaviruses are non-segmented, enveloped viruses with spikes on the envelope, containing helical negative-sense RNA, that cause acute respiratory distress syndrome. In recent years, SARS-CoV, MERS-CoV and SARS-CoV-2 have been recorded among the types that cause deadly pandemics.

1.3.2. Clinical Features

COVID-19 is transmitted by airborne droplets, and the incubation period from infection to symptoms is 5–14 days [10]. In the mild form, there may be fever $<38^{\circ}\text{C}$, cough, sore throat, weakness, muscle pain, headache, nausea, diarrhoea, and loss of smell and taste, but no signs of pneumonia. In the moderate form, in addition to these, there are signs of pneumonia (cough, sputum, fever $>38^{\circ}\text{C}$, shortness of breath, chest pain); on examination the respiratory rate is $<24/\text{min}$, peripheral oxygen saturation is 94%, and on imaging infiltrates cover $<50\%$ of the lung fields. In the severe form, peripheral oxygen saturation is $<94\%$, $\text{PaO}_2/\text{FiO}_2 <300$ mmHg or $\text{SpO}_2/\text{FiO}_2 >315$ mmHg, respiratory rate $>24/\text{min}$, infiltrates cover $>50\%$ of the lung fields, and comorbidities are decompensated. In the critical form, ARDS, septic shock and multiple organ failure develop.

In most cases the disease presents as mild respiratory illness with mild clinical symptoms and resolves without specific treatment [5]. With a moderate, severe or critical course, however, it carries a risk of hospitalisation and death from pneumonia and multiple organ failure. A meta-analysis of 20 studies conducted during the pandemic found that 974 of 5,390 clinical cases (18.07%), and a review of 72,314 cases in China found that 13.8%, had severe or critical disease complicated by pneumonia and respiratory failure. In another cohort study, 5.2% of all cases had a severe and 20.8% a moderate course [11,12]. In the study by Zunyou Wu, 15% of people with COVID-19 had severe or critical disease [13]. In the observational study by Elfatih A. Hasabo, of 243 participants diagnosed with COVID-19, 23.3% ($n=27$) had severe and 12.9% ($n=15$) critical disease [13]. In the study by Sally, 62.9% of all COVID-19 cases required supplemental oxygen; 18.3% were treated with high-flow oxygen, 8.6% with non-invasive ventilation and 20.6% with invasive mechanical ventilation [15]. The course and complications of infection are monitored with laboratory tests: complete blood count, biochemistry, D-dimer, C-reactive protein and ferritin. In COVID-19, the complete blood count shows decreased lymphocyte and platelet counts; biochemistry shows raised creatinine and urea; and markers of inflammation and disease severity C-reactive protein, ferritin, D-dimer and troponin increase [16]. A study in China observed increased white cells, neutrophils, C-reactive protein, procalcitonin, D-dimer and lactate dehydrogenase (LDH) in COVID-19, as well as decreased lymphocytes, monocytes and eosinophils, and hypercoagulation was significantly associated with

mortality [1]. Imaging is used in moderate, severe and critical acute respiratory infection to determine lung changes and the severity of disease [17]. Computed tomography (CT) is the gold standard imaging test for diagnosing lung changes in COVID-19; a chest X-ray can show pulmonary infiltrates and ground-glass opacities. In the study by Collado, chest CT changes in COVID-19, and scoring of those changes, were statistically significant predictors of disease severity and mortality [5].

1.3.3. Clinical Classification

COVID-19 symptoms depend on the patient's immune competence, and according to WHO guidance the clinical picture is classified by severity into 4 categories: mild, moderate, severe and critical [18]. In the epidemiological study by Zhonghua Liu. in China, among symptomatic people 40% had a mild course, 40% a moderate course and about 15% a severe course requiring oxygen, while 5% developed multiple organ failure with respiratory failure, ARDS, sepsis and septic shock, thrombosis, acute kidney failure and acute cardiac injury [1,5].

1.3.4. Complications

Age and sex influence a severe course of COVID-19. Hospitalisation and death were below 0.1% in children but rose above 10% in older people. Males had more COVID-19 complications than females [19]. Patients with cancer or organ transplants also had an increased risk of COVID-19 complications because of immunosuppression.

Main complications seen in COVID-19:

- Coagulopathy, most often venous thromboembolism, raised D-dimer and prolonged prothrombin time.
- Laryngeal oedema and laryngitis in severely ill patients.
- Complication by necrotising pneumonia due to the infection (usually Panton-Valentine leukocidin-secreting *Staphylococcus*).
- Cardiovascular complications, for example acute pericarditis, left ventricular dysfunction, acute myocardial injury and arrhythmias.
- Acute respiratory failure.
- Sepsis, septic shock and multiple organ failure.
- Hyperglycaemia and cardiac complications in male patients taking high-dose oral corticosteroids, increasing the risk of death.
- Ventilator-associated pneumonia in more than 30% of patients.
- Complication by massive pulmonary embolism leading to acute right ventricular failure.
- A meta-analysis of 192 studies on COVID-19 complications in pregnant women estimated the risks of complications and death. It included 67,271 pregnant women from 192 studies, 10% of whom were hospitalised because of COVID-19. Compared with non-pregnant women, pregnant women were twice as likely to be admitted to an ICU (OR=2.13, 95% CI 1.53–2.95) and 2.59 times as likely to receive invasive mechanical ventilation (OR=2.59, 95% CI 2.28–2.94). COVID-19 mortality in pregnant women was 2.85 times that of non-pregnant women (OR=2.85, 95% CI 1.08–7.52), and the risk of preterm birth was 1.47 times higher (OR=1.47,

95% CI 1.14–1.91). Of 41,664 pregnant women, 0.02%, or 339, died of COVID-19 [20].

1.4. Acute Respiratory Distress Syndrome (ARDS) (ICD-10 J80)

ARDS is diagnosed on the basis of the clinical picture, the $\text{PaO}_2/\text{FiO}_2$ ratio and chest CT. Reported incidence varies widely, from 1.5 to 75 per 100,000 people per year [21]. The syndrome occurs in children but is common in people over 65, which may be related to underlying disease. Kuang-Ming Liao and Chang-Wen Chen reported that ARDS mortality reaches 70% [22]. Mortality was reported at 30–40% until the 1990s, but over the past 20 years mortality from severe ARDS has fallen considerably [23]. This success is linked to mechanical ventilation, early start of antibiotics, and antibiotic therapy that is both targeted to the pathogen and broader in choice. In the study by Matthew Diamond, the main causes of death in patients with ARDS were sepsis or multiple organ failure. Current mortality was reported at 9–20%, and older age increased mortality. ARDS passes through exudative, proliferative and fibrotic stages, though not every case goes through all of them. Treatment requires treating the underlying disease together with the failing organ systems, with invasive ventilation early on. There are many advanced treatments for ARDS, one of which is ECMO [24]. In a study covering five countries, 33% of hospitalised COVID-19 patients were complicated by ARDS; of these, 26% required ICU care and 16% died [25,26]. In the review by Osman, mortality among ARDS patients receiving ECMO ranged from 22% to 62.6% [27]. In the study by Peter G. Gibson, among ICU patients, mortality was 35.3% for ARDS of usual (other) causes and 40.0% for ARDS caused by COVID-19 [28].

1.5. Historical Development of ECMO Therapy

The history of extracorporeal membrane oxygenation (ECMO) is tied to the human circulatory system and blood oxygenation. Scientific understanding of ECMO is inseparable from the circulatory system. From the 1970s, the foundation for ECMO was laid in connection with open-heart surgery and various cardiac procedures [29]. In the 17th–19th centuries, many scientists studied extracorporeal blood oxygenation and artificial mechanical support. From the 19th century, discoveries in organ perfusion and blood oxygenation research began to be recorded. These studies showed that organs could be perfused artificially and that organs supplied artificially with blood could maintain their function. In the late 19th century, von Frey and Gruber devised an artificial oxygenation procedure working as a closed system [30]. In the 20th century, many difficulties arose in developing ECMO. For example, it could not be used in humans because of gas bubbles forming in the blood and blood clotting. New discoveries in haematology made it possible to safely return a person's own blood to them, which made ECMO possible [31]. In 1920, the "Autoinjector" built by Brukhonenko and Tchetchuline made bypass possible. With this machine, whole-body perfusion of a dog was performed successfully, and blood was oxygenated using the lungs of various animals [32]. In 1930–1940, work

aimed at testing the therapy in humans. Dr John Gibbon Jr performed the first successful heart-lung bypass in a human. The main driver of this work was the treatment of a young woman with a massive pulmonary thromboembolism: the idea arose of supporting her with heart-lung bypass during thrombectomy surgery, creating the need for this new technology [33]. In the 1940s, patients became hypothermic during many types of cardiac surgery, so new technology was needed, and new techniques began to be tested by creating bypass in experimental animals. In the 1950s, bypass was first performed in humans. Heart-lung bypass during cardiac surgery was highly important and was implemented successfully in clinical practice. In the mid-1950s, film and bubble oxygenators were used, and ECMO emerged from 1970 [34]. This was linked to the start of oxygenators similar to haemodialysis. At this time, clots began to form on silicone oxygenators. Microporous polypropylene oxygenators were then introduced, reducing clotting and improving gas transfer. Although this technology was successful, a problem called "wetting" arose: plasma leaked through the small pores of the microporous membrane under blood pressure, shortening the membrane's life [35]. Oxygenators developed further into a "cross-flow" design, in which blood flows outside small hollow fibres and gas passes inside them [36]. ECMO was first used successfully in 1971 for severe lung injury after a motorcycle accident [37]. Although ECMO technology improved, poor outcomes in clinical studies hindered wider use. In 1980–1990, equipment improved and use expanded, and in 1990–2000 ECMO as we know it became an important treatment option, especially in paediatrics and neonatology [38]. From the 20th century, large children's hospitals installed the machines and ECMO teams began working. In the mid-2000s, ELSO studies on the use of ECMO in paediatric and congenital disease were published [39,40]. Guidelines for training and for the teams operating the machines began to be issued [41]. The 2009 H1N1 influenza pandemic caused severe respiratory failure in adults, and ECMO was proposed. ECMO for severe respiratory failure led to positive clinical outcomes; some studies report that 71% of all patients treated with ECMO survived [42]. The large CESAR clinical trial in the United Kingdom used a multicentre randomised design to compare patients on conventional ventilation with those transferred for ECMO. Mortality was 37% among patients transferred for ECMO and 53% among ventilated patients, so mortality was lower with ECMO [43,44]. When the COVID-19 pandemic spread worldwide in 2020, the number of patients with respiratory failure rose, and ECMO became one of the important options in the critical clinical stage [45]. Ahmad et al. studied outcomes with and without ECMO in 1,048,025 COVID-19 cases: in cases with ARDS, ECMO reduced the risk of death by 11% [4]. In the study by Urner et al. of 7,345 people, comparing ventilated cases with cases treated with ECMO, ECMO reduced mortality by 7.1% [46]. In Mongolia, this therapy was first performed successfully during the pandemic in February 2021 by a team led by Ts. Chinbayar, head of the NCCD intensive care unit, together with the ECMO team led by L. Munkh-Ochir, ICU physician at FSCH [47]. The introduction of this innovative global medical technology is a

historic achievement for Mongolian health care. Since ECMO was first introduced, it has been performed successfully in more than 20 cases at FSCH, NCCD, MCH and the National Cancer Center [9].

