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Post-COVID changes in respiratory function in patients supported with veno-venous extracorporeal membrane oxygenation (V-V ECMO)

PhD Thesis

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List of scientific papers included in this thesis:

I. Zöllei É, Rudas L, Hankovszky P, Korsós A, **Pálfi A**, Varga Z, Tomozi L, Hegedüs Z, Bari G, Lobozárné Szivós B, Kiszel A, Babik B. Venovenous extracorporeal membrane oxygenation for COVID-19 associated severe respiratory failure: Case series from a Hungarian tertiary centre. *Perfusion*. 2024; 39(4):790-796. doi: 10.1177/02676591231160272. [IF: 1.1, Q2]

II. **Pálfi A**, Balogh ÁL, Polónyi G, Schulcz D, Zöllei É, Bari G, Fodor GH, Baráth K, Somfay A, Peták F, Babik B. Post-COVID changes in lung function 6 months after veno-venous extracorporeal membrane oxygenation: a prospective observational clinical trial. *Front Med*. 2023; 10:1288679. doi: 10.3389/fmed.2023.1288679. [IF: 3.1, Q1]

III. **Pálfi A**, Zöllei É, Varga Z, Tomozi LB, Schulcz D, Bari G, Peták F, Kun-Szabó F, Baráth K, Rudas L, Balogh ÁL, Babik B. Venovenous Extracorporeal Membrane Oxygenation for COVID-19 in Postpartum Patients: 1-Year Outcome. *J Cardiothorac Vasc Anesth*. 2024 38(8): 1746-1752. doi: 10.1053/j.jvca.2024.04.027. [IF: 2.3, Q2]

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LIST OF ABBREVIATIONS

6MWT	6-minute walk test
ACE 2	Angiotensin converting enzyme 2
ACT	Activated clotting time
APACHE II	Acute Physiology and Chronic Health Evaluation score
aPTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
ATS	American Thoracic Society
BSI	Blood stream infection
COVID-19	Coronavirus disease 2019
CT	Computer tomography
DLCO	Diffusing capacity of carbon monoxide
ECBF	Extracorporeal blood flow
ECLS	Extracorporeal life support
ECMO	Extracorporeal Membrane Oxygenation
ELSO	Extracorporeal Life Support Organisation
ERS	European Respiratory Society
ERV	Expiratory reserve volume
$FEF_{25–75}$	Forced expiratory flow between 25 and 75% of the volume expired
FEV_1	Forced expiratory volume in 1 sec
FiO_2	Fraction of inspired oxygen
FRC	Functional residual capacity
FVC	Forced vital capacity
H1N1	Influenza A virus subtype H1N1
IBW	Ideal body weight
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
IRV	Inspiratory reserve volume
IU	International unit
KCO	Carbon monoxide transfer coefficient
LISS	Lung injury severity score
LRTI	Ventilator-associated lower respiratory tract infection
NIV	Non-invasive ventilation

PaO_2	Arterial partial pressure of oxygen
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2/FiO_2	Ratio of arterial partial pressure of oxygen and fraction of inspired oxygen
PCV	Pressure control ventilation mode
PCT	Procalcitonin
PEEP	Positive end expiratory pressure
PEF	Peak expiratory flow
PICS	Post-inensive care syndrome
P-SILI	Patient self inflicted lung injury
RASS	Richmond agitation sedation scale
RESP score	Respiratory ECMO prediction score
rt-PCR	Real-time polymerase chain reaction
RV	Residual volume
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SF-36	Short Form (36) Health Survey
SG	Sweep gas
TLC	Total lung capacity
UFH	Unfractioned heparin
UTI	Urinary tract infection
VA	Alveolar volume
VILI	Ventilator induced lung injury
V/Q	Ventilation /perfusion ratio
Vt/PBW	The ratio of tidal volume and predicted body weight

I. BACKGROUND

Severe coronavirus disease 2019 (COVID-19) and associated pneumonia can seriously affect the gas exchange in the lungs. Acute respiratory distress syndrome (ARDS) caused by the viral infection can result in severe impairment of the lung function, leading to life-threatening hypoxemia. Mainly, the disease is characterized by hypoxemic respiratory failure, and it may necessitate invasive mechanical ventilation. Furthermore, in the most severe cases, veno-venous extracorporeal membrane oxygenation (V-V ECMO) support is required. In our Tertiary Centre we followed the recommendations of the European Extracorporeal Life Support Organization (EURO ELSO) guidelines for the management of severe respiratory failure caused by COVID-19 and ECMO support. The V-V ECMO as a rescue therapy provides an opportunity to ventilate the lungs on resting parameters and minimalize ventilator induced lung injury (VILI), providing time for lung recovery. On the other hand, the inflammation cascade is activated during ECMO support and as a result, endothelial and/or epithelial damage occurs in the pulmonary system potentially leading to long-term gas exchange defect along with the fibrotic consequences of ARDS. During the COVID-19 pandemic, 18 patients were supported with V-V ECMO in our institution with nine patients surviving the hospitalization. Studies included in the present thesis gained information on this patient population in the acute phase, and extended assessments of the long-term consequences was also performed 6 months and 1 year after hospital discharge.

I.1. COVID-19: broad acute clinical spectrum with a dominance of pulmonary pathophysiology

I.1.1. Basic characteristics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Novel SARS-CoV-2 is an RNA virus causing infection later called COVID-19. Five main genetical variants of the virus have been identified during the pandemic: alpha, beta, gamma, delta and omicron. The global spreading of these 5 variants led to the pandemic and caused more than 6 millions deaths worldwide[1].

Coronavirus subfamily of Orthocoronavirinae forms 4 subgroups: alphacoronavirus, betacoronavirus, deltacoronavirus and gammacoronavirus. SARS-CoV-2 belongs to the subgroup of betacoronavirus, the same family of RNA viruses as the Middle East Respiratory Syndrome coronavirus (MERS-CoV) and as the severe acute respiratory syndrome coronavirus

(SARS-CoV). According to genomic examinations, zoonotic transmission of the novel coronavirus cannot be excluded[1].

The severity of the disease ranges from asymptomatic infection to severe respiratory failure, noted as COVID-19 pneumonia[2] and ARDS. The virus was first isolated in Wuhan region of China in 2019[1], and spreaded across the globe in the following months, causing several waves in the forthcoming years. One distinctive symptom of the viral infection is anosmia, and can be accompanied by influenza-like manifestation, including fever, dry cough, gastrointestinal dyscomfort, shortness of breath[1] and pneumonia[2]. The transmission of the virus is via respiratory droplets. Vertical transmission to neonates from COVID-19 infected mothers is possible, but infrequently happens[3].

The spike part of the virus binds to the angiotensin converting enzyme 2 (ACE2) receptors in the respiratory epithelium[1]. Coronavirus infection results in endothelial and epithelial damage and endotheliitis in the lung tissue, which exacerbates the permeability of the vasculature in the alveolo-capillary bed, and enhances the development of non-cardiogenic pulmonary oedema[1 4 5]. Cytokine storm is a result of excessive production of pro-inflammatory cytokines as interleukin-1, interleukin-6, and tumor necrosis factor alpha with extremely high mortality[1]. Pro-inflammatory cytokine release promotes systemic inflammatory response leading to tissue damage with increased mortality[1]. Lung injury causes very severe hypoxemic respiratory failure, called ARDS. Radiological signs of ARDS consist of bilateral pulmonary patchy infiltrates on chest imaging, resulting in severe hypoxemia. ARDS has 3 distinctive phases: exudative, proliferative and fibrotic[5 6]. As a consequence of the inflammation of the lung tissue and pulmonary endothelium, endogenous progenitor cells and lung fibroblasts migrate and proliferate [5]. As a result of excessive tissue repair process, fibrosis can develop in the respiratory system in later stages of the disease (fibrotic phase of ARDS)[5,7]. ACE2 receptors are also localised in extrapulmonar tissues, including myocardial cells and tubular cells of the kidney. As a consequence, cardiac and renal complications can occur after the infection[1].

I.1.2. Respiratory failure subsequent to COVID-19

The lungs are the primary target of SARS-CoV-2[1]. This mechanism can partly involve the local entry of the pathogen and endothelial dysfunction caused by the large endothelial surface per unit tissue mass in the pulmonary system[1]. Accordingly, the most evident outcomes that can determine overall patient status are commonly related to acute detrimental changes in lung function and structure. Life-threatening adverse events commonly manifest in the acute phase

of coronavirus infection[1,2]. However, the remaining symptoms after COVID-19 recovery also present a major challenge among healthcare providers[8–19]. Similar to the acute phase, the lungs are the most persistently and extensively affected among the organs after COVID-19 infection[1]. Several factors can influence the development and severity of post-COVID-19 pulmonary symptoms[1,2,20,21]. These include age, pre-existing medical conditions, and the severity of infection in the acute phase.

Patients barely suffer from subjective hypoxaemia at the beginning of COVID-19 pneumonia, a status called as "happy hypoxaemia"[22,23]. As the pneumonia progresses, severe gas exchange impairment evolves and patients can develop severe tachydyspnoea, with high respiratory drive and tidal volumes, referred as patient self-inflicted lung injury (P-SILI)[2,23,24]. Excessive respiratory muscle use contributes to mechanical stress (the force applied to the lung tissue, i.e. pressure ont he lung parenchyma) and strain (the deformation of the lung tissue in response to stress), similarly to mechanical ventilation and further aggravates lung injury[25]. Mechanoreceptors sending signals from the stiff lungs can further aggravate P-SILI[24,26]. It is crucial to detect the high respiratory drive, increased work of breathing at the bedside in order to prevent volutrauma (high volume lung injury), though not always visible if the patient is analgosedated[26]. Increased respiratory drive can result in increased inspiratory effort and distending pressures[24,26–28]. The overdistended alveoli have a mechanical effect on the vasculature of the respiratory system, and the compressing effect of the capillary bed leads to perfusion defects, and enhance the ventilation/perfusion (V/Q) mismatch. As a final result, gas exchange abnormalities intensify. Furthermore, negative pressure pulmonary oedema can occur as a consequence of large inspiratory effort, which completes the gas exchange defect[24].

I.1.3. Invasive mechanican ventilation

Early invasive mechanical ventilation could prevent the development of P-SILI and has the potential to reverse hypoxaemia[2]. Nevertheless, it can also injure healthy and impaired lungs, and could even provoke newly onset lung injury[29]. Ventilating the patients with high pressures and volumens lead to baro-, volu-, atelecto- and biotrauma[29,30]. The use of 100% oxygen on the respirator setting may result in denitrogenation absorbtion atelectasis particularly in an inhomogeneous lung[31]. Furthermore, epithelial hyperoxia activates mitochondrial reactive oxygen species-generating pathways, leading to accelereated cell apoptosis that further aggravates organ dysfunction[32,33]. These injuries are referred as ventilator-induced lung injury (VILI). Both P-SILI and VILI may converge to ARDS.

ARDS is an inflammatory reaction to different lung injury forms, such as viral, bacterial, fungal infection, or exposure to toxins and smoke[6]. Alveolar epithelial damage and vascular endothelial destruction, the release of inflammatory cytokins are pertinent characteristics of the following lung dysfunction in ARDS[26]. The functional lung size is decreased as a consequence of interstitial and alveolar oedema (so-called „baby-lung", demonstrating the size of the functional lung volume)[26,29]. The conceptualization of the baby lung redirected the attention to decrease the overdistending pressures (stress and strain) applied on the functioning lung parenchyma and reduce the risk of VILI[29]. The baby lung encompasses a functional rather than anatomical part of the lung tissue, oxygenation and carbon-dioxide clearence mainly occurs within it[34]. In the prone position, baby lung moves to the dorsal parts of the lungs and expands in size, increasing the available surface for gas exchange[34]. According to the Berlin Definition Consensus of ARDS, newly onset (<7 days) respiratory failure (arterial hypoxaemia) is present, with bilateral pulmonary infiltrates not cardiogenic of origin or not subsequent to fluid overload[1,5,7]. The severity of ARDS is defined by the ratio of partial arterial pressure of oxygen and inhaled oxygen ratio (PaO_2/FiO_2, known as Horowitz index). Mild ARDS is characterizd by 200 mmHg <PaO_2/FiO_2 <300 mmHg. Moderate ARDS is classified by 100 mmHg <PaO_2/FiO_2 <200 mmHg. Severe ARDS is defined by PaO_2/FiO_2) <100 with PEEP (positive end expiratory pressure) >5 cmH_2O[1,5,7,35,36]. In optimal cases, chest computed tomography (CT) scan is performed to quantify lung areas damaged by the noxous insult, or chest X-ray is done in lower income countries[36]. The diagnosis of ARDS is a non-specific clinical entity, and does not include the etiology of the acutely onset respiratory failure, but a globally accepted and helpful tool in the further management of patients suffering from respiratory failure[36].