1.6. Indications for ECMO Therapy

Because patient selection for ECMO is itself limited, ICU beds, the setting and staff needed for the therapy must be prepared. Patient selection must be wise and fair, and in settings with poor capacity and resources the criteria must be even stricter. Selecting a patient too late in the course of disease risks very long treatment, treatment failure and wasted resources. ECMO is more effective in ARDS if started early, before lung and bodily injury increase [48]. If the patient, or a legal guardian acting for a patient unable to decide, refuses treatment while knowing the physician's advance instructions and the real consequences, this decision must be respected [49]. Several studies of ECMO outcomes in older patients found ECMO mortality of 50% or more in patients over 65, which is a major selection criterion [50]. In the study by Nivedha et al. on neurological complications of ECMO, intracranial haemorrhage, ischaemic stroke and hypoxic-ischaemic injury occurred in 5.9%, 1.1% and 0.3%, showing that patients with cerebrovascular changes should not be selected for treatment [51,52]. ECMO centres develop indications and contraindications suited to their own capacity, usually using ICU scores. It is recommended not to perform ECMO when the SAPS II score is ≥ 60 , SOFA ≥ 12 , PRESERVE ≥ 5 , RESP ≤ -2 or PRESET ≥ 6 [53]. ECMO centres' correct assessment of their own capacity must be closely linked to patient selection criteria. Because mortality increases after prolonged mechanical ventilation or high-flow oxygen therapy, careful patient selection is recommended.

1.7. Principles of ECMO Therapy and Possible Complications

ECMO, extracorporeal membrane oxygenation, is an advanced technology used to replace the physiological functions of the lungs and heart in respiratory and cardiac failure of many causes. It effectively replaces heart and lung function by oxygenating the patient's blood and removing carbon dioxide. Unlike the heart-lung machine used for short-term bypass in cardiac surgery, an ECMO machine can replace heart and lung function for long periods hours, days or even weeks until heart and lung function recover. ECMO can be used in patients of all ages from newborns, including in cardiac arrest, respiratory failure and very severe heart and lung disease. It is used as a last resort when the patient needs time while the underlying heart or lung disease is treated [54,55]. ECMO can save lives, but it is not itself a treatment of the underlying disease. Rather, it is a temporary bridge that keeps the heart and lungs working while physicians treat the underlying disease. For example, ECMO is proposed when the lungs cannot supply the body with oxygen despite adequate oxygen, when the lungs cannot remove carbon dioxide despite mechanical ventilation, or when the heart cannot pump enough blood despite standard treatment and perfusion fails. Dr Arnar Geirsson of Yale School of Medicine

said: "ECMO is the most advanced supportive therapy available for critically ill patients with acute and chronic cardiac and respiratory failure. Not everyone can receive ECMO, but if it is started safely and quickly it will save lives [4,9]. After the machine is connected to the patient with large cannulas, it draws blood from the patient, carries it through plastic tubing to an artificial lung with a semi-permeable membrane that enriches the blood with oxygen and removes carbon dioxide. Because the blood cools considerably in this process, it is warmed to body temperature and pumped back to the patient. If the patient's heart cannot pump blood on its own, a mechanical pump does the heart's work and pumps blood through the circulation [56]. During therapy, sedatives and analgesics are usually used to keep the patient as calm and pain-free as possible. The therapy requires a broad team of physicians, nurses and engineers working together. X-rays to monitor results and the position of the cannulas, blood gas tests to assess oxygen and carbon dioxide levels, and other laboratory tests must be done regularly [57]. ECMO is usually run in 2 modes: V-V (veno-venous) and V-A (veno-arterial). V-V mode replaces only the lungs, carrying out gas exchange and supplying the body with oxygen, while V-A mode not only carries out gas exchange but also supports the circulation and replaces cardiac function. The mode is chosen according to the patient's organ system failure. In most ECMO cases during the COVID-19 pandemic, the indication was respiratory failure, so the mode chosen was lung-replacing V-V ECMO. In a few cases, respiratory failure occurred together with acute heart failure, so V-A mode was used. In the study by Shiqian Huang, in China, ECMO modes in COVID-19 were 90% V-V and 10% V-A, and mortality was higher with V-A ECMO [58]. Physicians aim to keep ECMO as short as possible, but because different diseases recover at different rates, duration varies between patients: some need only a few hours, others several weeks. When ECMO is no longer needed, a weaning trial is done, which takes some time. If the patient responds well and ending treatment is judged safe, the ECMO team ends treatment and disconnects the machine. If ECMO has been run for a long time without result and the team judges that the patient cannot improve, end of life and ending ECMO must be discussed with the family.

The following complications can occur during ECMO:

- **Bleeding:** Bleeding can occur in up to 50% of ECMO cases; life-threatening major bleeding is rare. The ECMO machine requires anticoagulant drugs during therapy, which increase the risk of bleeding. As a result, bleeding can occur in several organs such as the lungs, stomach, mouth, nose and brain. Physicians therefore constantly monitor for signs of bleeding and stop it with drugs or surgery when needed.
- **Kidney failure:** In some cases, reduced blood supply to the kidneys causes kidney failure requiring haemodialysis or continuous renal replacement therapy (CRRT). Kidney function usually recovers after the patient is disconnected from ECMO, but in a few cases it does not recover and lifelong renal replacement therapy is needed.
- **Bacterial infection:** Because dedicated plastic cannulas are placed in veins and arteries during ECMO, bacteria can enter

the bloodstream directly. Without good sterile conditions, bacteraemia or bacterial pneumonia can develop. If bacterial infection is suspected, appropriate antibiotics are started and, if needed, the cannulas are replaced.

• **Stroke:** Rarely, clots that reduce blood flow to the brain can form in ECMO patients, increasing the risk of stroke.

• **Pulmonary embolism:** Rarely, clots that block blood flow in the lungs form in some ECMO patients [59].

In the study by Shiqian Huang et al., risk factors for death despite ECMO included severe ARDS, older age, comorbidities (obesity, diabetes, hypertension) and secondary infection. ECMO complications in that study were venous thrombosis 33%, pulmonary embolism 29% and stroke 5–6%; severe bleeding was rare, and mechanical complications were recorded, including pump failure, circuit embolism, pump damage and oxygenator failure [60,61].

2. Chapter Two. Materials and Methods

2.1. Study Design

The study used a hospital-based retrospective design.

2.2. Study Methods

The study included patients treated in the intensive care units of the First State Central Hospital (FSCH), the Military Central Hospital (MCH) and the National Center for Communicable Diseases (NCCD) between February 2021 and July 2022, with respiratory failure and SARS-CoV-2 infection confirmed by real-time polymerase chain reaction (RT-PCR) of nasopharyngeal swabs. It covered patients who received VV-ECMO (lung replacement therapy) and patients who met the criteria for it (Murray score above 2.5 and the EOLIA criteria) but did not receive it. Data were collected from electronic medical records and ICU monitoring charts using a study form (Appendix 1).

Appendix 1: Study Form

The data collection form recorded the following fields for each patient (translated from the original form).

Section	Fields recorded
General	No.; surname/name; age; sex; medical record number; place of residence; vaccinated (yes/no, number of doses); comorbidities
BMI	Height; weight; BMI
Clinical signs and vital signs	Respiratory rate on ICU admission; respiratory rate after the first day of ECMO; temperature on ICU admission; temperature before ECMO; arterial pressure; mean arterial pressure; heart rate; O ₂ on ICU admission; SpO ₂ on ICU admission
Treatment	Antibiotics; antivirals; corticosteroids; neuromuscular blockade; vasopressors and inotropes; prone positioning; sedation
Diagnosis	Changes on CT; changes on X-ray; SARS-CoV-2 laboratory confirmation
Before starting ECMO	Time on O ₂ therapy; time on mechanical ventilation before ECMO; total time on mechanical ventilation; ventilation mode; PEEP; FiO ₂ ; VT before ECMO; VT during ECMO; MV before ECMO; MV during ECMO; SpO ₂ before; PaO ₂ ; PaCO ₂ ; pH; PaO ₂ /FiO ₂ ratio; bicarbonate; base excess
During ECMO	ECMO mode; vessel (cannulation) site; return cannula size; drainage cannula size; ECMO with or without sedation; ventilation mode on ECMO; PEEP on ECMO; FiO ₂ on ECMO; mean heparin dose; mean APTT on ECMO (s); pump speed (rpm); ECMO flow rate; P1 drainage pressure; P2 pre-oxygenator pressure; P3 return pressure; P4 artificial lung pressure; SatO ₂ ; ScvO ₂ %; cSvO ₂ %; complications; oxygenator changed
Scores and other	Blood products transfused (amount); Murray score; qSOFA; EOLIA criteria met; SAPS II score; nosocomial infection; renal replacement therapy (HD, CRRT) and mode
Laboratory	D-dimer, CRP, procalcitonin, fibrinogen, LDH, ferritin, troponin, white cells, lymphocytes, neutrophil/lymphocyte ratio, neutrophils, platelets, haemoglobin, creatinine, urea and lactate, each recorded on ICU admission and before ECMO
Outcome	Hospital where ECMO was performed; time from admission to ICU; ICU stay; total hospital stay; total ECMO duration; outcome; cause of death

Of the 66 cases included, 44 received standard treatment in the critical stage of COVID-19 and were classed as the "no lung replacement therapy group", and 22 received standard treatment plus lung replacement therapy and were classed as the "lung replacement therapy group". Length of hospital treatment was considered, and outcome was assessed at 30

days.