In the literature, three distinctive phases of ARDS present: exudative, proliferative, and fibrotic phases occur[5,7,36]. Molecular mechanism of lung tissue injury include the excessive production of cytokins, chemokins, oxidants, and proteases, further exasperating lung tissue damage and circulating to other organs[7]. In normal circumstances, the healthy lung has a crucial role in the innate and adaptive immune system[7], and also has important role in drug metabolism as well, but they are also diminished with lung injury[37].

I.1.4. Protective invasive ventilation

Avoiding this pathology (lung injury connected to mechanical ventilation) led to the concept of lung protective ventilation and rescue maneuvers. The concept of lung-protective ventilation mainly focuses on defendeing the baby lung from mechanical injuries associated with

mechanical ventilation[29]. During pressure-limited ventilation the main goal is to keep the plateau airway pressure <30 cmH_2O (minimizing barotrauma), and during volume-limited protective ventilation with tidal volumes 4-6 ml/kg ideal body weight (IBW) (decreasing the odds of volutrauma)[38]. Administration of higher PEEP values (10-15 cmH_2O) prevents cyclic collapse and reopening of alveoli, i.e. atelectotrauma and plays a role in right ventricle protective ventilation[29,39,40]. In addition, prone positioning can also be considered as a rescue maneuver to fragment large dorsal atelectatic lung regions allowing decreasing transpulmonary pressure and enhancing ventilation-perfusion matching and increase baby lung (functioning lung volume) size[2,9,29,34]. If these interventions are unable to provide adequete gas exchange, or gas exchange optimization can only occur with high distending pressures, V-V ECMO offers pivotal opportunity to maintain systemic oxygenation while preventing further lung injury by using lung-protective (or ultra-protective) ventilation settings[38,41].

I.2. ECMO as extracorporeal life support (ECLS) modality

I.2.1. ECMO as a high-level integral part of intensive therapy

The first successful use of V-V ECMO was in 1971 as an altered lung-heart machine[42]. Improvement of different methods and materials led to the renaissance of the V-V ECMO, especially in the 2009 influenza (H1N1) pandemic[41,43–45]. Since then, new materials and new technologies were born to help physicians across the globe in order to make the extracorporeal support more feasible and safe[46–48].

The two major configurations of the ECLS are the veno-venous and the veno-arterial extracorporeal membrane oxygenation (ECMO)[43,46,49]. Veno-venous (V-V) support is indicated in patients with preserved right heart function with severe respiratory failure, either due to hypoxemic or global respiratory insufficiency[43,44,46,49]. The other main configuration is the veno-arterial (V-A) form, which is the complete support for cardiac and respiratory function, the main indication is either cardiogenic shock or the performance of extracorporeal cardiopulmonary resuscitation (eCPR)[43,46]. Extracorporeal Life Support Organization (ELSO) provided guidelines[50] for the initialization of the ECMO support in COVID-19 pandemic and patient selection was based on individual decisions, taking into consideration the overall health data of the patients, and institutional availability of the resources, materials and equipments for the ECMO support. **(Figure 1)**

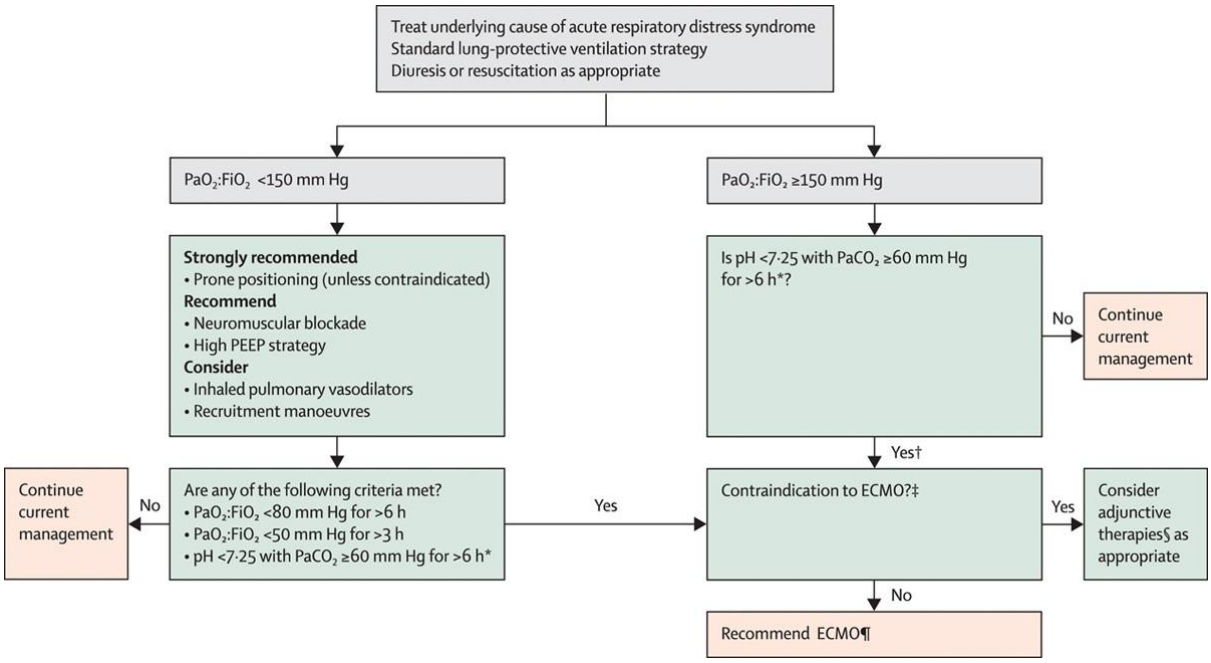

***Figure 1**: Decision making algorithm for the indication of ECMO support in adult ARDS*
Source: Ref.[50]

I.2.2. Ventilation management during V-V ECMO

Airway management during ARDS and V-V ECMO support includes deep analgosedation and the endotracheal intubation of the patients and using invasive mechanical ventilation (IMV) during the majority of the V-V ECMO support[30,38]. In some centres, patients are extubated after the initialization of ECMO, this led to the concept of awake ECMO[51]. The main goal during ventilation is the prevention of atalectasis, applying frequent chest physiotherapy and clearing secretions from the respiratory system. In our tertiary centre we performed percutaneous tracheostomy in majority of the cases due to prolonged IMV. Invasive mechanical ventilation via tracheostomy cannula permits the decrease and eventually ceasing sedative agents and more active involvement in physitoherapy sessions. Once the patients were weaned from V-V ECMO and the lung compliance returned to normal, gas exchange completely relies on the native lung function. In cases when the respiratory system does not need any further support from the ventilator, patients can be weaned from mechanical ventilation and tracheostomy cannula can be removed.

After the cannulation of the patients, and commencing V-V ECMO support, lung protective ventilation could take place[30,38,48]. The major components of ventilation is to decrease the plateau pressure, and to keep the lungs open with higher PEEP (10-15 cmH_2O) and prevent atelectotrauma[30,38,48,51]. Protective lung ventilation is useful in decreasing the harmful effects

of invasive mechanical ventilation and further injury of the respiratory epithel and endothel, mainly in the baby lung. This ventilation strategy applies low tidal volumes and low plateau pressures[30]. One of the specific aspects of ARDS is the production of pro-inflammatory molecules, circulating far from the lungs[7]. It can exacerbate primary hypoxemic extrapulmonary damage to the tissues, e.g. resulting in acute kidney injury, cardiac dysfunction[1,7], especially with increased right ventricle afterload. Right sided heart failure could aggravate the clinical state[39,52]. Pro-inflammatory cytokin production is enhanced due to the biotrauma[7,23] of the lungs, which is the result of barotrauma, volutrauma, oxytrauma and atelectotrauma[40]. Ergotrauma (application of excessive mechanical energy during invasive ventilation) and myotrauma (diaphragm injury) are also part of the evolvement of VILI[25,38,53]. Arterial oxygen saturation (SaO_2) of 100% is barely achievable with the use of V-V ECMO if the lungs are severely injured due to the intrapulmonary shunt contributing to the systemic cardiac output[43,54].

I.3. Population at risk for severe COVID-19 requiring V-V ECMO

According to multiple studies[1,20,21], there are several risk factors in the development of severe COVID-19 ARDS. The population at risk includes patients with obesity, elderly age and patients with cardiovasular comorbodities (i.e. hypertension)[1]. Obesity, hypertension and diabetes mellitus[20] have a high impact on poor clinical outcome due to the fundamental changes in cardiovascular system, including the presence of chronic inflammatory phenotype of the vessels. Diabetes-associated hyperglicaemia has a negative impact on the overall function of the immune system and oxidative stress, endotheliopathies in various organs and coagulation disturbances further enhance this negative trajectory[20]. Alveolar microangiopathy may lead to further deterioration of gas exchange in COVID-19 pneumonia in patients with diabetes[20]. Another main risk factor is pregnancy associated altered immunological state[3,55,56]. Severe COVID-19 infection of otherwise healthy and young parturient women were observed globally[3]. Pregnant women are naturally in a meticulously planned immunocompromised state to prevent the rejection of the fetus and they are at higher risk to develop serious coronavirus infection[3].

I.4. Post-intensive care syndrome (PICS)

PICS refers to a group of physical, cognitive, and psychological symptoms that may persist after a patient is discharged from the intensive care unit[57]. Common physical issues include breathing difficulties, muscle weakness, fatigue, often resulting from deep sedation, mechanical

ventilation and prolonged immobility. Cognitive problems such as memory loss, attention deficits, and impaired executive function are also common. Many patients experience mental health challenges, including anxiety, depression, and post-traumatic stress disorder. These symptoms have been increasingly recognized in survivors of severe COVID-19, especially those who required ICU care[8,58].

II. AIMS AND HYPOTHESIS

Treatment of severe respiratory dystress resulting from SARS-CoV-2 infection may comprise the application of V-V ECMO if the conventional ventilatory strategy involving protective lung ventilation and prone posisitoning is ineffective[2]. However, patient outcomes following V-V ECMO support in these patients have not been chracterized in short and longer time window. Therefore, studies included in the present thesis aim at investigating the characteristics and outcomes of patients needing V-V ECMO in our ICU, whith specific focus on the

- survival rate;
- assessing the surviving patients' ability to perform activities of daily living in a follow-up manner;
- long-term (6 months) pulmonary effects;
- describing the clinical course of 3 postpartum women who required V-V ECMO support immediately after their urgent cesarean sections.

To address these aims, we collected data on the baseline demographics, patient history regarding COVID-19 infection and respiratory failure, including disease severity scores, and the specific challenges and time intervals of the invasive mechanical ventilation and V-V ECMO support. Regarding the respiratory and pulmonary effects of severe COVID-19 forced oscillation technique, spirometry, whole body pletysmography and alveolar gas diffusion measurement were used. Six-minute walk test (6MWT) and data from the 36 Item Short Form Survey (SF-36) were collected to measure physical and pschycological health and quality of life, social recovery.

Our hypothesis was that severe COVID-19 pneumonia requiring invasive mechanical ventilation and V-V ECMO is a highly valuable rescue treatment modality to facilitate patient survival, thereby allowing reintegration into the society, achieving independence and the ability to maintain self-sustaining live. However, long-term detrimental effect on the respiratory system may be anticipated after hospital discharge, which may require a regular follow-up and

treatment to maintain good general health and social embedding with active participation in the society.

III. METHODS

III.1. Ethics approvals

Studies included in the present thesis were approved by the Regional and Institutional Review Board of Human Investigations of University of Szeged (SZTERKEB No: 145/2022. and 143/2021; Trial registration no. NCT05812196). Informed consent was waived for the case controll studies due to the retrospective nature of the study and the lack of intervention. For the respiratory follow-up, the patients provided a written informed consent. This study was performed in accordance with the CONSORT guidelines. The studies were conducted in accordance with the local legislation and institutional requirements.