2.2.1. Inclusion Criteria

- Cases treated in the critical stage of COVID-19
- Cases that received lung replacement therapy
- Cases that met the criteria for lung replacement therapy

but did not receive it

- Patients aged 18 years or older
- Citizens of Mongolia

2.2.2. Exclusion Criteria

- Cases treated in the mild, moderate or severe stage of COVID-19
- Cases that did not meet the criteria for lung replacement therapy
- Cases with insufficient data for research use
- Patients under 18 years of age
- Foreign citizens

2.2.3. Basic Patient Data

- Medical record number
- Patient's surname and name
- Age (years)
- Sex
- Body weight (kg)
- Height (cm)
- Presenting complaints
- Main diagnosis
- Diagnosis of complications
- Clinical comorbidity diagnoses
- Outcome (died, discharged)

2.2.4. Selected Laboratory Parameters

- White blood cells (WBC, $\times 10^9/L$)
- Neutrophils
- Lymphocytes
- Haemoglobin
- Platelets (PLT, $\times 10^9/L$)
- C-reactive protein
- Lactate dehydrogenase
- Neutrophil-to-lymphocyte ratio
- Creatinine
- Urea

2.2.5. Criteria for ECMO Therapy

Indications:

- Respiratory failure (when the lungs cannot keep blood oxygen at an adequate level or cannot remove enough carbon dioxide from the blood)
- Heart transplant surgery
- Lung transplant surgery
- Cardiac arrest (the heart cannot pump blood effectively)
- Cardiogenic shock (the ventricles do not work normally and blood flow is inadequate)
- Pulmonary embolism (blockage of the pulmonary artery)
- Congenital heart defects
- Acute respiratory distress syndrome ($PaO_2/FiO_2 < 150$, high PEEP, EOLIA criteria met)
- Contraindications:
- Patient refuses organ replacement therapy
- Patient over 70 years of age
- Moderate or severe cerebrovascular disease
- Moderate or severe cognitive impairment
- End-stage chronic obstructive lung disease
- Chronic heart failure ($EF < 35\%$)
- Chronic kidney failure ($GFR < 30$)
- Chronic liver failure ($Child \geq 8$)
- Malignancy requiring palliative care
- Uncontrollable shock, lactic acidosis, or treatment with high-dose norepinephrine

Neutrophil-to-lymphocyte ratio: $NLR = \text{neutrophil } \% \div \text{lymphocyte } \%$. Normal: 0–2.80. A value of 2.80 or above is considered abnormal.

2.6. Arterial blood gas analysis

The PaO_2/FiO_2 ratio is calculated by dividing the arterial partial pressure of oxygen (mmHg) by the fraction of inspired oxygen (e.g. $21\% = 0.21$, $100\% = 1$).

Parameter	Normal range	Unit
pH	7.35–7.45	
PaO_2	75–100	mmHg
$PaCO_2$	35–45	mmHg
HCO_3	22 ± 4	mmol/L

Note: PaO_2 , arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; HCO_3 , bicarbonate ion.

Table 1: Normal Arterial Blood Gas Values

Parameter	Normal range	Unit
White cells	4.5–11	$\times 10^9$
Neutrophils	1.2–8	$\times 10^3$
Lymphocytes	1–4	$\times 10^3$
Haemoglobin	11.5–16.5	g/dL
Platelets	160–320	$\times 10^9$
C-reactive protein	0–5	mg/L
LDH	135–225	U/L

Fibrinogen	2–4	g/L
Creatinine	0.5–0.9	mg/dL
Urea	0–48.5	mg/dL

Note: LDH, lactate dehydrogenase.

Table 2: Normal Ranges for Complete Blood Count and Biochemistry

Selected scores used in intensive care

Parameter / points	0	1	2	3	4
PaO ₂ /FiO ₂ (mmHg)	≥300	225–299	175–224	100–174	<100
Chest X-ray (quadrants with infiltrates)	Normal	1	2	3	4
PEEP (cmH ₂ O)	≤5	6–8	9–11	12–14	≥15
Compliance (mL/cmH ₂ O)	≥80	60–79	40–59	20–39	≤19

- 0 points: excludes lung injury
- 1–2.5 points: mild to moderate lung injury
- ≥2.5 points: severe lung injury, indicates ARDS; ECMO is recommended

Table 3: Murray score (grading of lung injury)

- PaO₂/FiO₂ ratio <50 mmHg for >3 hours
- PaO₂/FiO₂ ratio <80 mmHg for >6 hours
- Arterial pH <7.25 with PaCO₂ ≥ [threshold as given in the original] for >6 hours

Table 4: EOLIA Criteria (criteria for early lung replacement therapy in severe ARDS)

Assessment	Points
Low blood pressure (systolic ≤100 mmHg)	1
Raised respiratory rate (≥22 breaths/min)	1
Altered mental status (Glasgow Coma Scale ≤14)	1

- 1 point: not high risk; continued monitoring needed
- 2 points: high risk; risk of in-hospital death
- 3 points: high risk; risk of in-hospital death

Table 5: qSOFA Score (rapid assessment of multiple organ failure)

The SAPS II score table for estimating risk of death is included as an appendix. It covers age, heart rate, systolic pressure, body temperature, Glasgow Coma Scale, clinical laboratory values, chronic disease and type of admission (Appendix 2).

Appendix 2: SAPS II Score for Estimating Risk of Death

Parameter	Category	Points
Age (years)	<40 / 40–59 / 60–69 / 70–74 / 75–79 / ≥80	0 / 7 / 12 / 15 / 16 / 18
Heart rate	<70 [as printed] / <40 / 40–69 / 70–119 / 120–159 / ≥160	13 / 11 / 2 / 0 / 4 / 7
Systolic pressure (mmHg)	<70 / 70–99 / 100–199 / ≥200	13 / 5 / 0 / 2
Body temperature ≥39°C	Yes / No	3 / 0
Glasgow Coma Scale	14–15 / 11–13 / 9–10 / 6–8 / <6	0 / 5 / 7 / 13 / 26
PaO ₂ /FiO ₂ (mmHg)	<100 / 100–199 / ≥200	11 / 9 / 6
Creatinine (mg/dL)	28 / 28–83 / ≥84 [as printed]	0 / 6 / 10
Urine output (mL/day)	<500 / 500–999 / ≥1000	11 / 4 / 0
Sodium (mmol/L)	<125 / 125–144 / ≥145	5 / 0 / 1

Potassium (mmol/L)	<3 / 3–4.9 / ≥5	3 / 0 / 3
Bicarbonate (mEq/L)	<15 / 15–19 / ≥20	6 / 3 / 0
Bilirubin (mg/dL)	<4 / 4–5.9 / ≥6	0 / 4 / 9
White cells ($\times 10^3$)	<1 / 1–19.9 / ≥20	12 / 0 / 3
Chronic disease	None / Metastatic cancer / Haematological disease / Immunosuppressive disorder	0 / 9 / 10 / 17
Type of admission	Scheduled surgery / Medical / Emergency surgery	0 / 6 / 8

SAPS II risk of death was estimated as follows:

SAPS II score	Risk of death
0–29	10%
30–40	25%
41–52	50%
53–64	75%
65–80	90%

2.7. Study Sample

In 2021–2022, 28 patients in Mongolia received heart-lung replacement therapy; the 22 cases that met the inclusion criteria were included retrospectively. The comparison group of 44 patients was sampled according to the inclusion criteria from patients in the same units who had an indication for lung replacement therapy in the critical stage of COVID-19 but did not receive it.

2.8. Statistical Analysis

Statistical analysis was done in SPSS 25, using descriptive statistics. For quantitative variables, the mean and standard deviation ($M \pm SD$), 95% confidence interval, median

and range (maximum and minimum) were calculated. Associations were tested with Spearman's rho, the chi-square test and Fisher's exact test; outcome was analysed with Cox regression and Kaplan-Meier curves. $p < 0.05$ was considered statistically significant.

3. Chapter Three. Results

3.1 Clinical Status and Complications in Critically ill COVID-19 Patients Who did and did not Receive Lung Replacement Therapy

The 66 cases treated in the ICUs of FSCH, NCCD and MCH in our study had a mean age of 53 ± 11.7 (23–69) years; 54.5% (36) were female and 45.5% (30) male (Figure 1).

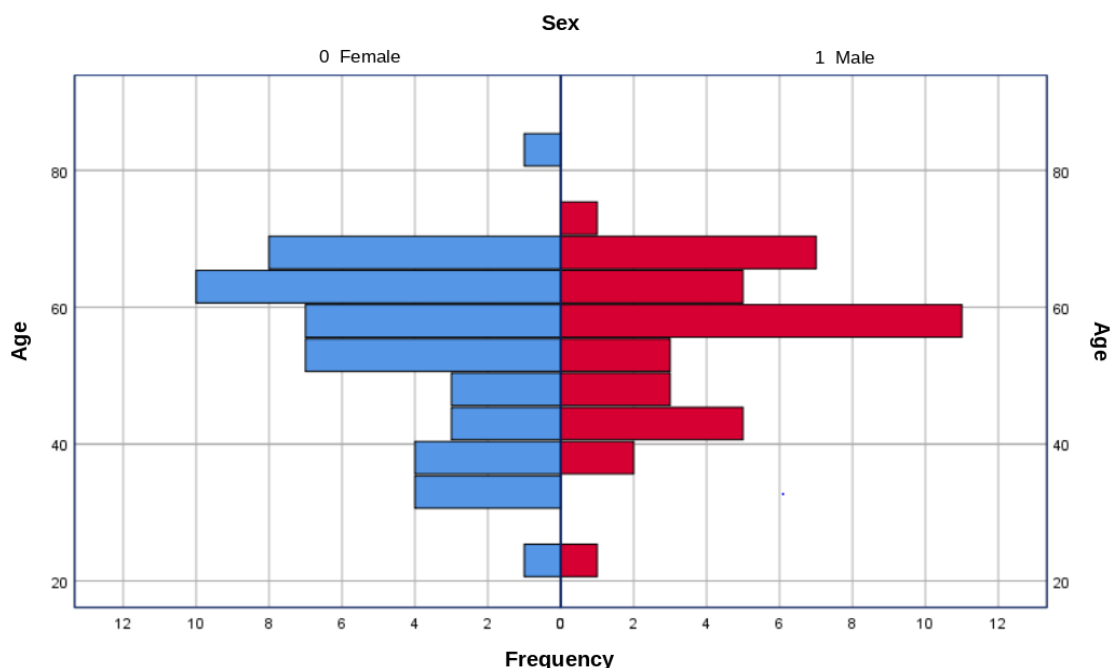


Figure 1: Age and Sex Distribution

Of all cases, 33.3% (22) received lung replacement therapy and 66.7% (44) did not. Among cases without lung replacement therapy, 4.5% (2) recovered and 95.5% (42) died. Among cases with lung replacement therapy, 36.4% (8) recovered and 63.6% (14) died. Of the 66 patients in our study, we studied 22 cases with and 44 cases without lung replacement therapy. The mean age was 46.8 years in the LRT group and 56.1 years in the non-LRT group; LRT was

given to significantly younger people ($p=0.001$). The Murray score (lung injury score) was also significantly higher in the LRT group ($p=0.023$). Sex ($p=0.294$), BMI ($p=0.268$), qSOFA score (organ failure score) ($p=0.060$) and SAPS II score (estimated percentage risk of death) ($p=0.479$) did not differ significantly between the groups, showing that all patients in the study had high organ failure and death risk (Table 6).