III.2. Patients

III.2.1. Patients with severe COVID-19 requiring V-V ECMO

We included all SARS-CoV-2 positive patients who received V-V ECMO support at our centre between March 2021 and May 2022 in our studies. During the selection of patients for V-V ECMO, we followed the updated ELSO guidelines[50] and the final decisions were made on a case-by-case basis. Eighteen patients were eligible for the V-V ECMO support, we achieved ICU and inhospital survival rates of 56% and 50%, respectively. Five patients were retrieved to our department on mobile ECMO from county hospitals. None of the patients had any serious comorbidity in their previous medical history, except one who had psoriasis.

III.2.2. Patients in the 6-month respiratory follow-up

For the 6-month respiratory follow-up study, 55 subjects were assessed for eligibility and were divided into the two study groups. Nine post-ECMO patients were eligible for the follow-up measurements 6 and 12 month after hospital discharge (Group COVID). Control group of patients were recruited from an ongoing study applying the same methodology as for healthy adults (Group H). Exclusion criteria comprised a history of smoking, chronic respiratory disease, or COVID-19-induced pneumonia requiring hospitalization. We selected 9 control subjects using propensity score matching, based on demographic characteristics relevant to lung function outcomes such as sex, age, height, and weight. **(Figure 2)**

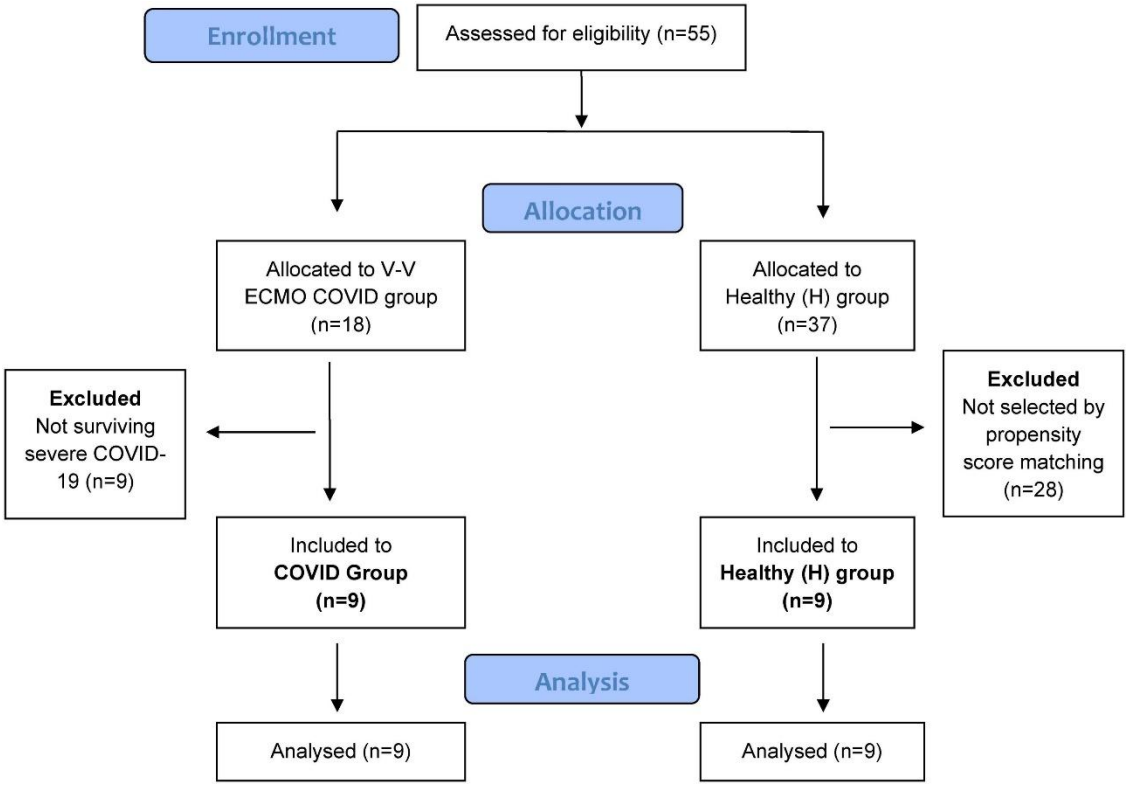

Figure 2: *Patient flow chart*

At the 6-month assessments, results from the V-V ECMO patients were compared to those obtained in a control group of patients. They were recruited from an ongioing study that applied the same methodology used for healthy adults, with the exclusion criteria of history of smoking, chronic respiratory disease, or hospitalization for COVID-19 induced pneumonia. We used propensity score matching to select the healthy, matched control group. This selection was based on demographic characteristics relevant to lung function outcomes, such as sex, age, height and weight, from the control cohort.

III.2.3. Peripartum women with life-threatening COVID-19 with V-V ECMO support

One noteworthy patient population is the peripartum women, who are particularly susceptible to severe respiratory symptoms. This complex pathophysiology involves mechanical and hormonal pathways, lung restriction[59] and increased oxygen demand by pregnancy[60–62]. We supported 3 postpartum patients in our ICU immediately after their urgent cesarean sections due to severe hypoxemic respiratory failure and all of them survived the hospital discharge hence they were also included in the follow-up examinations. These postpartum women had distinguised pathophysiological characteristics and thus, detailed description of their individual course of disease and management warrant attention.

Case 1

A 26-year old pregnant woman presented with upper airway symptoms and was tested positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) at the 32nd week of gestation. Ten days later, she was admitted to the emergency department with an oxygen saturation of 60% on room air. A chest radiograph revealed bilateral patchy infiltrates indicative of COVID-19 pneumonia. Despite oxygen therapy, her condition worsened, necessitating an urgent cesarean section under regional anesthesia with non invasive ventilation (NIV) at 100% FiO_2. After delivery, she was admitted to the intensive care unit (ICU), intubated, and mechanically ventilated on the first postpartum day due to severe respiratory failure. Prone positioning was also performed for better oxygenation. On the following day, she was referred to the regional tertiary center's ECMO service. An expert team from this center was mobilized to initiate ECMO support at the county hospital and she was transferred to our centre with ongoing mobile ECMO support. Standard ECMO support continued in our intensive care unit. Alongside ongoing COVID-19-specific treatment, standard, whole-spectrum intensive therapy was established. Ceftriaxone (1 g, IV, twice daily) was added due to suspected bacterial superinfection. Owing to insufficient improvement in respiratory mechanics and gas exchange, as estimated by a 100% oxygen test, a percutaneous tracheostomy was performed on the day 12 of ECMO support. On day 20 of ECMO support, she developed fever, and her serum procalcitonin level increased. Microbiological sampling confirmed catheter-related bloodstream infection and ventilator-associated pneumonia caused by multidrug-resistant Acinetobacter baumannii, leading to the initiation of colistin therapy (3 million IU, IV, 3 times daily). Additionally, she developed purulent sinusitis and corneal ulceration with purulent keratitis in her right eye, caused by Pseudomonas aeruginosa. These conditions were treated with specific nasal drops of oxymetazoline hydrochloride (2 drops into each nasal opening, 4 times daily) and topical antibiotics (neomycin and dexamethasone/tobramycin 5-7 times daily) along with a cycloplegic solution (cicloplegicedol drops locally, 4 times daily). On day 25 of ECMO support, after a 5-hour period without the sweep gas (SG), she was successfully weaned from ECMO. However, an additional 10 days of mechanical ventilation was needed to wean from the ventilator. Two days after ventilator weaning, her tracheostomy cannula was removed. She left the ICU for a rehabilitation facility 38 days after ECMO initiation.

Case 2

A 28-year old woman with no history for major diseases tested positive for SARS-CoV-2 at the 26th gestational week of pregnancy. She was admitted to the ICU at a county hospital where an urgent cesarean section was performed under general anesthesia and invasive ventilation. Two days later, she was referred to V-V ECMO because of respiratory therapy refracter hypoxia. Our mobile ECMO team initiated the extracorporeal life support, and she was subsequently transferred to our tertiary centre to continue standard ECMO support along with standard intensive therapy. We continued invasive mechanical ventilation on rest settings under deep sedation, and she also received her COVID-19 specific therapy. After 10 days of extracorporeal support, the tidal volume on rest ventilation setting normalized, allowing weaning from ECMO and decannulation. On the next day, the level of sedation was decreased, and she was successfully weaned from the ventilator and extubated. As a part of the post decannulation routine examination, Doppler ultrasound examination revealed mural thrombi at both cannulation sites, prompting the initiation of enoxaparine in a therapeutic dose (80 mg, subcutaneously, twice daily). On day 14 of her ICU stay, she became febrile without elevation in the procalcitonin level (0.10 ng/mL). Samples for microbiological examination were collected. Abdominal ultrasound examination confirmed the presence of a hematoma anterior to the uterus. Ultrasound-guided drainage was performed, and amoxicillin/clavulanic acid antibiotic (1.2 g, IV, 3 times daily) was started. Meanwhile, her oxygen demand increased, necessitating the start of intermittent NIV therapy, alternating with high flow nasal oxygen administration. As the overall status of the patient deteriorated, procalcitonin level increased and hemodynamic instability occurred, we empirically escalated the antimicrobial therapy to imipenem/cilastatin (1g/1g, IV, 4 times daily), despite previous cultures still being negative. A few days later, her gas exchange improved, the fever resolved, and the procalcitonin level returned to the normal range. Control abdominal ultrasound examination showed no residual hematoma, allowing for the discontinuation of antibiotic therapy. After mobilization, she was discharged on day 29 to a rehabilitation facility and was able to return home in good general condition 5 days later.

Case 3

A 30-year old woman at the 38th week of her pregnancy tested positive for SARS-CoV-2 and was presented to the emergency department 2 days later due to fever and mild dyspnea. She had no earlier medical history for major diseases. She underwent an uncomplicated cesarean section under spinal anesthesia while receiving 3 L/min oxygen supplementation through a

nasal cannula. A postpartum chest computed tomography (CT) scan showed a pneumonia severity index of 3 to 4, reflecting lung involvement of approximately 50%[63]. She was admitted to the ICU, where her respiratory failure rapidly progressed, necessitating immediate NIV. NIV therapy with an FiO_2 of 100% was continued for the next 8 days. Repeated chest CT scan revealed radiological progression to pneumonia severity index of 5 (ie, >75% lung involvement)[63] accompanied by segmental pulmonary embolism and pneumomediastinum with subcutaneous emphysema. Macklin's sign[64–66] was also seen on the chest CT scan meaning excessive barotrauma to the lungs. On postpartum day 10, her hypoxemic respiratory failure worsened, necessitating urgent endotracheal intubation and prone positioning. Subsequently, she was referred to and accepted for ECMO support and transferred to our ICU. ECMO was initiated, and she was ventilated with rest settings. From day 6 on ECMO support, the respiratory system compliance deteriorated to 2 to 5 mL/cmH_2O, and the patient became completely ECMO dependent. Prone positioning was applied to facilitate lung aeration. From day 9 of ECMO, bradycardic and asystolic periods occurred frequently, requiring the administration of 0.5 mg atropine IV and occasionally chest compressions. However, echocardiography revealed no cardiac dysfunction, leading to the assumption of a vaso-vagal mechanism. During the second week of ECMO, there was an increase in the amount of the purulent tracheal secretion and inflammatory markers, with procalcitonin level increasing from <0.06 ng/mL to 0.27 ng/mL and C-reactive protein increasing from 140 mg/L to 331 mg/L in 24 hours. After microbiological sampling, empiric antibiotic therapy with meropenem was initiated (1 g, IV, 3 times daily). Klebsiella pneumoniae and Streptococcus pneumoniae were isolated from the tracheal secretions. Based on their sensitivities, we were able to de-escalate to ceftriaxone (1 g, IV, twice daily). Although the procalcitonin level decreased below 0.5 ng/mL by day 7 of administration, her gas exchange remained completely dependent on ECMO. Consequently, a chest CT scan performed on day 13 revealed progression of the lung injury. In the next 2 days, the patient was repeatedly placed in the prone position for 16 to 20 hours per day. Percutaneous tracheostomy was performed on day 20, and the subsequent chest radiography revealed a complete left-sided pneumothorax. After chest drain insertion, an air leak comprising 70% to 80% of inspiratory minute volume was observed, mechanical ventilation was completely ceased for the next 14 days. Sedation was deepened to decrease her oxygen consumption administering additional 0.4% to 0.6%v/v sevoflurane through the oxygenator and continuous intravenous administration of thiopental (maximum 200 mg/h), in addition to the intravenous fentanyl (200 mcg/ h), propofol (200 mg/h), midazolam (30 mg/h), and clonidine (225 mcg/h), along with the application of mild hypothermia (36°C). The patient