Parameter	Total (n=66)	LRT (n=22)	No LRT (n=44)	p*
Age	53±11.7	46.8±10.9	56.1±10.9	0.001
Sex				0.294
Female	36 (54.5%)	10 (45.5%)	26 (59.1%)	
Male	30 (45.4%)	12 (54.5%)	18 (40.9%)	
BMI	27.1±3.22	28.0±4.0	26.6±2.6	0.268
Murray score (median)	3.14±1.16	3.43±1.93	3.0±0.40	0.023
qSOFA score (median)	1.92±0.56	1.95±0.72	2±0.47	0.060
SAPS II score (median)	39.8±11.31	37.45±10.28	40.98±11.72	0.479

Note: BMI, body mass index; qSOFA, quick sequential organ failure assessment; SAPS II, Simplified Acute Physiology Score II; *chi-square test, $p<0.05$.

Table 6: Clinical Scores of Study Participants (n=66)

Table 7 shows comorbidities and outcome in cases with and without lung replacement therapy. Our study included 10 mothers, 90% of whom were delivered by caesarean section; 1 pregnant woman was at 25–26 weeks' gestation. 60% received LRT and 40% did not. Mothers were in the majority in the LRT group compared with the non-LRT group, but the difference was not statistically significant ($p=0.052$). Comorbidities—hypertension ($p=0.617$),

diabetes ($p=0.079$), number of comorbidities ($p=0.612$) and bacterial infection ($p=0.116$)—did not differ significantly in the choice of LRT. Unvaccinated cases predominated in the LRT group, which was statistically significant ($p=0.002$); unvaccinated cases may have been more severe, with greater lung injury. Recovered cases predominated in the LRT group, a statistically significant difference ($p=0.001$).

Parameter	Total (n=66)	LRT (n=22)	No LRT (n=44)	p*
Pregnant or postpartum				0.052
Yes	10 (15.2%)	6 (27.3%)	4 (9.1%)	
No	56 (84.8%)	16 (72.7%)	40 (90.9%)	
Hypertension				0.262
Yes	21 (31.8%)	5 (22.7%)	16 (36.4%)	
No	45 (68.2%)	17 (77.3%)	28 (63.6%)	
Diabetes				0.079
Yes	18 (27.3%)	3 (13.6%)	15 (34.1%)	
No	48 (72.7%)	19 (86.4%)	29 (65.9%)	
Comorbidities				0.643
None	9 (13.6%)	4 (18.2%)	5 (11.4%)	
1 comorbidity	36 (54.5%)	11 (50.0%)	25 (56.8%)	
2 comorbidities	15 (22.7%)	4 (18.2%)	11 (25.0%)	
3 comorbidities	6 (9.1%)	3 (13.6%)	3 (6.8%)	
Bacterial infection				0.116
Present	30 (45.4%)	13 (59.1%)	17 (38.6%)	

Absent	36 (54.5%)	9 (40.9%)	27 (61.4%)	
Vaccinated				0.002
Yes	44 (66.7%)	9 (40.9%)	35 (79.5%)	
No	22 (33.3%)	13 (59.1%)	9 (20.5%)	
Outcome				0.001
Recovered	10 (15.2%)	8 (36.4%)	2 (4.5%)	
Died	56 (84.8%)	14 (63.6%)	42 (95.5%)	

Note: *chi-square test, $p < 0.05$.

Table 7: Comorbidities and Outcome in Patients with and without Lung Replacement Therapy (n=66)

Total duration of mechanical ventilation ($p < 0.001$) was significantly longer in the LRT group. Length of ICU stay ($p < 0.001$) and total length of hospital stay ($p < 0.001$) were also significantly longer in the LRT group, indicating that LRT cases were able to be treated for longer. Duration of oxygen

therapy ($p < 0.285$) was longer in the non-LRT group, and time in other wards ($p < 0.077$) was shorter in the non-LRT group, but these differences were not statistically significant (Table 8).

Parameter	Total (n=66)	LRT (n=22)	No LRT (n=44)	p*
Oxygen therapy (hours)	83.5 (0-551)	65.64 (0-240)	92.45 (0-551)	0.285
Total mechanical ventilation (hours)	187.3 (0.5-816)	326.63 (1-816)	64 (0.5-594)	<0.001
Time in other wards (days)	2.2 (0-34)	2.63 (0-13)	2.01 (0-34)	0.077
ICU stay (days)	11.06 (1-46)	18.5 (1-46)	7.34 (1-23)	<0.001
Total hospital stay (days)	13.26 (1-46)	21.14 (2-46)	9.32 (1-36)	<0.001

Note: Spearman's rho test, $p < 0.05$. (The original header gives n=66 for the non-LRT column.)

Table 8: Duration of Treatment in Cases with and without Lung Replacement Therapy (n=66)

We compared selected blood gas and oxygen requirement parameters. In the LRT group, pH ($p = 0.001$), bicarbonate ($p = 0.022$) and SpO₂% (peripheral oxygen saturation) ($p = 0.028$) were significantly higher than in the non-LRT

group. PaCO₂ ($p = 0.363$), PaO₂ ($p = 0.147$), FiO₂ ($p = 0.367$) and PaO₂/FiO₂ ($p = 0.077$) did not differ significantly between the groups (Table 9).

Parameter	Total (n=66)	LRT (n=22)	No LRT (n=44)	p*
pH	7.25±0.12	7.32±0.10	7.22±0.12	0.001
PaCO ₂	48.94±16.63	47.61±15.98	49.6±17.08	0.363
PaO ₂	59.65±20.26	60.5±20.48	59.23±20.38	0.147
FiO ₂	96.14±12.17	97.5±8.96	95.45±13.5	0.367
PaO ₂ /FiO ₂	65.34±26.36	69.45±28.60	63.29±25.25	0.077
SpO ₂ %	78.23±1.31	81.64±10.05	76.52±10.68	0.028
Bicarbonate	17±6.5	19.84±7.89	16.03±5.34	0.022

Note: Spearman's rho test, $p < 0.05$.

Table 9: Selected Blood Gas and Oxygen Requirement Parameters (n=66)

We compared respiratory parameters during lung replacement therapy. Before LRT, full mandatory ventilation (AC-VC) predominated; during LRT, mixed support (SIMV) increased and full mandatory support decreased. During LRT, positive end-expiratory pressure (PEEP) fell, while tidal volume, minute volume and peripheral haemoglobin oxygen

saturation rose, and oxygen requirement fell. This shows that LRT successfully replaced lung function and reduced the need for ventilator support (Table 10). In all LRT cases, therapy was completed without changing the artificial lung (oxygenator), and cannula sizes varied. Parameters during LRT are given in the appendix (Appendix 3).

Parameter	Category	Value
ECMO mode	VV-ECMO	22 (100%)
Cannula position	Right internal jugular, right femoral vein	13 (59.0%)
	Left internal jugular, left femoral vein	1 (4.5%)
	Right internal jugular, left femoral vein	7 (32.0%)
	Left internal jugular, right femoral vein	1 (4.5%)
Return cannula size	15 Fr	9 (40.9%)
	17 Fr	8 (36.4%)
	19 Fr	5 (22.7%)
Drainage cannula size	21 Fr	2 (9.0%)
	23 Fr	18 (82.0%)
	24 Fr	1 (4.5%)
	25 Fr	1 (4.5%)
Pump speed (rpm)		2640.23 (1500–3185)
Central venous saturation (cSvO ₂ %)		68.5 (55–83)
Oxygenator changed	Yes	0 (0.0%)
	No	22 (100%)
ECMO patients	Sedated	13 (59.0%)
	Not sedated	9 (41.0%)
Complications during therapy	Yes	11 (50.0%)
	No	11 (50.0%)
Heparin (U/hour)		573.91 (110–1100)
Coagulation: APTT (seconds)		65.1 (39–79)
Blood flow rate (L/min)		6.16 (3–10)

Appendix 3: Selected Parameters of Lung Replacement Therapy (n=22)

Respiratory parameter	Before LRT	During LRT	p*
Ventilation mode	PS 1 (4.5%); SIMV 2 (9.1%); AC-VC 19 (86.4%)	PS 1 (4.5%); SIMV 8 (36.4%); AC-VC 13 (59.1%)	
Positive end-expiratory pressure (PEEP)	11.4 (5–15)	7.95 (6–10)	
Tidal volume (VT)	401.27 (290–600)	415.59 (250–650)	NS
Minute volume (MV)	6.77 (2.6–10)	6.68 (2.1–10.2)	
Peripheral haemoglobin oxygen saturation (SpO ₂ %)	81.64 (58–95)	92.55 (90–100)	
Oxygen requirement (FiO ₂ %)	97.5 (60–100)	57.23 (30–100)	

Note: PS, pressure support; SIMV, synchronised intermittent mandatory ventilation; AC-VC, assist control–volume control; NS, non-significant.

Table 10: Respiratory Parameters During Lung Replacement Therapy (n=22)

Table 11 compares complications during lung replacement therapy with outcome. Cases without complications predominated in the recovered group, and cases with complications predominated in the group that died. Bleeding

due to cannula or vascular injury occurred in 36.4% of all cases and 50.0% of those who died, but LRT complications were not associated with outcome (p=0.225); no statistically significant difference was observed.

Parameter	Total (n=22)	Recovered (n=8)	Died (n=14)	p*
No complications	10 (45.5%)	5 (62.5%)	5 (35.7%)	0.225
Complications	12 (54.5%)	3 (37.5%)	9 (64.3%)	
Bleeding due to cannula or vascular injury	8 (36.4%)	1 (12.5%)	7 (50.0%)	
Stroke	1 (4.5%)	0 (0.0%)	1 (7.15%)	
Peripheral perfusion failure	1 (4.5%)	0 (0.0%)	1 (7.15%)	
Venous thrombosis	1 (4.5%)	1 (12.5%)	0 (0.0%)	
Secondary infection	1 (4.5%)	1 (12.5%)	0 (0.0%)	

Note: Spearman's rho test, $p < 0.05$.

Table 11: Complications and Outcome Indicators During Lung Replacement Therapy (n=22)

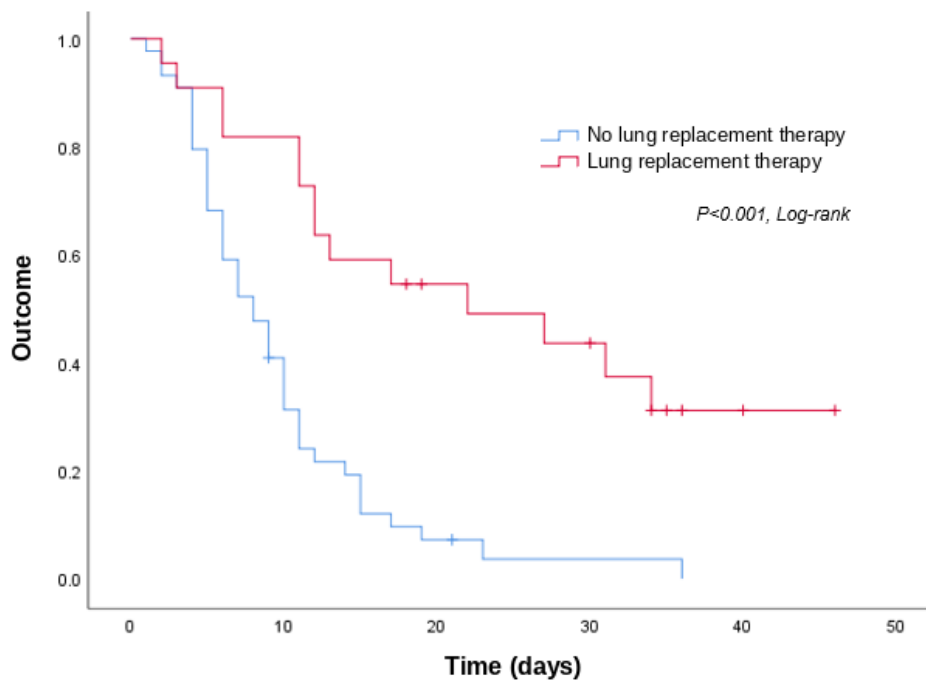


Figure 2: Results of Lung Replacement Therapy

Of the 22 cases that received lung replacement therapy in the critical stage of COVID-19, 8 (36.4%) recovered and 14 (63.6%) died; lung replacement therapy reduced mortality considerably (Figure 2).

3.2 Some Risk Factors Influencing Mortality in Critical COVID-19

Comparing the recovered and deceased groups, age ($p=0.255$), sex ($p=0.754$), BMI ($p=0.126$), vaccination ($p=0.052$) and the ICU scores—Murray score for lung injury ($p=0.281$), qSOFA score for organ failure ($p=0.666$) and SAPS II score for risk of death ($p=0.523$)—did not differ significantly (Table 12).

Parameter	Total (n=66)	Recovered (n=10)	Died (n=56)	p*
Age	53.05±11.7	50.8±8.32	53.45±12.23	0.255
Murray score	3.0 (2.0–3.5)	3.0 (2.5–3.0)	3.0 (2.0–3.5)	0.281
qSOFA score	2.0 (1–3)	2.0 (1–3)	2.0 (1–3)	0.666
SAPS II score	39.8 (18–80)	36.3 (31–40)	40.4 (18–80)	0.523
Sex				0.754
Male	36 (54.5%)	5 (50.0%)	31 (55.4%)	
Female	30 (45.5%)	5 (50.0%)	25 (44.6%)	

Vaccinated				0.052
No	26 (33.3%)	6 (60.0%)	16 (28.6%)	
Yes	44 (66.7%)	4 (40.0%)	40 (71.4%)	
BMI				0.126
Normal	16 (24.3%)	2 (20.0%)	14 (25.0%)	
Overweight	42 (63.6%)	6 (60.0%)	36 (64.3%)	
Obesity class 1	7 (10.6%)	1 (10.0%)	6 (10.7%)	
Obesity class 2	1 (1.5%)	1 (10.0%)	0 (0.0%)	

Note: BMI, body mass index; qSOFA, quick sequential organ failure assessment; SAPS II, Simplified Acute Physiology Score II; *chi-square test, Spearman's rho test, $p < 0.05$.

Table 12: Clinical Parameters, Clinical Scores and Outcome (n=86, as printed in the original)

Table 13 compares selected clinical parameters with outcome. Respiratory rate ($p=0.887$), body temperature ($p=0.278$), mean arterial pressure ($p=0.547$), heart rate ($p=0.986$), oxygen requirement ($p=0.134$) and peripheral oxygen saturation ($p=0.154$) did not differ significantly between the groups.

Parameter	Total (n=66)	Recovered (n=10)	Died (n=56)	p*
Respiratory rate	32.05±8.53	32.90±9.93	31.89±8.34	0.887
Body temperature	36.98±0.78	37.26±1.02	36.93±0.73	0.278
Mean arterial pressure	89.29±18.48	92.50±17.41	88.71±8.34	0.547
Heart rate	99.27±21.45	100.00±22.96	99.14±21.38	0.986
Oxygen requirement (O ₂)	87.24±19.45	81.50±17.64	88.27±19.73	0.134
Peripheral oxygen saturation (SpO ₂)	84.70±1.12	88.30±7.68	84.05±10.42	0.154

Note: Spearman's rho test, $p < 0.05$.

Table 13: Selected Clinical Parameters and Outcome (n=66)

Table 14 shows the relationship between comorbidities and outcome. Recovery predominated among pregnant and postpartum mothers ($p=0.155$), while hypertension ($p=0.108$), diabetes ($p=0.575$), comorbidities ($p=0.677$) and bacterial co-infection ($p=0.707$) were more frequent in the group that died, but no statistically significant differences were observed.

Parameter	Total (n=66)	Recovered (n=10)	Died (n=56)	p*
Pregnant or postpartum				0.155
Yes	10 (15.2%)	3 (30.0%)	7 (12.5%)	
No	56 (84.8%)	7 (70.0%)	49 (87.5%)	
Hypertension				0.108
Yes	21 (31.8%)	1 (10.0%)	20 (35.7%)	
No	45 (68.2%)	9 (90.0%)	36 (64.3%)	
Diabetes				0.575
Yes	18 (27.3%)	2 (20.0%)	16 (28.6%)	
No	48 (72.3%)	8 (80.0%)	40 (71.4%)	
Comorbidities				0.677
None	9 (13.6%)	1 (10.0%)	8 (14.3%)	
1 comorbidity	36 (54.5%)	6 (60.0%)	30 (53.6%)	
2 comorbidities	15 (22.7%)	3 (30.0%)	12 (21.4%)	
3 comorbidities	6 (9.1%)	0 (0.0%)	6 (10.7%)	

Bacterial infection present				0.707
Yes	30 (45.5%)	4 (40.0%)	30 (53.6%)	
No	36 (54.5%)	6 (60.0%)	26 (46.4%)	

Note: *chi-square test, $p < 0.05$.

Table 14: Comorbidities in Relation to Outcome (n=66)

Table 15 classifies selected laboratory parameters by abnormality and compares them between the recovered and deceased groups. A high urea level predominated significantly in the group that died ($p=0.009$). White cells ($p=0.366$), lymphocytes ($p=0.509$), neutrophils ($p=0.906$), NLR ($p=0.100$), platelets ($p=0.880$), haemoglobin ($p=0.668$), C-reactive protein ($p=0.575$), fibrinogen ($p=0.868$), LDH ($p=0.670$) and creatinine ($p=0.308$) did not differ significantly between the groups.

Parameter	Total (n=66)	Recovered (n=10)	Died (n=56)	p*
White cells				0.366
$<4.5 \times 10^9$	2 (3.0%)	1 (10.0%)	1 (1.8%)	
$4.5-11.0 \times 10^9$	19 (28.8%)	3 (30.0%)	16 (28.6%)	
$>11 \times 10^9$	45 (68.2%)	6 (60.0%)	39 (69.6%)	
Lymphocytes				0.509
$0-1 \times 10^3$	40 (60.6%)	7 (70.0%)	33 (58.9%)	
$1-4 \times 10^3$	26 (39.4%)	3 (30.0%)	23 (41.1%)	
$>4 \times 10^3$	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Neutrophils				0.906
$0-1.2 \times 10^3$	1 (1.5%)	0 (0.0%)	1 (1.8%)	
$1.2-8 \times 10^3$	14 (21.2%)	2 (20.0%)	12 (21.4%)	
$>8 \times 10^3$	51 (77.3%)	8 (80.0%)	43 (76.8%)	
NLR				0.100
Low	0 (0.0%)	0 (0.0%)	0 (0.0%)	
High	66 (100%)	10 (100%)	56 (100%)	
Platelets				0.880
<160	24 (36.4%)	3 (30.0%)	21 (37.5%)	
160–320	37 (56.1%)	6 (60.0%)	31 (55.4%)	
>320	5 (7.6%)	1 (10.0%)	4 (7.1%)	
Haemoglobin				0.668
0–11.5	21 (31.8%)	3 (30.0%)	18 (32.1%)	
11.5–16.5	42 (63.6%)	6 (60.0%)	36 (64.3%)	
>16.5 g/dL	3 (4.5%)	1 (10.0%)	2 (3.6%)	
C-reactive protein				0.575
0–5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
5–100	18 (27.3%)	2 (20.0%)	16 (28.6%)	
>100	48 (72.7%)	8 (80.0%)	40 (71.4%)	
Fibrinogen				0.868
0–2 g/L	9 (13.6%)	1 (10.0%)	8 (14.3%)	
2–4 g/L	16 (24.2%)	3 (30.0%)	13 (23.2%)	
>4 g/L	41 (62.1%)	6 (60.0%)	35 (62.5%)	
LDH				0.670
0–135	1 (1.5%)	0 (0.0%)	1 (1.8%)	

135–225	0 (0.0%)	0 (0.0%)	0 (0.0%)	
>225	66 (98.5%)	10 (100%)	55 (98.2%)	
Creatinine				0.308
0–0.5 mg/dL	11 (16.7%)	3 (30.0%)	8 (14.3%)	
0.5–0.9 mg/dL	22 (33.3%)	4 (40.0%)	18 (32.1%)	
>0.9 mg/dL	33 (50.0%)	3 (30.0%)	30 (53.6%)	
Urea				0.009
0–48.5 mg/dL	28 (42.4%)	8 (80.0%)	20 (35.7%)	
>48.5 mg/dL	38 (57.6%)	2 (20.0%)	36 (64.3%)	

Note: NLR, neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; chi-square test, $p < 0.05$.