was subsequently referred to the National Institute of Oncology, Budapest, Hungary for consideration for lung transplantation. However, she remained SARS-CoV-2 positive and exhibited high levels of anti-human leukocyte antigen antibodies (>5,000 mean fluorescent intensity), which precluded lung transplantation. After 11 days, it became feasible to restart invasive mechanical ventilation, allowing for gradual increases in respiratory support. On day 42 of ECMO, the patient developed septic shock, necessitating high doses of vasopressors (norepinephrine 40 mcg/min and vasopressin 2.4 IU/h). Broad-spectrum empiric antibiotic therapy was initiated with meropenem (1 g, IV, 3 times daily) and IV linezolid (600 mg, IV, twice daily). Subsequently, Klebsiella pneumoniae was isolated from blood cultures. Oxygen balance was inadequate due to high cardiac output and increased oxygen consumption, necessitating the administraion of beta-blocker therapy with bisoprolol (5 mg, enteral route, twice daily) and heart rate control with ivabradine (15 mg, enteral route, twice daily). After resolving the nosocomial blood stream infection, respiratory system compliance slowly improved, allowing a decrease in the level of sedation. She regained consciousness, but suffered from severe critical illness polyneuromyopathy. With the assistance of physiotherapists and a psychologist, her condition gradually improved. After 70 days of ECMO support, she was weaned successfully from the extracorporeal circulation and decannulated. She was weaned finally from the ventilator on day 83, and the tracheostomy cannula was removed 2 days later. The patient was discharged to a rehabilitation facility on day 91 and eventually discharged home with minimal need for oxygen supplementation.

III.3. V-V ECMO methodology

III.3.1. V-V ECMO indications

We supported 18 patients during the COVID-19 pandemic with V-V ECMO due to SARS-CoV-2 infection and ARDS, based on the recommendations of the ELSO[50,67,68]. (**Figure 1)**

III.3.2. V-V ECMO setup

For V-V ECMO support either the Cardiohelp System with HLS Set Advanced (Maquet, Gothenburg, Sweden), or the Novalung Heart and Lung Therapy System with Xlung patient kit (Fresenius, Bad Homburg, Germany) was used. The ECMO setup includes the cannulas (access and return), the oxygenator, the centrifugal pump, and pipes connecting them[43,46,69]. For access, we mostly used 25 Fr, 38 cm long cannula, for return, 19-25 Fr 15 or 55 cm long cannula, depending on the configuration (femoro-jugular or femoro-femoral). The setup contained

hollow fibre oxygenators that consists two separate paths for blood flow and for fresh gas flow, known as sweep gas. The lumen of the hollow fibre is for the fresh gas flow and the space between fibres is the path for blood to flow[43,44,49,69].

III.3.3. Patient management with V-V ECMO

Eighteen patients were placed on ECMO support during this period, (5 women, age (mean ± SD) 44 ± 10 years, APACHE II score (median (interquartile range)) 12 (10–14.5)). Before ECMO support, they had been hospitalised for 6 (4–11) days. Fifteen patients received noninvasive ventilation for 4 (2–8) days, two patients had high flow nasal oxygen therapy, for one day each. They had already been intubated for 2.5 (1–6) days. Prone position was applied in 15 cases.

V-V ECMO cannulation was performed by transoesophageal ultrasound guiding. The access cannula was inserted percutaneously in the femoral vein and the return cannula was inserted either to the internal jugular vein or the femoral vein. The insertion of the ECMO cannulas took place either at the ICU or at the referring hospital. The extracorporeal blood flow (ECBF) was adjusted to reach an SaO_2 greater than 88–90%, and the SG flow to reach a normal pH. The blood is circulated to the oxygenator through the cannulas and continuous strictly monitored anticoagulation is needed to prevent clotting in the ECMO circuit, yet anticoagulation entails a higher risk for bleeding. Hemolysis and hyperfibrinolysis have a negative impact on membrane function[70]. For anticoagulation, unfractionated heparin was used, monitored by activated clotting time (ACT) or activated partial thromboplastin time (aPTT). The target level of anticoagulation was ACT 160–180 s or aPTT 46–55 s, modified as necessary during complications. The antithrombin III concentration was monitored daily, because its low level may preclude the achievement of the target ACT. Two patients had severe COVID-related coagulopathy affecting the perfusion of the fingers and one of them also had pulmonary embolism, celiac trunk thrombosis, spleen and pancreas infarcts and ischemic liver injury. In these two patients we suspected heparin induced thrombocytopenia (which was not proven later) and switched to argatroban anticoagulation. Five patients had pulmonary embolism and were provided with systemic thrombolytic therapy with alteplase before or during V-V ECMO support. We targeted negative fluid balance if the patients were hemodynamically stable. Regarding COVID-19 specific therapy, all patients received remdesivir, corticosteroid and vitamin D, four of them were given tocilizumab and three of them received convalescent plasma. The patients were invasively mechanically ventilated, they were sedated with infusion

of propofol (2-3mg/kg/h), sufentanil (10 mcg/h) or fentanyl (100-200 mcg/h), and midazolam (0.5-5.0 mg/h) targeting Richmond Agitation and Sedation Score (RASS) of -5, meaning the deepest sedation. During the initiation of ECMO, a muscle relaxant (rocuronium bromide, 0.6-1.0 mg/kg, IV bolus and maintenance with pipecuronium 4-6 mg/h as needed) was administered. The ventilator was set to pressure control (PCV) mode, with low FiO_2 (40%), PEEP between 10 and 15 cmH_2O, driving pressure of 10 cmH_2O and respiratory rate of 10/min to allow lung rest[30,51].

III.3.4. Weaning from V-V ECMO and discharge

Weaning from V-V ECMO is a dynamic process. As the lungs are ventilated on a protective or ultra-protective volume parameters (TV 4-6 ml/IBW or 2-4 ml/IBW) healing of the injured parenchyma can occur[30,51,71]. The combination of native lung gas exchange and gas exchange through the oxygenator result in the optimal oxygenation and elimination of carbon-dioxide in patients[46]. Negative fluid balance and fluid restriction has a crucial role in the healing process of the injured lungs[72]. Daily assessment of native lung function by 100% oxygen test, also called as Cilley test[43] (setting the ventilator FiO_2 to 100% from 40% with unchanged other parameters) can confirm increasing oxygen transfer capacity of the lungs, achieving $PaO_2 \geq 250$ mmHg is a sign of lung recovery. Reduction of ECBF by 300-500 ml/min decrements is useful tool to detect the ideal ECBF to maintain arterial oxygen saturation ≥88-90%. Stopping neuromuscular blocking agents and weaning from analgosedative medications and titration to achieve RASS -1 is part of the weaning process. Gradual decrease and cessation for hours (4-24 hours) of SG eventually decides if the patient is ready to wean from V-V ECMO[43]. If the patient is able to maintain stable respiratory and hemodynamic state while SG is off and the ECBF is the lowest possible without adverse events (e.g. clotting in the circuit), weaning and decannulation can be considered. Maintaining normocarbia and oxygenation on rest ventilation parameters while SG is completely turned off is a great sign of improvement of native pulmonary function[46]. Daily assessment of lung compliance and increased tidal volumes on unaltered pressure control is a sign of improvement in pulmonary compliance[43]. Weekly performed chest X-rays are useful tools in visualization of air-content of the lungs and any signs of amelioration is a supportive sign of successful weaning[43].

Once the patients are weaned from ECMO and eventually mechanical ventilation is no longer needed, they are cardiorespiratory stable, analgosedative agents are stopped and they can fully cooperate with nurses and physiotherapists, discharge off the ICU can occur. Ameliorating

muscle weakness is the limiting factor in their quality of life, in most cases they are discharged to a rehabilitation facility to improve physical strength[73].

III.4. Post-intensive care evaluation of quality of life

To assess the physical consequences of PICS, we used 6MWT as simple and globally used method to assess activity limitation[58]. Furthermore, health-related quality of life comprising to physical, mental, psychological and social well-being was measured by 36-Item Short-Form Health Survey referred as SF-36[74]. The survey consists of 8 sections and each section transforms into 0-100 scale, and the lower the point the more decreased life quality. Furthermore, the Rankin score was used to measure disability scale, with scores ranging from 0 to 5. Score 0 means no impairment, whereas 5 denotes severe disability[75].

III.5. Comprehensive respiratory function follow up: lung function tests

III.5.1. Measurement of airway and respiratory tissue mechanics

Respiratory oscillometry was used to measure the mechanical properties of the airways and the respiratory tissues. The technique is based on the introduction of small-amplitude pressure oscillations into the airway opening by using an external pressure generator[76]. Recording of the oscillatory pressure (Pao) and airflow (V') at various frequencies allows the calculation of the input impedance of the respiratory system, as Zrs = Pao/V'. Zrs data at each oscillatory frequencies can be expressed as a complex quantity represented by the respiratory resistance and reactance. Resistance expresses the oscillatory pressure in phase with the flow and reflects the resistive loss in the respiratory system. Reactance is defined as the oscillatory pressure component out of phase with oscillatory flow and demonstrates respiratory tissue elasticity at low oscillatory frequencies.

In the present study, Zrs was measured during spontaneous breathing with a pseudorandom forcing signal at a frequency range of 5–19 Hz (Resmon Pro Full system, Restech S.r.l, Italy). Measurements were performed while the patients were in an upright sitting position with cheeks supported in accordance with the European Respiratory Society (ERS) guidelines[77]. Participants wore a nose clip, and they were instructed to breathe normally via a tightly sealed mouthpiece. At least three technically acceptable and reproducible 30-s long recordings were then performed. The impedance of the antibacterial filter was measured before each test, and this instrumental component was subtracted from the Zrs data.

The resistance values of the whole breath at 5 Hz (R_5) and 19 Hz (R_{19}) were extracted from the Zrs data for further analyses. Large and small airways contribute to the parameter R_5, whereas R_{19} reflects mainly the airflow resistance of the central conducting airways with less influence from the smaller bronchi. Accordingly, subtracting R_{19} from R_5 (R_5–R_{19}) reveals the contribution of the small airways to the overall airway resistance, with providing information on the ventilation inhomogeneities[16,78]. The area under the reactance curve from 5 Hz until the resonant frequency (AX_5) represented the respiratory tissue stiffness (elastance). The resonant frequency (f_{res}) at which Xrs crosses zero (where the elastic and inertial forces equilibrate with each other) was included in the data analyses.

III.5.2. Spirometry

Spirometry was performed in accordance with the ATS/ERS guidelines[79]. Forced expiratory flow-volume curves were measured with a commercially available spirometer (MasterScreen PFT, CareFusion, Höchberg, Germany). The flow signal was integrated to identify changes in lung volume during the forced expiratory maneuvers. Data on forced expiratory volume in the first second of expiration (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, peak expiratory flow (PEF), and forced expiratory flow between 25 and 75% of the volume expired ($FEF_{25–75}$) were extracted from the recordings. Three technically acceptable reproducible measurements were performed, and the highest values on spirometry were extracted from the maneuvers for the final analyses.

III.5.3. Whole body plethysmography

Functional residual capacity (FRC) and expiratory reserve volume (ERV) were measured via whole-body plethysmography (MasterScreen Body, Höchberg, Germany) using standard techniques established by the ERS/ATS Task Force[80].

III.5.4. Measurement of alveolar gas diffusion

A single-breath method was used to evaluate the diffusing capacity of carbon monoxide (DLCO), carbon monoxide transfer coefficient (KCO), and alveolar volume (VA) (MasterScreen Diffusion, Höchberg, Germany).

III.6. Statistical analyses

Continuous variables were expressed as mean ± SD or median and interquartile range (IQR), as appropriate.

The reference values for the oscillometry outcomes were based on earlier established equations[81]. The reference values of the parameters obtained via spirometry and gas diffusion were established according to the Global Lung Function Initiative Network guidelines[82]. The measured values were reported as absolute values with scatter expressed as standard deviations, percentage predicted, and Z-score if applicable. Data normality was tested with the Shapiro–Wilk test. The independent *t*-tests were used to compare the measured variables.