Table 15: Laboratory Parameters and Outcome (n=66)

Table 16 shows the relationship between treatment and outcome for all cases. Vasopressor therapy ($p < 0.001$) predominated significantly in the group that died. Neuromuscular blockade ($p = 0.032$), prone positioning ($p = 0.039$), transfusion of blood and blood products ($p = 0.006$) and lung replacement therapy ($p = 0.001$) were

given predominantly in the recovered group, with statistically significant differences. Sedation ($p = 0.454$), antiviral therapy ($p = 0.716$), corticosteroid therapy ($p = 0.823$) and antibiotic therapy ($p = 0.427$) did not differ significantly between the recovered and deceased groups.

Parameter	Total (n=66)	Recovered (n=10)	Died (n=56)	p*
Vasopressor therapy				<0.001
Yes	57 (86.4%)	5 (50.0%)	52 (92.9%)	
No	9 (13.6%)	5 (50.0%)	4 (7.1%)	
Sedation				0.454
Yes	63 (95.5%)	10 (100%)	53 (94.6%)	
No	3 (4.5%)	0 (0.0%)	3 (5.4%)	
Neuromuscular blockade				0.032
Yes	26 (39.4%)	7 (70.0%)	19 (33.9%)	
No	40 (60.6%)	3 (30.0%)	37 (66.1%)	
Prone positioning				0.039
Yes	16 (24.2%)	5 (50.0%)	11 (19.6%)	
No	50 (75.8%)	5 (50.0%)	45 (80.4%)	
Antiviral therapy				0.716
1 drug	57 (86.4%)	9 (90.0%)	48 (85.7%)	
2 drugs	9 (13.6%)	1 (10.0%)	8 (14.3%)	
Corticosteroid therapy				0.823
1 drug	58 (87.9%)	9 (90.0%)	49 (87.5%)	
2 drugs	8 (12.1%)	1 (10.0%)	7 (12.5%)	
Antibiotic therapy				0.427
1 drug	4 (6.1%)	0 (0.0%)	4 (7.1%)	
2 drugs	19 (28.8%)	2 (20.0%)	17 (30.4%)	
3 drugs	21 (31.8%)	3 (30.0%)	18 (32.1%)	
4 drugs	13 (19.7%)	2 (20.0%)	11 (19.6%)	
5 drugs	5 (7.6%)	1 (10.0%)	4 (7.1%)	
6 drugs	4 (6.1%)	2 (20.0%)	2 (3.6%)	
Transfusion of blood and blood products				0.006

Yes	27 (40.9%)	8 (80.0%)	19 (33.9%)	
No	39 (59.1%)	2 (20.0%)	37 (66.1%)	
Renal replacement therapy				0.052
Yes	16 (24.2%)	0 (0.0%)	16 (28.6%)	
No	50 (75.8%)	10 (100%)	40 (71.4%)	
Lung replacement therapy				0.001
Received	22 (33.3%)	8 (80.0%)	14 (25.0%)	
Not received	44 (66.7%)	2 (20.0%)	42 (75.0%)	

Note: *chi-square test, $p < 0.05$.

Table 16: Treatment and Outcome (n=66)

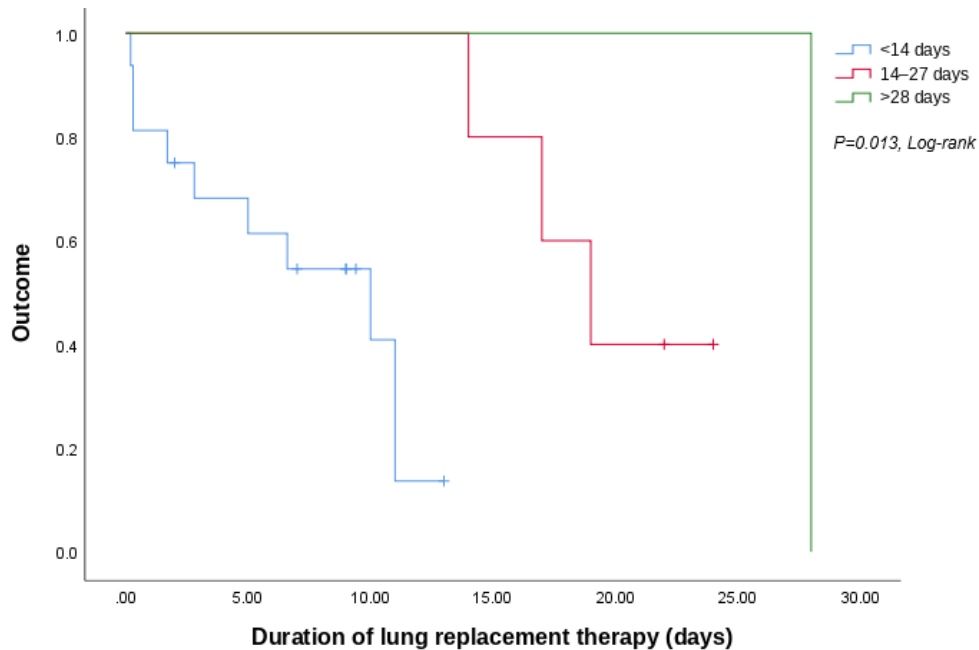


Figure 3: Effect of Duration of Lung Replacement Therapy on Mortality

Figure 3 shows that a longer duration of lung replacement therapy was associated with lower mortality ($p=0.013$).

Table 17 compares outcome with selected time indicators for cases that received lung replacement therapy. Longer total mechanical ventilation ($p=0.037$), ICU stay ($p=0.003$) and

total hospital stay ($p=0.001$) predominated in the recovered group, with statistically significant differences. Duration of oxygen therapy ($p=0.486$), duration of ventilation before LRT ($p=0.691$), duration of LRT ($p=0.426$) and time in other wards ($p=0.066$) did not differ significantly between the groups.

Parameter	Total (n=22)	Recovered (n=8)	Died (n=14)	p*
Oxygen therapy (hours)	65.64 (0-240)	82.75 (2-240)	55.86 (0-192)	0.486
Mechanical ventilation before LRT (hours)	71.41 (0-432)	102.25 (0-432)	53.79 (0-144)	0.691
Total mechanical ventilation (hours)	323.63 (1-816)	424.37 (192-768)	270.78 (1-816)	0.037
Duration of LRT (hours)	241.75 (0.5-672)	285.75 (48-576)	216.60 (0.5-672)	0.426
Time in other wards (days)	2.63 (0-13)	4.62 (0-13)	1.50 (0-7)	0.066
ICU stay (days)	18.5 (1-46)	27.63 (14-46)	13.29 (1-34)	0.003
Total hospital stay (days)	21.14 (2-46)	32.25 (18-46)	14.79 (2-34)	0.001

Note: Spearman's rho test, $p < 0.05$.

Table 17: Cases with Lung Replacement Therapy Compared by Outcome and Time Indicators (n=22)

All deaths in the study were due to COVID-19 (U07.1) and its complications. Table 18 shows the relationship between complications and mortality in all cases. Septic shock ($p=0.001$) and multiple organ failure ($p<0.001$) predominated in the group that died, with statistically significant differences between the groups. Pneumonia

($p=1.000$), sepsis ($p=1.000$), respiratory failure ($p=1.000$) and ARDS ($p=1.000$) were present in all cases; acute kidney failure did not occur in the recovered group ($p=0.147$), but there was no statistically significant difference between the groups.

Parameter	Total (n=66)	Recovered (n=10)	Died (n=56)	p*
Sepsis				1.000
Yes	66 (100%)	10 (100%)	56 (100%)	
No	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Septic shock				0.001
Yes	46 (69.7%)	6 (60.0%)	53 (94.6%)	
No	20 (30.3%)	4 (40.0%)	3 (5.4%)	
Respiratory failure				1.000
Yes	66 (100%)	10 (100%)	56 (100%)	
No	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Pneumonia				1.000
Yes	66 (100%)	10 (100%)	56 (100%)	
No	0 (0.0%)	0 (0.0%)	0 (0.0%)	
ARDS				1.000
Yes	66 (100%)	10 (100%)	56 (100%)	
No	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Acute kidney failure				0.147
Yes	10 (15.2%)	0 (0.0%)	10 (17.9%)	
No	546 (84.8%) [as printed]	10 (100%)	48 (87.1%)	
Multiple organ failure				<0.001
Yes	60 (90.9%)	6 (60.0%)	54 (96.4%)	
No	6 (9.1%)	4 (40.0%)	2 (3.6%)	

Note: *chi-square test, $p<0.05$.

Table 18: Complications and Mortality (n=66)

Figure 4 and Table 19 show ROC curves for lymphocytes, NLR, pH and urea. For predicting complication by ARDS in critical COVID-19: lymphocytes AUC 0.778 (95% CI 0.929–0.400, cut-off 0.49), NLR AUC 0.699 (95% CI 1.000–0.900,

cut-off 3.50), pH AUC 0.785 (95% CI 1.000–0.393, cut-off 7.24) and urea AUC 0.746 (95% CI 0.643–0.200, cut-off 48.5), all statistically significant.

Parameter	AUC	Sensitivity	Specificity	Cut-off value	p* (95% CI)
Lymphocytes	0.778	0.929	0.400	0.49	0.005
NLR	0.699	1.000	0.900	3.50	0.045
pH	0.785	1.000	0.393	7.24	0.004
Urea	0.746	0.643	0.200	48.5	0.014

Note: NLR, neutrophil-to-lymphocyte ratio.

Table 19: Diagnostic Accuracy of Indicators in Critically ill Patients

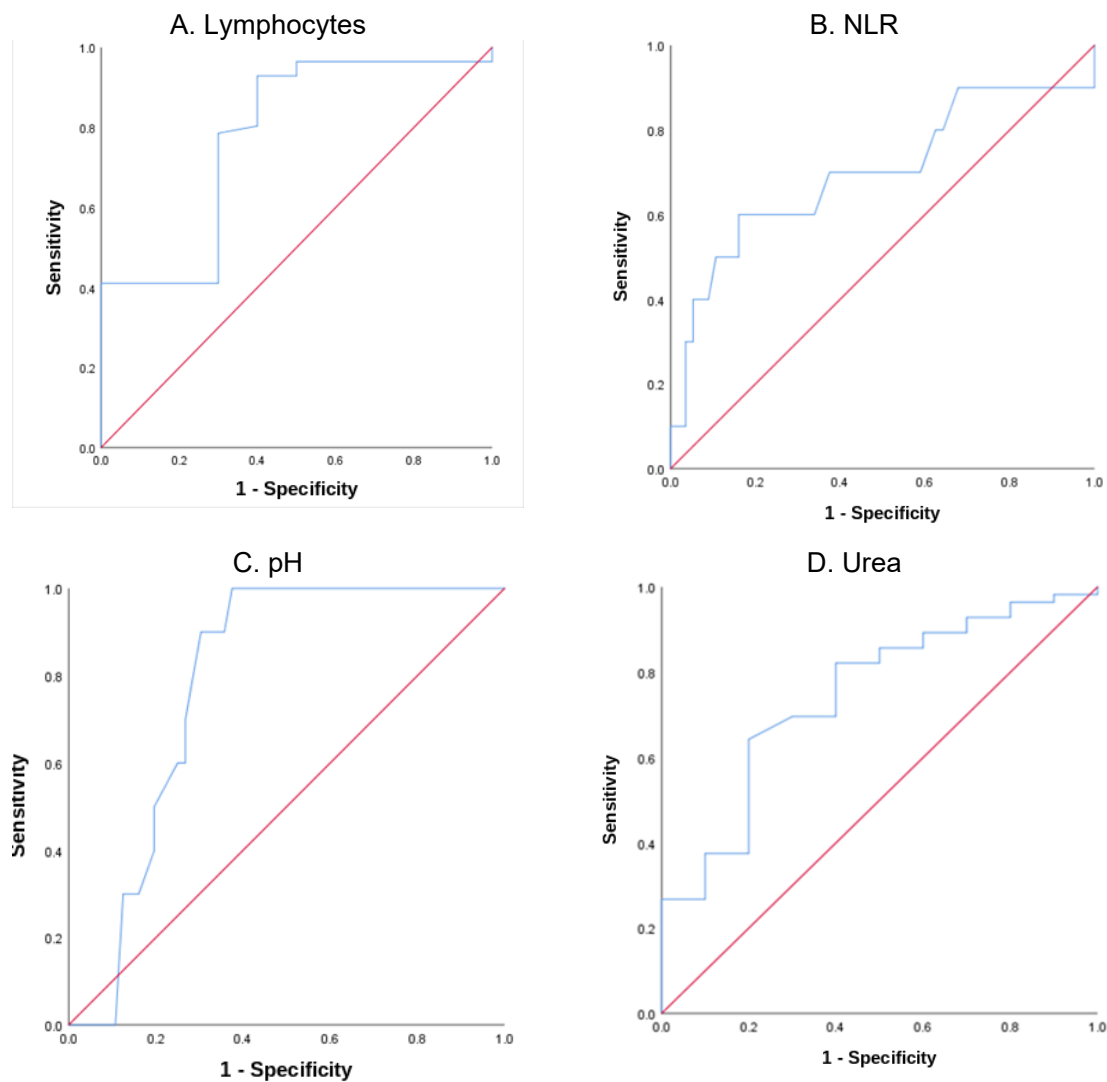


Figure 4: ROC Curves of Diagnostic Accuracy of Indicators in Critically ill Patients

In regression analysis of factors influencing mortality across all study cases, univariate analysis showed that higher pH (HR 0.008, 95% CI 0.001–0.095, $p < 0.001$) and higher bicarbonate (HR 0.947, 95% CI 0.901–0.996, $p = 0.033$) on blood gas analysis reduced the risk of death. In blood tests, higher white cells (HR 1.032, 95% CI 1.006–1.032, $p = 0.017$), lower lymphocytes (HR 1.916, 95% CI 1.321–2.781, $p = 0.001$) and loss of kidney function, i.e. higher creatinine (HR 1.210, 95% CI 1.073–1.364, $p = 0.002$) and higher urea (HR 1.1010, 95% CI 1.004–1.016, $p < 0.001$), increased the risk of death. Regarding treatment, transfusion of blood and blood products (HR 0.354, 95% CI 0.198–0.636, $p = 0.001$), sedation (HR 0.286, 95% CI 0.085–0.968, $p = 0.044$), prone positioning (HR 0.446, 95% CI 0.229–0.872, $p = 0.018$), neuromuscular blockade (HR 0.525, 95% CI 0.298–0.924, $p = 0.026$) and lung replacement therapy (HR 0.278, 95% CI 0.146–0.529, $p = 0.001$) reduced the risk of death, whereas vasopressor therapy (HR 2.927, 95% CI 1.056–8.112, $p = 0.039$), given to patients in shock with an indication for it, increased the risk of death. Longer total mechanical ventilation (HR 0.996, 95% CI 0.994–0.998, $p < 0.001$) and longer ICU stay (HR 0.897, 95% CI 0.865–0.930, $p < 0.001$) reduced the risk of death. The SAPS II score (organ failure and risk of death score) (HR 1.023, 95% CI 0.999–1.049, $p = 0.064$) was not associated.

When these factors were assessed together with age and sex, higher pH (HR 0.009, 95% CI 0.001–0.113, $p < 0.001$) and higher bicarbonate (HR 0.948, 95% CI 0.900–0.999, $p = 0.046$) reduced the risk of death, while higher white cells (HR 1.040, 95% CI 1.011–1.088, $p = 0.006$), lower lymphocytes (HR 2.206, 95% CI 1.449–3.361, $p < 0.001$), loss of kidney function—higher creatinine (HR 1.254, 95% CI 1.104–1.425, $p < 0.001$) and urea (HR 1.012, 95% CI 1.006–1.019, $p < 0.001$)—and a higher SAPS II score (HR 1.028, 95% CI 1.002–1.054, $p = 0.036$) increased it. Transfusion of blood and blood products (HR 0.303, 95% CI 0.153–0.600, $p = 0.001$), prone positioning (HR 0.462, 95% CI 0.223–0.907, $p = 0.025$), neuromuscular blockade (HR 0.525, 95% CI 0.298–0.924, $p = 0.026$) and lung replacement therapy (HR 0.234, 95% CI 0.114–0.480, $p < 0.001$) reduced the risk of death, whereas vasopressor therapy (HR 3.036, 95% CI 1.089–8.467, $p = 0.034$), given to patients in shock with an indication for it, increased it. Longer total mechanical ventilation (HR 0.996, 95% CI 0.994–0.998, $p < 0.001$) and longer ICU stay (HR 0.889, 95% CI 0.855–0.926, $p < 0.001$) reduced the risk of death. Sedation (HR 0.320, 95% CI 0.093–1.104, $p = 0.071$) was not significant (Table 20).

Parameter	cHR	95% CI	p	aHR	95% CI	p
pH	0.008	0.001–0.095	<0.001	0.009	0.001–0.113	<0.001
Bicarbonate	0.947	0.901–0.996	0.033	0.948	0.900–0.999	0.046
White cells	1.032	1.006–1.032	0.017	1.040	1.011–1.088	0.006
Lymphocytes	1.916	1.321–2.781	0.001	2.206	1.449–3.361	<0.001
Creatinine	1.210	1.073–1.364	0.002	1.254	1.104–1.425	<0.001
Urea	1.010	1.004–1.016	<0.001	1.012	1.006–1.019	<0.001
SAPS II score	1.023	0.999–1.049	0.064	1.028	1.002–1.054	0.036
Blood and blood products	0.354	0.198–0.636	0.001	0.303	0.153–0.600	0.001
Sedation	0.286	0.085–0.968	0.044	0.320	0.093–1.104	0.071
Prone positioning	0.446	0.229–0.872	0.018	0.462	0.235–0.907	0.025
Vasopressor therapy	2.927	1.056–8.112	0.039	3.036	1.089–8.467	0.034
Neuromuscular blockade	0.525	0.298–0.924	0.026	0.526	0.287–0.965	0.038
Lung replacement therapy	0.278	0.146–0.529	<0.001	0.234	0.114–0.480	<0.001
Total mechanical ventilation time	0.996	0.994–0.998	<0.001	0.996	0.994–0.998	<0.001
ICU stay	0.897	0.865–0.930	<0.001	0.889	0.855–0.926	<0.001

Note: HR, hazard ratio; aHR, adjusted hazard ratio; SAPS II, Simplified Acute Physiology Score II; Cox regression*, $p < 0.05$. Only significant variables were included.

Table 20: Univariate Analysis of Factors Influencing Mortality in Study Participants (n=66)

In multivariate analysis, lower lymphocytes (HR 2.189, 95% CI 1.258–3.800, $p=0.006$) increased the risk of death, and lung replacement therapy (HR 0.307, 95% CI 0.131–0.722, $p=0.007$) reduced it. pH (HR 0.348, 95% CI 0.016–7.736, $p=0.505$), bicarbonate (HR 0.974, 95% CI 0.917–1.036, $p=0.403$), white cells (HR 0.989, 95% CI 0.955–1.025, $p=0.544$), creatinine (HR 1.131, 95% CI 0.780–1.639,

$p=0.517$), urea (HR 1.006, 95% CI 0.988–1.024, $p=0.524$), prone positioning (HR 0.585, 95% CI 0.798–1.723, $p=0.331$), vasopressor therapy (HR 0.585, 95% CI 0.798–1.723, $p=0.331$) and neuromuscular blockade (HR 1.072, 95% CI 0.475–2.424, $p=0.867$) were not statistically significant (Table 21).

Parameter	HR	95% CI	p
pH	0.348	0.016–7.736	0.505
Bicarbonate	0.974	0.917–1.036	0.403
White cells	0.989	0.955–1.025	0.544
Lymphocytes	2.186	1.258–3.800	0.006
Creatinine	1.131	0.780–1.639	0.517
Urea	1.006	0.988–1.024	0.524
Prone positioning	0.788	0.338–1.837	0.581
Vasopressor therapy	0.585	0.798–1.723	0.331
Neuromuscular blockade	1.072	0.475–2.424	0.867
Lung replacement therapy	0.307	0.131–0.722	0.007

Note: HR, hazard ratio; Cox regression*, $p < 0.05$.