Sample sizes were estimated to detect a clinically relevant 25% difference in one of the primary outcome parameters (AX_5). This parameter was selected because restrictive dysfunction was mainly anticipated in patients with post-COVID-19 syndrome[17,18], and was best reflected by the oscillometric parameters reflecting respiratory tissue stiffness. Accordingly, nine patients in the control and diseased groups were sufficient for detecting a statistically significant difference, with a variability of 10%, power of 80%, and a significance level of 5%. Propensity score matching was performed using the *MatchIt* package (version 4.4.0)[83] in the R software environment (version 4.2.1). Statistical tests were performed with the SigmaPlot statistical software package (version 13, Systat Software, Inc., Chicago, IL, USA), and a *p*-value of <0.05 was considered statistically significant.

IV. RESULTS

IV.1. Results in the patients with severe COVID-19 requiring V-V ECMO

IV.1.1. Demographic data and clinical characteristics

The demographic data of the 18 patients underwent V-V ECMO support are sumamrized on **Table 1**. Patients were middle-aged with male dominance and severe general and respiratory conditions. Our institute followed the ELSO recommendations to maintain relative short time intervals for starting extracorporeal support as seen on **Table 1**[50]. Before initiating V-V ECMO, repiratory parameters reflected the severe lung injury with a need for a 100% oxygen therapy supplemented with high PEEP, driving pressure and tidal volume associated with low respiratory compliance. The blood gases show decompensated respiratory acidosis with low arterial oxygen partial pressure.

Demographics (mean ± SD, median, (IQR)) (n = 18)	
Age (years)	44 ± 10
Sex (Male/Female)	13/5
APACHE II score	12 (10–14.5)
LISS score	3.25 (3.0–3.26)
RESP score	5 (2–7)
Time intervals before initiating V-V ECMO (days, mean ± SD, median, IQR)	
From first positive SARS-CoV-2 rt-PCR	9 (7–15)
From hospital admission	6 (4–11)
Time on NIV	4 (2–8)
From intubation	2.5 (1–6)
Respiratory parameters before initiating V-V ECMO (mean ± SD, median, IQR)	
FiO_2 (mmHg)	100 (100–100)
PEEP (cmH_2O)	9±2
Driving pressure (cmH_2O)	21 ± 5
Vt/PBW (mL/kg)	7.6 ± 1.9
Cstat (mL/cmH_2O)	27 ± 10
Arterial blood gase parameters before initiating V-V ECMO (mean ± SD, median, IQR)	
pH	7.33 (7.28–7.39)
$PaCO_2$ (mmHg)	65 ± 15
PaO_2 (mmHg)	67 ± 14
PaO_2/FiO_2 (mmHg)	71 ± 19

Table 1: Demographic data and patient management before initiating V-V ECMO

ECMO: Extracorporeal membrane oxygenation; APACHE II score: Acute Physiology and Chronic Health Evaluation score; LISS score: Lung Injury Score; RESP score: Respiratory ECMO prediction score; SARS-CoV-2 rt-PCR: Severe acute respiratory syndrome Coronavirus real-time polymerase chain reaction; NIV: Non-invasive ventilation; FiO_2: fraction of inspired oxygen; PEEP: positive end-expiratory pressure; Vt/PBW: the ration of tidal volume and predicted body weight; Cstat: static compliance; $PaCO_2$: partial pressure of arterial carbon dioxide tension; PaO_2: partial pressure of arterial oxygen tension; PaO_2/FiO_2: the ratio of partial pressure of arterial oxygen tension and fraction of inspired oxygen

IV.1.2. Clinical outcomes and complications

Femoro-jugular configuration was applied in 17 cases, and femoro-femoral configuration in 3 cases. Two patients had a second ECMO run because of the deterioration of gas exchange, 2 and 9 days after the initial decannulation. One patient was turned prone three times for 16–20 h while on ECMO because no improvement of lung function occurred for 2 weeks. For the 20

ECMO runs, 31 oxygenators were used; 7 oxygenators were changed because of clot formation, increased membrane pressure drop and decreased oxygen transfer capacity. The duration of V-V ECMO support was prolonged, the longest run lasted 70 days. Eleven patients were successfully weaned from ECMO and decannulated. The patients were also mechanically ventilated for an extended period, in 15 cases we performed dilatational percutaneous tracheostomy. Average ICU and hospital length of stay were around 6–7 weeks. ICU and inhospital survival rates were 56% and 50%., respectively. The surviving patients were discharged to another acute care or rehabilitation facility. **(Table 2)**

Complications occurred in 16 patients. Clinically significant bleeding affected half of the patients. The most serious one was a vascular injury during cannulation, leading to hemothorax and fatal exsanguination. The other sites of major bleeding were the upper airways, the upper and lower gastrointestinal tract, intrapleural and intraabdominal bleeding. There was no intracranial bleeding. Minor bleedings occurred at cannulation sites in almost all patients. Two patients had severe COVID-related coagulopathy affecting the perfusion of the fingers and one of them also had pulmonary embolism, celiac trunk thrombosis, spleen and pancreas infarcts and ischemic liver injury. In these two patients we also suspected heparin induced thrombocytopenia (which was not proven later) and switched to argatroban anticoagulation. In case of heparin resistance, argatroban and bivalirudin are useful alternatives for anticoagulation in ECMO patients[84]. After decannulation, six patients had deep vein thrombosis in the cannulated veins. Five patients had pneumothorax, either spontaneous or iatrogenic, which required the insertion of chest drains. In two cases, the air leakage was so significant that we were unable to ventilate them at all, therefore we switched off ventilators. During this period, when they were totally dependent on ECMO, we further deepened sedation and applied mild hypothermia to decrease the oxygen consumption. In one case, we were able to ensure adequate oxygen delivery, and after 11 days could restart IMV, and after 70 days stop extracorporeal support. That patient survived and was discharged home. Nosocomial infections were frequent, occurring in 16 patients. The most common were LRTI, BSI and UTI. Other infections developed in 8 patients, including sinusitis in 5, purulent keratitis in 1, and intraabdominal infection in 1 case. One woman had puerperal fever. These infections were often caused by multidrug-resistant pathogens, especially Acinetobacter Baumanii and Pseudomonas aeruginosa. Other organ failures in addition to respiratory failure included circulatory failure in 10 patients (8 septic and 4 hemorrhagic shock), 5 acute kidney injury (3 patients were treated with continuous renal replacement therapy) and one acute liver failure. (**Table 2)**

Duration of ECMO support (day)	26 ± 20
Duration of IMV (day)	34 ± 23
ICU LOS (day)	40 ± 28
Hospital LOS (day)	45 ± 31
ICU survival n (%)	10 (56%)
Hospital survival n (%)	9 (50%)
Complications (patients)	16
Bleeding n (%)	9 (50%)
PTX n (%)	5 (28%)
DVT n (%)	6 (33%)
Nosocomial infections (patients)	16
LRTI n (%)	14 (77%)
BSI n (%)	11 (61%)
UTI n (%)	7 (39%)
Other n (%)	8 (44%)

Table 2: Outcomes and complications. (mean ± SD)

ECMO: Extracorporeal membrane oxygenation; IMV: invasive mechanical ventilation; ICU LOS: intensive care unit length of stay; hospital LOS: hospital length of stay; PTX: pneumothorax; DVT: deep vein thrombosis; LRTI: lower respiratory tract infection; BSI: blood stream infection; UTI: urinary tract infection

IV.1.3. Outcomes at discharge

Nine patients were discharged home after rehabilitation. At the follow-up that occurred between 150 to 489 days after ICU admission, we assessed their functional recovery and health-related quality of life. The results of 6-min walk tests showed that none of them was able to walk the distance expected for age, gender, height, and body weight; they reached 36–74% of predicted values. The Rankin score was 0 in three, 1 in three and 2 in three patients, corresponding with no symptoms at all; no significant disability despite symptoms; or slight disability. The SF-36 Survey showed that the mean scores in all eight categories were above 70, corresponding with good health related quality of life, except role limitation due to physical health, which received a slightly lower score. **(Table 3)**

6MWT (Percentage of expected (%))	60 ± 13
SF-36	
Physical functioning	75 (70–94)
Role limitation due to physical health	58 ± 42
Role limitations due to emotional problems	100 (67–100)
Energy/fatigue	73 ± 14
Emotional well-being	92 (82–96)
Social functioning	82 ± 13
Pain	83 ± 20
General health	68 ± 12

Table 3: *Follow-up (mean ± SD, median; IQR)*

6 MWT: 6 min walking test; SF-36: 36-Item Short Form Survey

IV.2. Results in the ECMO-patients in the 6-month respiratory follow-up

IV.2.1. Demographic data and clinical characteristics

Regarding the clinical characteristics and anthropometric data of the COVID and healthy (H) matched control groups, no significant differences were observed between the groups COVID and H in terms of female/male ratio, height, age, and body mass index. Patients requiring V-V ECMO support received invasive ventilation for 0 to 10 days under pressure-controlled mode with specific ventilation parameters. None of the patients were smokers and none had chronic respiratory disease. **(Table 4)**

		Group COVID (n=9)	Group H (n=9)	p
Anthropometric data mean±SD	**Female/Male (n)**	4/5	4/5	1.0
	Age (years)	42.0±11.1	45.0±11.5	0.6
	Height (cm)	167±9.4	172±6.6	0.7
	Weight (kg)	91.6±14.2	84.2±7.4	0.18
	BMI (kg/m^2)	32.7±5.2	28.2±2.7	0.14
Status mean (range)	**Apache II score**	14.4 (9-33)		
	LISS score	3.2 (3-3.5)		
	RESP score	4.9 (2-7)		
Length of stay mean (range)	**Hospital (days)**	58.3 (34-94)		
	Total ICU (days)	55.0 (24-94)		
	V-V ECMO (days)	33.1 (10-65)		
	Duration of mechanical ventilation	44 (11-79)		
Pre-ECMO managem	**Duration of mechanical ventilation before ECMO (days)**	2.5 (1-6)		
	ICU before V-V ECMO (days)	7.1 (2-18)		
	Prone position (number)	7		
Pre-ECMO parameters mean (range)	**PEEP (cmH_2O)**	9.3 (8-12)		
	Driving pressure (cmH_2O)	21.4 (15-26)		
	VT (ml/kg)	7.8 (6-10.7)		
	Crs (ml/cmH_2O)	26.3 (17-41)		
	FiO_2 (%)	97.5 (90-100)		
	PaO_2 (mmHg)	68.0 (42-90)		
	PaO_2 / FiO_2 (mmHg)	69.8 (47-100)		
	$PaCO_2$ (mmHg)	61.8 (44-84)		
	pH	7.31 (7.13-7.39)		
ECMO parameters	**Mean gas flow (l/min)**	4.4 (3.0-5.5)		
	Blood flow (l/min)	4.6 (3.0-5.9)		

Table 4: *Anthropometric data and clinical characteristics of the patients involved in the study groups*

IV.2.2. Respiratory mechanics assessed by forced oscillations

Significant differences were observed in some of the primary outcome variables reflecting the mechanical properties of the airways and the respiratory tissues between the two groups. (**Table 5**) No statistically significant difference was observed in terms of R_5 and R_{19} between the healthy matched control and COVID groups. (**Figure 3**) Conversely, the COVID group had a significantly higher R_5–R_{19} than in the control group. The difference in R_5 and R_{19} was associated with a significantly higher AX_5 and f_{res} in patients with COVID-19 (**Figure 4**), with these differences remaining if these parameters are expressed as a percentage of predicted values or Z-scores. **(Table 5)**

		Group H	**Group COVID**	**p**
R_5	Absolute value ($cmH_2O.s/l$)	3.22±1.13	3.31±0.58	0.84
	% predicted	101.8±27.7	89.9±21.8	0.33
	Z score	-0.06±0.94	-0.47±0.91	0.36
R_{19}	Absolute value ($cmH_2O.s/l$)	3.21±1.03	2.90±0.40	0.42
	% predicted	106.5±27.7	87.9±18.6	0.12
	Z score	0.10±0.93	-0.59±0.85	0.12
R_5-R_{19}	Absolute value ($cmH_2O.s/l$)	0.013±0.23	0.411±0.26	**0.003**
AX_5	Absolute value (cmH_2O/l)	3.20±3.29	6.24±3.31	**0.02**
	% predicted	93.99±37.6	181.1±111.9	**0.03**
	Z score	-0.21±0.67	0.62±0.79	**0.03**
f_{res}	Absolute value (Hz)	12.2±3.6	15.7±2.6	**0.03**
	% predicted	99.1±25.6	114.6±18.9	**0.04**
	Z score	-0.24±0.80	0.52±0.65	**0.04**

Table 5: *Mechanical parameters obtained via respiratory oscillometry characterizing airflow resistance at oscillation frequencies of 5 and 19 Hz (R_5, R_{19}), and their difference (R_5–R_{19}) reflecting the frequency dependence of the real part of the respiratory impedance spectra, area under the reactance curve at 5 Hz, and the resonant frequency (AX_5) and the resonant frequency (f_{res})*

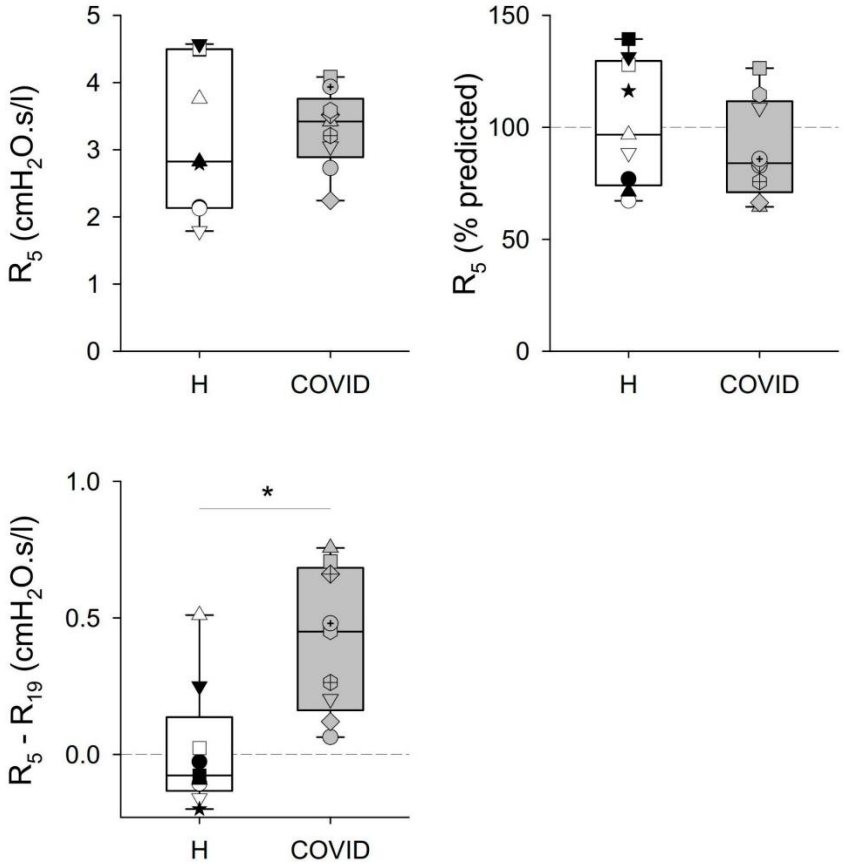

***Figure 3**: Mechanical parameters obtained via respiratory oscillometry characterizing airflow resistance at oscillation frequencies of 5 and 19 Hz (R_5, R_{19}), and their difference (R_5–R_{19})*

Data were obtained at 6 months after hospital discharge in patients requiring veno-venous extracorporeal membrane oxygenation in the acute phase of coronavirus disease 2019 (COVID, gray shading) and in healthy matched controls (H, white shading). Data were reported as absolute values (**left** panels) and percent predicted (**right** panel), where the latter is available. Different symbols represent parameter values obtained in the individual patients. *p <0.05 between the COVID-19 and healthy matched control groups.

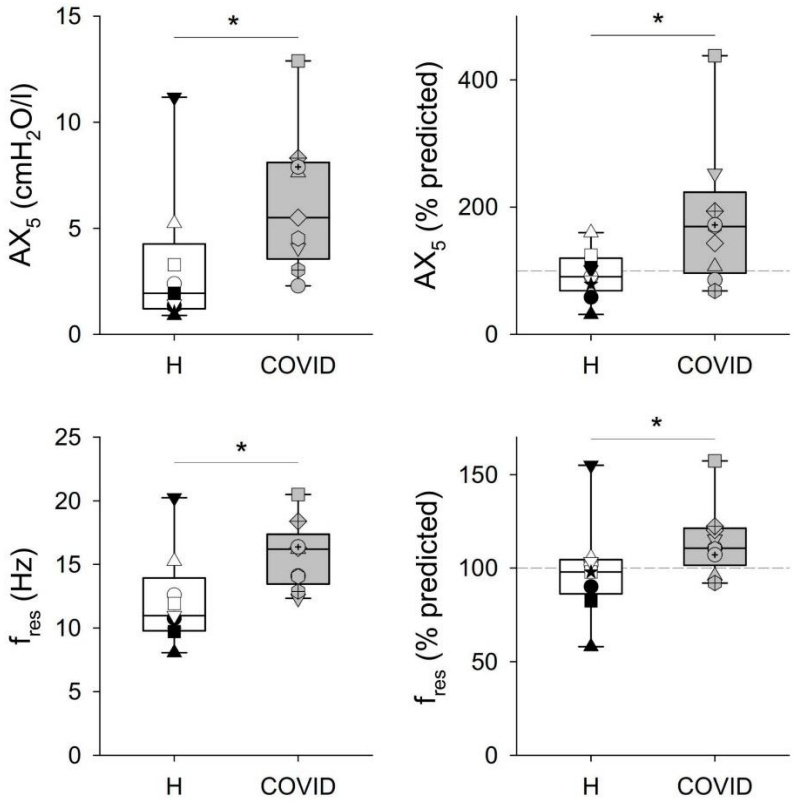

Figure 4: *Respiratory tissue mechanical parameters obtained via respiratory oscillometry representing the area under the reactance curve at 5 Hz, and the resonant frequency (AX_5) and the resonant frequency (f_{res})*

Data were obtained at 6 months after hospital discharge in patients requiring veno-venous extracorporeal membrane oxygenation in the acute phase of coronavirus disease 2019 (COVID, gray shading), and in healthy matched controls (H, white shading). Data were reported as absolute values (**left** panels) and percent predicted (**right** panels). *p <0.05 between the COVID-19 and healthy matched control groups.

IV.2.3. Lung function measured by spirometry

The COVID group exhibited a significantly lower FEV_1 and FVC than the healthy matched control group. Due to the more severe decrease in FVC compared to FEV_1, the COVID group showed a significantly higher FEV_1/FVC ratio, expressed as absolute values, percentage predicted, or Z-scores. Meanwhile, there were no significant differences in terms of $FEF_{25–75}$ or PEF between the healthy matched control and COVID groups. **(Table 6)**

		Group H	Group COVID	p
FEV_1	Absolute value (liters)	3.51±0.89	2.68±0.50	**0.01**
	% predicted	97.6±7.5	79.5±18.2	**0.02**
	Z score	-0.18±0.56	-1.54±1.28	**0.01**
FVC	Absolute value (liters)	4.39±1.04	3.04±0.45	**<0.001**
	% predicted	101.2±7.8	73.4±15.9	**<0.001**
	Z score	0.05±0.67	-2.0±1.18	**<0.001**
FEV_1/FVC	Absolute value (%)	79.9±4.7	87.9±4.8	**0.001**
	% predicted	100.0±4.9	114.1±10.0	**0.05**
	Z score	0.02±0.71	1.09±0.69	**0.002**
FEF_{25-75}	Absolute value (l/s)	3.34±0.98	4.05±1.51	0.24
	% predicted	93.2±17.8	118.1±41.5	0.12
	Z score	-0.27±0.61	0.57±1.49	0.14
PEF	Absolute value (l/s)	8.12±1.43	7.50±1.48	0.33
	% predicted	98.9±10.3	96.9±20.0	0.78
	Z score	-0.10±0.7	-0.23±1.44	0.81

Table 6: *Lung function parameters obtained via spirometry at 6 months after hospital discharge in patients requiring veno-venous extracorporeal membrane oxygenation in the acute phase of coronavirus disease 2019 (Group COVID) and in healthy matched controls (Group H)*

IV.2.4. Gas exchange assessments

Regarding the diffusion capacity measurements, the COVID group had a significantly lower DLCO and VA, expressed as absolute or percentage predicted values than the healthy matched control group. However, there was no difference in terms of KCO between the COVID and healthy matched control groups. **(Table 7)**

		Group H	Group COVID	p
DLCO	Absolute value (ml/min/mmHg)	26.7±6.9	18.9±4.3	**0.003**
	% predicted	90.0±12.9	66.9±14.5	**0.001**
VA	Absolute value (liters)	5.96±1.2	4.11±0.4	**<0.001**
	% predicted	94.9±7.4	73.9±15.8	**0.004**
KCO	Absolute value (1/min)	4.48±0.69	4.56±0.81	0.82
	% predicted	96.7±11.5	94.1±17.4	0.70

Table 7: *Diffusing capacity of carbon monoxide (DLCO), alveolar volume (VA), and carbon monoxide transfer coefficient (KCO) measured at 6 months after hospital discharge in patients requiring veno-venous extracorporeal membrane oxygenation in the acute phase of severe coronavirus disease 2019 (Group COVID) and healthy matched healthy controls (Group H)*

IV.2.5. Lung volumes measured by whole-body plethysmography

As for the results using whole-body plethysmography, the significantly low FRC values obtained in the COVID group were associated with a remarkable decrease in ERV and its percentage predicted value. **(Table 8)**

		Group H	Group COVID	p
FRC	Absolute value (liters)	3.22±0.71	2.21±0.30	**<0.001**
	% predicted	99.2±15.6	73.0±9.4	**<0.001**
ERV	Absolute value (liters)	1.33±0.54	0.87±0.28	**0.01**
	% predicted	104.0±30.1	66.9±211	**0.002**

Table 8: *Functional residual capacity (FRC) and expiratory reserve volume (ERV) measured using whole-body plethysmography at 6 months after hospital discharge in patients requiring veno-venous extracorporeal membrane oxygenation in the acute phase of severe coronavirus disease 2019 (Group COVID) and healthy matched healthy controls (Group H)*

IV.3. Results in the postpartum patients

IV.3.1. Demography and clinical parameters of parturient patients

		Patient 1.	Patient 2.	Patient 3.
Demography	Age (years)	26	28	30
	Height (cm)	160	153	170
	Weight (kg)	108	81	70
	Gestational age at CS (weeks)	34	27	38
Severity scores (points)	APACHE II	9	14	13
	LISS	3.3	3.5	3.25
	RESP	7	7	7
Pre-ECMO time (days)	Positive SARS-CoV-2 PCR	16	4	10
	Hospital admission	4	4	10
	Time NIV	1	1	8
	From intubation	2	3	1
Pre-ECMO ventilation	Mode	PCV	PRVC	PCV
	FiO_2 (%)	100	100	100
	$P_{driving}$ (cmH_2O)	15	19	26
	PEEP (cmH_2O)	10	12	8
	Prone position	Yes	Yes	Yes
Pre-ECMO blood gas parameters	PaO_2 (mmHg)	70	81	65
	$PaCO_2$ (mmHg)	70	57	55
	pH	7.20	7.28	7.31
ECMO management	Duration on ECMO (days)	25	10	70
	Number of oxygenators	1	1	4
	Prone position	No	No	Yes
	Pneumothorax	No	No	Yes
Post-ECMO outcomes	Duration of IMV (days)	35	11	73
	ICU LOS (days)	38	29	91
	Hospital LOS (days)	41	34	97
	Pneumothorax	No	No	Yes

Table 9: *Demography and clinical parameters of parturient patients*
PRVC: pressure-regulated volume control mechnical ventilation mode

All three women included in the study already had 2 older children, and their third child was delivered by cesarean section at the time of COVID infection. All parturient patients received

the same management regarding COVID infection. All of the patients were otherwise healthy and young women, and V-V ECMO support started immediately after cesarean section. Patient number 3 had the longest run on ECMO and 4 oxygenators were used in the course of 70 days long ECLS. Pneumothorax occured in 1 patient and prone positioning was applied in 1 patient as rescue maneuver to refractory hypoxaemia despite V-V ECMO support. All patients were successfully weaned from V-V ECMO and IMV and 1 patient was extubated after successful cessation of ECLS. Extracorporeal life support durations were 25 and 10 days for *Cases 1* and *2*, respectively; the third patient required an extended 70-day ECMO course, including an interim 2-week period without mechanical ventilation. Life support was successful for all 3 women regarding in regaining most of their physical and psychological health and performing similar social tasks with some help from their family as before the COVID-19 ARDS. **(Table 9)** Their babies had normal physical and cognitive develpoment.