Table 21: Multivariate Analysis of Factors Influencing Mortality in COVID-19 Cases (n=66)

4. Chapter Four. Discussion

In Mongolian health care, ECMO has been performed since February 2021 for patients with critical heart and lung disease at the referral-level hospitals FSCH, TSCH, MCH and NCCD. ECMO, extracorporeal membrane oxygenation, is an advanced technology used to replace the physiological functions of the lungs and heart in respiratory and cardiac

failure of many causes. It is performed in two modes, V-V (veno-venous) and V-A (veno-arterial): V-V mode replaces only the lungs, carrying out gas exchange and supplying the body with oxygen, while V-A mode not only carries out gas exchange but also supports the circulation and replaces cardiac function. We studied 22 patients who received lung replacement therapy in critical COVID-19 in the ICUs of

FSCH, MCH and NCCD in 2021–2022, and 44 patients who had an indication for it but did not receive it. In most ECMO cases during the COVID-19 pandemic, the indication was respiratory failure, so the mode chosen was lung-replacing V-V ECMO. In a few cases, respiratory failure occurred together with acute heart failure, so V-A mode was used. In the study by Shiqian Huang et al. in China, 90% of ECMO in COVID-19 was V-V and 10% V-A, consistent with the modes used in Mongolia [59]. In the observational study by Armin, 117 of 4,510 ICU patients received lung replacement therapy; 82.9% (n=97) received it for more than 2 weeks, 12.8% (n=15) for more than 50 days, and 2 patients for more than 100 days, which was consistent with our results. In our study, 24.0% of LRT cases had obesity, 12.0% diabetes, 32.0% hypertension and 45.5% co-infection. Shiqian Huang et al. considered severe ARDS, older age, comorbidities (obesity, diabetes, hypertension) and secondary infection to be risk factors for death during lung replacement therapy. In their study, LRT complications were venous thrombosis 33%, pulmonary thromboembolism 29% and stroke 5–6%; severe bleeding was rare, and mechanical complications were recorded, including pump failure, circuit embolism, pump damage and oxygenator failure. In our study, complications were bleeding due to cannula or vascular injury 36.4%, stroke 4.5%, peripheral perfusion failure 4.5%, venous thrombosis 4.5% and secondary infection 4.5%, consistent with those findings [59]. The mean age of LRT cases was 46 years; the mean age of those who died was 53 years, and 9.1% of those who died were over 65. Volpi, S., Hayanga, J. A. noted that age is an important factor in lung replacement therapy and a main factor increasing the risk of death in the ICU. Several studies of LRT outcomes in older patients found mortality of 50% or more in patients over 65, consistent with our results [59]. Our finding that sex had no significant effect on mortality agrees with the study by Hayanga, J. A. (p=0.28). In the study by Nivedha. on neurological complications of LRT, intracranial haemorrhage, ischaemic stroke and hypoxic-ischaemic injury occurred in 5.9%, 1.1% and 0.3%, showing that cases with neurovascular changes should not be selected for treatment; in our study, intracranial haemorrhage occurred in 4.5% during LRT, slightly different from those findings [60–63].

In our study, the mean BMI of all LRT patients was 28 kg/m², mean age 46 and male sex 54.5%, slightly different from the study by Armin N. Flinspach. (BMI 31.3 kg/m², mean age 54, male 84.6%). In the study by James Szymanski. of 166 patients, sex and body weight were not significant for risk of death, and high blood pressure significantly influenced recovery (p=0.025). In our study, sex and body weight were not significant, but younger patients predominated among those receiving LRT (p=0.001), and blood pressure was not significant for recovery, which differs. In their univariate regression, creatinine (p=0.003), bicarbonate (p=0.015) and pH (p=0.03), and in multivariate analysis pH (OR 3.35; 95% CI 1.89–5.9; p<0.0001), were risk factors for 30-day mortality, consistent with our results [64]. A Mongolian study by N. Suvd-Erdene. on risk and complication indicators of COVID-19

ARDS found that complication by ARDS was associated with increased white cells and neutrophils (p=0.009), NLR (p<0.001) and C-reactive protein (p<0.001) and decreased lymphocytes (p=0.001), consistent with our results. That study also found sepsis increased the risk of death 5.84-fold, whereas in our study sepsis (p=1.000) showed no significant difference in risk of death, while septic shock (p=0.001) and multiple organ failure (p<0.001) were risks for death, which differs [65]. Armin N. Flinspach et al. found no significant association between duration of lung replacement therapy and mortality (p=0.15), consistent with our results. In our study, complications during therapy occurred in 54.5%, with no significant difference by duration, whereas in the study by Armin N. Flinspach, 2 cases treated with LRT for over 100 days died of septic shock.⁶⁷ Norbert Banjas et al., in a study covering 6 years, divided LRT cases into 3 groups. In the first group (respiratory failure), respiratory infection accounted for 57%, and before LRT the mean SOFA (Sequential Organ Failure Assessment) score was 6 and mean SAPS II (Simplified Acute Physiology Score) 40. In the second group, myocardial infarction, the commonest cause of heart failure, accounted for 69%, with mean SOFA 10 and mean SAPS II 67.2 before LRT. In the third group, the main cause of septic shock was respiratory infection (53%), the second abdominal infection (pancreatitis, gastric perforation, cholangitis, etc.), with mean SOFA 8 and mean SAPS II 42. Mean hospital stays for the three groups were 11, 5 and 14 days. After LRT began, blood pH and other laboratory values improved. In our study, 64% of LRT cases died, slightly higher than the overall mortality of 56% in the study by Norbert Banjas et al. That study found LRT reduced hospital mortality compared with the period 6 years earlier, before LRT was available [67]. In another study, hospital mortality with LRT was 69%, and in multivariate analysis >72 hours in hospital before starting LRT, SOFA score >14, PaO₂/FiO₂ <60 and pH <7.2 predicted hospital mortality [68]. In the study by Thomas Orthmann et al., ICU survival with LRT was 49%; in univariate analysis, high ventilator pressures lasting 24 and 48 hours during LRT (all LRT patients), longer mechanical ventilation before LRT, and high ventilator pressures lasting 24 hours during LRT (patients with ARDS) were associated with mortality. In the multivariate analysis by Andreas Peer, duration of ventilation before LRT was not associated with mortality, consistent with our results [69]. Also, in the study by Andreas Peer, 59.5% recovered and 40.5% died after LRT, which differs from our mortality of 64% and recovery of 36%; this may be linked to the treating team's many years of experience and to patient selection. The main cause of death was sepsis and resulting multiple organ failure (53.3%), and one patient died of a bleeding complication. Pulmonary embolism, a complication of therapy, occurred in 2 survivors and 5 who died. Deep vein thrombosis continued to be diagnosed among survivors. Among the 22 LRT patients in our study, bleeding occurred in 12.5% of the recovered group and 50.0% of the group that died, lower than the 36.4% and 73.3% in the study by Andreas Peer. In that study, bacterial co-infection was found in 100% of ICU deaths, fungal infection in 73.3% and fungal co-infection in 9.1%, while in the recovered group bacterial

co-infection was 86.4% and fungal co-infection also 86.4%. These are higher than our figures of 53.6% in the group that died and 40.0% in the recovered group [70]. During the COVID-19 pandemic, many countries newly introduced lung replacement therapy and began using it on a large scale, and many studies have been done on its outcomes in COVID-19. In the review by Pietro Bertini, ICU mortality with LRT was 39%, males made up 71%, and mean duration of LRT was 15 days [71]. In the study by Yingchun Zeng et al., 50% of LRT patients died of septic shock and multiple organ failure, and late complications, infection and bleeding occurred. That study noted high mortality and a treatment cost of USD 73,122 [72]. A study of 673 COVID-19 ARDS patients treated at 26 LRT centres, examining factors in recovery, found comorbidities of cardiovascular disease 62%, diabetes 28% and chronic lung disease 15%. Age, time to mechanical ventilation, BMI, renal replacement therapy and patient selection were associated with the chance of recovery. O₂, SpO₂, pCO₂ and pH did not differ importantly between those who recovered and those who died. Mean ventilation time before LRT was 1.8–2 days in those who recovered and 4–5 days in those who died. On this basis, survival was more likely if LRT began within 5 days of ventilation. Treatment complications were bleeding and thromboembolism in 66% and secondary respiratory and bloodstream infection in 62%; bleeding and thromboembolism worsened mortality [73]. In the cohort study by Raphaël Giraud et al., mortality among patients with COVID-19 respiratory failure treated with LRT was 60%; 50% developed pulmonary fibrosis preventing weaning from the ventilator, and 10% died of massive stroke. All cases ventilated for 7 days or more before LRT died. Duration of ventilation before LRT, duration of LRT and length of ICU stay had important effects on recovery [74]. In our study, increased urea ($p < 0.001$) and creatinine ($p = 0.002$) increased the risk of death. ECMO guidelines note that ECMO carries a risk of reducing renal blood supply and causing kidney failure.

A study by Xiaolan Gao. of 454 patients at the Mayo Clinic, USA, published in 2023, concluded that mortality in ECMO patients with acute kidney failure was 3.7 times that of ECMO patients without it. However, the study concluded that ECMO was not associated with developing acute kidney failure; rather, norepinephrine, vasopressin, vancomycin, proton pump inhibitors, contrast agents and infection caused it [75]. In the review by Nik Muhammad Faiz Bin Nik Sofizan et al. covering 18 countries, the cause of COVID-19 death in 348 cases was respiratory system failure; on histology, diffuse alveolar damage (DAD) progressing to ARDS and multiple organ failure led to death [76]. In the COVID-19 autopsy study by Saskia von Stillfried. in Germany, 86% of 1,095 cases died of COVID-19 and 14% of comorbidities. The male-to-female ratio was 1:8 [as printed], with men aged 60–65 and women aged 80–84 predominating; histology of COVID-19 deaths showed death from diffuse alveolar damage (DAD), ARDS and multiple organ failure [77]. The study by Hetal C. Kyada et al. in India included 33 cases, 28 men and 5 women. Macroscopically, diffuse pulmonary oedema and thrombi were found; microscopically, diffuse alveolar damage (DAD)

in 87.88%, secondary bacterial pneumonia and lung abscess in 51.52%, and acute tubular injury and microthrombi in the heart, lungs and kidneys in 63.65% [78].

4.1. Limitations of the Study

This study used a hospital-based retrospective design. Of the 28 patients who received heart-lung replacement therapy in Mongolia in 2021–2022, we selected the 22 cases meeting our inclusion criteria; others were excluded because, on review of the records, some clinical data were not recorded and ventilator parameters during the critical phase were missing. No pathological autopsies were done in cases that died of critical COVID-19, so the fatal complications could be assessed only from clinical findings, not differentiated at the tissue, cell and organ level. We used only clinical symptoms, laboratory results and ICU care indicators from medical records in a retrospective design, and data on infectious pathogens and antibiotic resistance among participants were lacking. These were limitations of our study [79].

5. Chapter Five. Conclusions

- In critical COVID-19, lung replacement therapy was given mainly to younger patients, patients with more severe lung tissue injury and unvaccinated patients, and lung replacement therapy reduced the risk of death by 70%.
- In critical COVID-19, acidosis, loss of kidney function and acute inflammatory complications increased the risk of death, while sedation (induced sleep and calming), prone positioning and neuromuscular blockade reduced it.

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