IV.3.2. Outcomes obtained in the parturient patients

Respiratory outcomes obtained 6 and 12 months after hospital discharge in the postpartum women are summarized on **Table 10.**

In our parturient case series, in *Case 1*, after 6 months, there were no signs of abnormalities in the central conductive airways as indicated by the spirometric (FEV_1, FEF_{25-75}, and PEF) and forced oscillometry (R_5 and R_{19}) outcomes. However, small airway dysfunction was detectable from the R_5-R_{19} data, which was associated with moderate lung restriction indicated by the diminished FVC, FRC, VA, and ERV. The decreased DLCO without alterations in the KCO suggests loss of alveolar surface, with maintained ventilation and perfusion in the working lung compartments. These mild respiratory symptoms allowed her to perform daily activities and care for her family without exhaustion, although she continued receiving treatment for her eye injury. After 12 months, there was a mild improvement in the mechanical properties of the conducting airways in KCO. However, no improvement was observed in small airway function or lung volumes, which can be attributed to the opposing effect of respiratory regeneration and increase in body mass.

In *Case 2*, at the 6-month follow-up, this patient showed no evidence of airway abnormalities, either in the central conductive airways as indicated by the normal spirometric (FEV_1, $FEF_{25–75}$, and PEF) or forced oscillometry outcomes (R_5 and R_{19}, and R_5-R_{19}). The mild lung restriction affected the expiratory lung volumes only (FRC and ERV). The decreased DLCO was

associated with diminished KCO, suggesting gas diffusion abnormalities through the alveolo-capillary barrier. However, the Rankin score demonstrated the maintenance of normal daily activities. After 12 months, the patient exhibited no obvious change in her lung function outcomes. The slight further decreases in FRC and ERV could be explained by the slight gain in body mass.

In *Case 3* lung function assessment 6 months after discharge showed marked lung restriction, as evidenced by markedly elevated AX_5 and deteriorated FVC, VA, FRC, and ERV. This resulted in a mild elevation in the tone of the central conducting airways. Persistent gas diffusion abnormalities through the alveolo-capillary barrier were indicated by the decreased DLCO and diminished KCO. This decrease in lung function was also reflected in her Rankin score. After 12 months, there was an improvement in lung restriction, as shown by improvements in AX_5, spirometric parameters, DLCO, and plethysmographic measures. Accordingly, the improved Rankin score parallelled these beneficial pulmonary changes.

		6-month follow-up			12-month follow-up		
		Case 1	**Case 2**	**Case 3**	**Case 1**	**Case 2**	**Case 3**
Spirometry	FEV_1 (% predicted)	94.6	102.2	73.7	104.4	109.6	88.7
	FVC (% predicted)	86.8	92.0	71.7	97.7	110.3	94.0
	FEF_{25-75} (% predicted)	178.5	113.0	87.3	184.4	124.5	109.1
	PEF (% predicted)	120.4	97.0	109.9	147.1	126.8	114.9
Diffusion capacity	DLCO (% predicted)	82.0	70.6	60.3	83.5	87.1	64.7
	VA (% predicted)	88.3	93.7	74.7	85.8	99.5	84.2
	KCO (% predicted)	95.9	77.8	83.0	105.0	90.3	79.1
Plethysmography	FRC (% predicted)	70.1	87.7	80.0	71.4	79.8	90.4
	ERV (% predicted)	68.7	79.6	72.1	67.5	75.9	96.7
Forced oscillations	R_5 (% predicted)	64.5	75.7	108.8	72.6	82.7	120.5
	AX_5 (% predicted)	106.7	68.4	253.0	103.6	59.7	214.8
	R_{19} (% predicted)	59.7	74.8	97.4	73.8	83.7	103.7
	R_5-R_{19} ($cmH_2O.s/l$)	0.76	0.26	0.20	0.82	0.32	0.43
Body weight	(kg)	110	82	70	120	85	72
Rankin score		0	0	1	0	0	0

Table 10: *Parturient results at 6 months and 12 months after hospital discharge*

V. DISCUSSION

At our tertiary university center, we provided V-V ECMO support for 18 patients with severe ARDS caused by COVID-19 pneumonia. Of these, 9 patients survived to hospital discharge and were evaluated 6 to 12 months later. Among them, 3 subjects underwent V-V ECMO support immediately after cesarean section. V-V ECMO plays a crucial role in the management of these patients experiencing high and heterogeneous lung strain and stress. It enables lung-protective ventilation, allowing the lungs to rest and recover while minimizing ventilator-induced lung injury. This strategy forms a solid foundation for the regeneration of normal lung function. Our findings demonstrate that V-V ECMO is a vital and effective life-saving intervention in critical and even desperate clinical situations resulting in favorable long-term respiratory, physical and mental outcomes.

V. 1. Discussion of case series including all patients receiving V-V ECMO

In this case series of SARS-CoV-2 positive patients receiving V-V ECMO support we achieved ICU and inhospital survival rates of 56% and 50%, respectively. However, most of these patients required very long ECMO runs, a long duration of IMV with extended ICU and hospital stay. Complications were frequent; the most common ones were nosocomial infections, clinically significant bleeding, and pneumothorax. At the 5–16 month follow-up assessment, all survivors reported good health-related quality of life.

At the beginning of the pandemic, there was uncertainty about the role of extracorporeal respiratory support in the management of patients suffering from severe respiratory failure as a consequence of COVID-19. Early studies from China reported an unacceptably high, 94% mortality rate[85]. However, later, even during the first wave of the pandemic, considerably better results were reported. The Paris-Sorbonne ECMO-COVID investigators found 36% mortality at 60 days[86]. Of note, Pitie-Salpetriere is one of the largest ECMO centres in Europe with a long-established expertise. They organised and centralised ECMO support in the Greater Paris region, including 17 ICUs with a common referral system, protocols and mobile ECMO teams. They published 46% survival at 90 days that was even better, 60% among the patients cared for at the 3 high volume centres. They concluded that a shorter time on invasive ventilation before ECMO initiation, younger age, lower pre-ECMO renal component of Sequential Organ Failure Assessment score and treatment at centres managing at least 30 V-V ECMO cases annually were independently associated with 90-day survival[87]. These survival rates are similar to data

from the pre-COVID era, supporting the recommendation that experienced centres should consider V-V ECMO support for COVID-19 associated SRF.

Several observational studies were published during the pandemic, reporting data from large registries and from single centres, and the outcomes show great variability. The Extracorporeal Life Support Organization (ELSO) Registry contains data from 213 hospitals in 36 countries. During the first wave, 90-day mortality was 38% in patients supported by V-V ECMO[88]. EuroELSO also initiated near real-time prospective data collection from centres in Europe and Israel including both V-A and V-V ECMO cases. They published the first results from the EuroECMO COVID-19 Survey of 1531 patients, who had 55% chance of survival[89]. The best outcomes so far were published by Mustafa[90]. They used a single-access, dual-lumen right atrium-to- pulmonary artery cannula. That configuration, besides ensuring gas exchange, also supports the right ventricle. In addition, they tried to wake up and extubate the patients while on ECMO support and achieved only 15% in-hospital mortality[90]. However, there are several studies reporting significantly higher mortality. In Germany, throughout the first three waves of the pandemic, in-hospital mortality was 68%[91]. In a similar nationwide analysis from the same country, Friedrichson reported 65.9% in-hospital mortality for V-V ECMO support. It is remarkable that CPR was performed in 16.4% of the V-V ECMO-supported patients and patients in these cohorts were older compared to others. Another contributor could be that the use of ECMO in Germany is not centrally regulated[92]. In Poland, the ICU mortality rate was high as well, 74.1% for patients requiring ECMO support[93]. In a recent systematic review and meta-analysis, Ramanathan included 22 observational studies and 1896 patients and found 35.7% in-hospital mortality in those patients who received V-V ECMO support[94].

These data support that high-volume centres with previous expertise in V-V ECMO and those with early centralised referrals, organised transport and protocolized management achieved better result. These ICUs had the infrastructure, equipment, and qualified personnel, and could therefore cope with the very high demand. Our centre was in a unique position. We started to provide ECMO support before the pandemic, though we managed only 16 cases during a 4-year period including V-V and veno- arterial (V-A) runs[95]. However, we had equipment, trained physicians and nurses, previous experience and management protocols. The multidisciplinary involvement, including cardiac surgeons, perfusionists, occasionally pulmonologists, physiotherapists, psychologists also helped to achieve an acceptable survival rate.

An important factor influencing survival is the duration of non-invasive and especially IMV before ECMO initiation; in general, the longer it lasts, the worse the outcome is[87]. Interestingly, results from the first wave seem to be better than the ones achieved later, which may be associated with timing. Braaten found a significantly worse survival after October 2020, and, of note, the median interval from hospital admission to V-V ECMO initiation was longer in that cohort (10 days vs 6 days) and it was associated with 60-day mortality[96]. The pooled mean duration of IMV prior to ECMO initiation was 4.4 days in Ramanathan's metaanalysis, but it was not associated with mortality[94]. In our case series, the median length of IMV before ECMO was 2.5 days, but because of the small number of patients we could not compare survivors with non-survivors.

During the pandemic it was impossible to compare outcomes with V-V ECMO or IMV alone in a randomized study. Whebell used propensity score matching to compare hospital mortality of patients receiving ECMO at specialist centres with a cohort of patients referred for ECMO but managed conventionally. In the United Kingdom, a centralised national referral system was established early on during the pandemic. This multicenter retrospective cohort study was conducted at two national ECMO centres, the Guy's and St Thomas' Foundation Trust and the Royal Brompton and Harefield Trust. They found an absolute in-hospital mortality reduction of 18.2%, from 44% in conventionally treated patients to 25.8% for patients supported with ECMO in a specialist centre[67].

STOP-COVID investigators in the United States and COVID-ICU investigators in France, Belgium and Switzerland performed emulated target trial analyses during the first half of 2020. Shaefi examined clinical features and outcome of patients supported with ECMO using data from the STOP-COVID multicenter study. One hundred and thirty patients receiving ECMO support were compared with 1,167 who did not. During a median follow-up of 38 days, 34.6% of the ECMO group and 47.4% of the non-ECMO group died (HR 0.52, $p < 0.001$)[97]. Hajage investigated the effect of ECMO support on 90-day mortality compared to IMV only. The ECMO strategy resulted in higher 90-day survival if it was performed in a high-volume centre or where an organized ECMO network was set up and when initiated within the first 4 days of IMV[98].

The duration of ECMO support was longer in our cohort than the 15.8 days or 18 days reported by Lorusso[89] and Ramanathan[94]. We had two very long runs (65 and 70 days), and both patients survived, which is in line with previous data[99]. The ICU length of stay was longer, too, which

is partly the result of the low number of high dependency beds at our hospital, and the fact that even most of the high-dependency unit personnel worked at the ICU with us during the pandemic. The long ICU stay was associated with unexpectedly high rate of nosocomial infections.

This single centre analysis has certain limitations. It is a retrospective analysis involving a relatively small number of patients, from a low-volume centre. In addition, as probably in every similar case, the level of surge capacity continuously changed with the ever-changing management system, which made it more difficult to maintain high quality care.

V. 2. Discussion of results obtained in the 6-month respiratory follow-up

The main findings of this study demonstrate long-term detrimental pulmonary changes six months after hospital discharge, with deteriorations in the respiratory oscillometric parameters reflecting the frequency dependence of resistance (R_5–R_{19}) and the respiratory tissue stiffness (AX_5). These adverse alterations in the oscillometric respiratory mechanical parameters were associated with reduced forced expiratory volumes (FEV_1, FVC) and static lung volumes (VA, FRC, and ERV) in patients with post-COVID-19 syndrome. The adverse changes in lung function were reflected in reduced lung diffusion capacity (DLCO) without alterations in the carbon monoxide transfer coefficient (KCO).

An important feature of the current study is the ability to individually characterize the long-term effects of severe COVID-19 on the airway and respiratory tissue compartments. Resistance parameters obtained via respiratory oscillometry have the ability to characterize both overall and peripheral airway function, taking advantage of the fact that low-frequency oscillatory signals can reach even the small airways. Thus, this part of the oscillatory impedance reflects energy loss in the entire bronchial tree. Conversely, the proximal airways are mainly accessed by applying higher oscillatory frequencies. That is, these resistance components reflect central airway properties. Since R_{19} did not exhibit detrimental changes in patients with COVID-19, the mechanical properties of the large conducting airways were not affected by post-COVID-19 syndrome. On the contrary, the COVID group exhibited a significantly higher frequency dependence of respiratory resistance than the healthy matched control group, as evidenced by elevated R_5–R_{19} data. This indicates the presence of a distal airway dysfunction at >6 months after severe COVID-19 infection, which is a result of heterogeneous peripheral airway constriction and/or permanent closure of terminal airspaces. These oscillometric

findings are also supported by the results obtained via spirometry, thereby demonstrating a significant decrease in FVC. This dominant change affects the changes in other forced expiratory volumes and flow parameters. The decrease in FEV_1 associated with a greater reduction in FVC results in an increased FEV_1/FVC ratio in patients with COVID-19. This finding also suggests that the central conducting airways have normal function. FEF_{25-75} reflects small airway function; however, this parameter did not differ between the healthy matched control and COVID groups. This apparent controversy regarding oscillometric findings can also be attributed to a significant decrease in FVC without changes in PEF, which results in a preserved mid-expiratory flow in patients with post- COVID-19 syndrome.

To the best of our knowledge, there are no previous studies that have assessed the long-term changes in lung function in patients with severe COVID-19 requiring V-V ECMO support. The only publication in this clinical scenario is a case report focusing on radiological changes during V-V ECMO support[100]. Accordingly, our findings can be compared with previous findings obtained in patients with post-COVID syndrome with various severity and time windows. In accordance with the findings of the current study, the dominance of peripheral airway dysfunction was observed in hospitalized non-ventilated patients with COVID-19 at 3 months after hospital discharge[101,102]. The lack of remanent airway dysfunction was also found at 1-year follow-up among patients with post-COVID-19 syndrome. However, the involvement of a mixed population with only 24% of patients requiring invasive mechanical ventilation explains the discrepancy in our data[16]. Furthermore, the decrease in FEV_1 without a detrimental change in FEV_1/FVC and PEF in our patients with post-COVID-19 syndrome is in agreement with previous results reported in similar clinical settings[12,13,17,18,103]. A previous study also showed an involvement in persistent dysfunction in the conducting airways[15]. However, older patients were included in these analyses, and smokers and participants with cardiopulmonary comorbidities were not excluded. These factors could explain the elevated low-frequency resistance and the abnormal FEV_1/FVC ratio and FEF_{25-75}.

Another important finding of the current study is the presence of persistent deterioration in respiratory tissue elastance, as reflected by the sustained elevations in AX_5. No change in the resistive properties of the conducting large airways was detected, and the inertive forces remained unchanged. Therefore, the high f_{res} also reflects stiffer respiratory tissues in patients with post-COVID-19 syndrome compared to in healthy matched controls. This respiratory mechanical defect can be explained by two different mechanisms: a loss of lung volume leading to a stiffer working lung and intrinsic alteration in the respiratory tissues due to chronic

remodeling. Our findings on the static lung volumes obtained via spirometry (FVC), plethysmography (FRC and ERV), and gas washout (VA) uniformly demonstrate the presence of persistent lung volume loss in patients with post-COVID-19 syndrome, thereby indicating the primary involvement of this mechanism in elevated respiratory tissue elastance. Regarding the potential additional effect of intrinsic changes in the respiratory tissues, our findings provide indirect evidence of the lack of tissue remodeling. Decreased DLCO, reflecting the overall gas-exchanging function of the whole lungs, was not associated with any change in KCO representing gas exchange per unit of lung volume. Since the changes in KCO were not statistically significant, these findings indicate the dominance of lung volume loss over lung tissue remodeling.

There are no earlier studies assessing long-term changes in lung tissue mechanics and related lung volume and gas exchange outcomes in patients with severe COVID-19 requiring V-V ECMO support during the acute phase of infection. Therefore, our findings can only be compared with previous data obtained from patients with COVID-19 requiring invasive ventilation and/or intensive care. Our results on the persistent stiffening of respiratory tissues are consistent with the high AX_5 at 30 days and 3 months after hospital discharge, considering the changes in this elastance parameter[101,102]. Due to the mechanisms responsible for this restrictive persistent lung mechanical defect, low static lung volumes have been consistently reported in patients with severe post-COVID-19 syndrome[17,103–107]. This finding is similar to ours. The dominance of lung volume loss over the fibrotic lung tissue modeling according to the long-term effects of severe COVID-19 is also in agreement with previous results showing consistent decreases in DLCO[14,16,17,101,103,105,108,109] with preserved KCO[14,16,17,105].

V-V ECMO is an acute, life-saving extracorporeal gas exchange support modality. However, it has several direct and indirect pulmonary consequences. In terms of the direct effects of V-V ECMO, it can facilitate protective lung ventilation possibly, by applying low driving pressure and tidal volume (VT) with low FiO_2 and ventilation frequency. Conversely, the application of low VT may cause the development of persistent atelectasis, despite the maintenance of a relatively high positive end-expiratory pressure. In addition, the systemic inflammatory response induced by the pathogen may be further aggravated by indirect mechanisms related to the large artificial instrumental surface of the V-V ECMO[110]. The resultant long-term effects of these pathophysiological processes are not completely understood. The respiratory outcomes of patients with severe COVID-19 requiring V-V ECMO support were comparable to those in earlier studies on patients with COVID-19 who presented with a more moderate disease

severity, with[12,16,17,103,104,107,109] or without[12,16–18,101–104,107–109] the need for invasive ventilation. Hence, the long-term pulmonary protective features may outweigh the temporary negative effects of V-V ECMO, which is associated with good health-related quality of life.

The current study had several limitations. At our institution, 18 patients with COVID-19 were supported with V-V ECMO; however, the survival rate of this cohort was 50%. This resulted in a relatively small sample size, allowing the recruitment of a maximum of nine patients discharged from the hospital. However, the power level of the statistical tests was sufficient to detect differences with confidence. Thus, conclusions are supported by the current datasets.

Patients who received V-V ECMO underwent highly invasive diagnostic and therapeutic procedures, supplemented by radiological imaging involving radiation exposure in the acute phase of COVID-19. Therefore, in this follow-up study, we aimed to apply techniques that are noninvasive and do not expose patients to ionizing radiation. If these noninvasive techniques promote sufficient recovery, invasive modalities may be considered to complete post-COVID-19 follow-up.

Another aspect of our work is related to the time window of 6 months after hospital discharge. Since adverse pulmonary effects[16,19,111] and worsening of health-related quality of life[112] persist following COVID-19 infections over a longer term, an extension of the study period beyond 6 months is planned to reveal temporal changes in the outcomes reported in the present study.

Since the present study focused on lung function outcomes 6 months after hospital discharge, a further limitation of our study is the lack of identification of biomarkers specific to ARDS[113]. Accordingly, investigating the potential correlation between the biomarkers specific to endothelial and/or alveolar epithelial injuries in ARDS with post-COVID lung functional outcomes is a subject of further investigation.

V. 3. Discussion of results obtained in the postpartum patients

In this thesis based on our case steries study, we present three postpartum patients who required V-V ECMO support due to life-threatening COVID-19 pneumonia. Extracorporeal life support durations were 25 and 10 days for *Cases 1* and *2*, respectively, while the third patient required an extended 70-day ECMO course, including an interim two-week-period without mechanical ventilation. Life support was successful for all three women. At the 6-month follow-up, the patients exhibited good general physical condition, characterized by Rankin scores of 0 to 1, and moderately impaired lung function, primarily restrictive in nature. At the 12-month follow-

up, improvements in both physical condition and lung function were observed for all three patients, as evidenced by uniform Rankin scores of 0 and only mild restrictive lung function impairment.

Application of V-V ECMO during pregnancy was considered even before the COVID-19 era, particularly in cases of severe respiratory failure. From 1997 to 2017, the Extracorporeal Life Support Organization (ELSO) registry recorded 280 peripartum women[114]. In this report, the overall maternal survival rate was 70%, with a noticeable decrease in the mortality among these patients over the 21-year period. Subsequently, numerous case reports and small case series documented the benefits of V-V ECMO support during the H1N1 influenza pandemic, including pregnant and peripartum patients[115–117]. Furthermore, a previous review and meta-analysis, which included all available case reports and case series of extracorporeal life support in pregnancy, identified 177 cases of acute respiratory distress syndrome as the most common indication in the study. This analysis reported survival rate of 79.7%[118]. These findings have contributed to the global promotion of the ECMO use, and our small cohort of peripartum cases reaffirms the particular value of this life-saving modality during the peripartum period.

Pregnant women were affected by the COVID-19 pandemic, with concerns about increased vulnerability due to characteristic metabolic and immunological changes, alongside restrictive lung disorder. Indeed, the UK Obstetric Surveillance System (UKOSS) reported an elevated risk of hospitalization and intensive care admission for pregnant women with symptomatic SARS-CoV-2 infection[119]. While the absolute risk for poor outcome was low, there was an increase in cesarean deliveries and neonatal unit admissions[119]. Nevertheless, ECMO support in pregnant or postpartum patients with COVID-19 is often required in cases of severe pneumonia, and there is a considerable survival from the acute phase of the respiratory distress[61,120]. Similar outcomes were reported recently in the ELSO Registry, which included 100 pregnant or peripartum women with severe SARS-CoV-2 infection. This registry documented an 84% in-hospital survival rate, with no excessive ECMO-related complications during the hospitalization period[121].

While outcomes following ECMO support in postpartum women have been documented in a few previous studies[61,120], there have been no earlier reports detailing the post-discharge period for this patient population. Our results in this case-series indicate no major airway abnormalities even six months after hospital discharge. However, moderate lung volume loss is evident, as

reflected by the peripheral airway resistance in *Case 1*, and in the diminished static lung volumes and gas diffusion indices observed in all 3 patients. At the 1-year follow up, beneficial changes in lung function parameters were observed in all three patients, aligning with those observed in non-pregnant population who received ECMO support for COVID-19 pneumonia[122–124]. However, the weight gain exceeding 10% in *Case 1* may have masked the intrinsic improvements in lung function outcomes. This underscores the importance of lifestyle counseling in post-COVID care. The lack of severe lung function defects is in accordance with the fairly normal Rankin scores obtained during the one-year follow-up period.

VI. SUMMARY AND CONLUSIONS

The studies presented in this thesis reveal that in patients with severe COVID-19 who required veno-venous extracorporeal membrane oxygenation (V-V ECMO) support for acute respiratory failure:

- Hospital survival rates exceeded 50%, even when complex extracorporeal life support modalities were employed, including V-V ECMO and, in some cases, blood purification therapies such as continuous renal replacement therapy;
- Survival outcomes were comparable to those reported by other centers treating similar critically ill patient populations;
- Residual pulmonary dysfunction was frequently observed at the 6-month follow-up, most notably in the form of small airway impairment and loss of functional lung volume;
- Multidisciplinary long-term follow-up is essential to evaluate persistent effects on lung function and gas exchange;
- Ongoing respiratory assessment is strongly recommended in patients who received V-V ECMO support during the acute phase of COVID-19, even six months post-discharge;
- Particular attention is warranted for postpartum patients, a subgroup that received ECMO for COVID-19-associated pneumonia and exhibited a distinct susceptibility to severe respiratory symptoms;
- Favorable long-term outcomes are achievable even in these high-risk individuals, as evidenced by preserved health-related quality of life during the 6–12 months follow-up period, despite undergoing prolonged, complex, and complicated life support therapy.

These findings underscore the potential benefits of early and optimal consideration of ECMO support. The complex and long intensive therapy require longitudinal perspectives to prove an

optimal quality of life for the patients. A particularly compelling example is the successful delivery of a healthy "post-ECMO baby" by one of the postpartum patients in our cohort two years after hospital discharge.

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