


# COVID-19 Pulmonary Failure and Extracorporeal Membrane Oxygenation: First Experience from Three European Extracorporeal Membrane Oxygenation Centers

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## Abstract

### Keywords

- ▶ acute respiratory failure
- ▶ GARDs
- ▶ advanced life support
- ▶ VV ECMO, VA ECM
- ▶ pulmonary thrombosis (microthrombosis, systemic microthrombosis, thrombolysis)

On April 17, 2020, a coronavirus disease 2019 (COVID-19) webinar was held by selected international experts in the field of intensive care and specialized respiratory ECMO centers from Germany, Italy, Spain, and the United Kingdom, which was hosted by the German Heart Centre Berlin/Charité. The experts shared their experience about the treatment of 42 patients with severe acute respiratory failure requiring venovenous extracorporeal membrane oxygenation (VV-ECMO). Patients were predominantly male (male-to-female ratio: 3:1), with a mean age of 51 years (range: 25–73 years). VV-ECMO support was indicated in 30% of the ventilated COVID-19 patients. The mean time requiring mechanical ventilation was 16.5 days, with a mean duration of ECMO support of 10.6 days. At the time of the webinar, a total of 17 patients had already been decannulated from ECMO, whereas six died with multiorgan failure. 18 patients remained on ECMO, with their final outcomes unknown at the time of the webinar. Hospital mortality was 25.6% (as of April 17, 2020). In this respect, VV-ECMO, provided by expert centers, is a recognized and validated mode of advanced life-support during the recent COVID-19 pandemic with good outcomes.

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## Introduction

The outbreak of coronavirus disease 2019 (COVID-19) was first reported in December 2019 in the central Chinese city of Wuhan, which was characterized by acute respiratory distress syndrome (ARDS) caused by severe or fatal pneumonia.<sup>1</sup> Initial clinical reports showed mortality of 49% or more among patients with coexisting diseases who developed severe COVID-19 ARDS (C-ARDS) refractory to maximal therapy.<sup>1</sup> A venovenous extracorporeal membrane oxygenation (VV-ECMO) can be used to rescue eligible patients.<sup>2–4</sup>

To date, refractory C-ARDS has claimed many lives worldwide, with more than 434,793 deaths among 7,973,302 confirmed cases (Johns Hopkins University in Baltimore, June 15, 2020).<sup>5</sup> This has challenged health care providers to strengthen their strategic response and develop more capacity for COVID-19 critical care including VV-ECMO services to eligible patients at centers of excellence.<sup>4</sup>

The World Health Organization (WHO) declared a COVID-19 pandemic on March 11, 2020. In the preliminary guidelines for the management of COVID-19, the WHO recommended that “In settings with access to expertise in extracorporeal life support (ECLS), consider referral of patients with refractory hypoxemia despite lung protective ventilation.” This was supported in a statement from the Extracorporeal Life Support Organization (ELSO), stating “If the hospital feels that ECMO can be safely provided, then it should be offered to patients with a good prognosis with the use of ECMO.”<sup>6,7</sup>

The first European COVID-19 webinar on “Acute Cardio-Pulmonary Failure” was held on April 17, 2020. The experiences of the frontline critical care physicians from leading European VV-ECMO centers with the use of VV-ECMO in COVID-19 were shared. Additional discussions were held regarding the use of COVID-19 convalescent plasma antibody for treating patients, as well as potential future antiviral strategies, for example, the antiviral protease inhibitor remdesivir. The management of COVID-19 patients with the introduction of early application of immune-modulatory therapy to inhibit the life-threatening cytokine storms, thus preventing multiorgan failure, was also discussed.<sup>8–10</sup>

The decision to implement VV-ECMO, however, remains challenging, particularly where resources are limited due to excessive demand such as a pandemic. This is further compounded when a novel pathogen is encountered, with uncertain patterns of progression, recovery and mortality, and uncertain efficacy of conventional therapies such as VV-ECMO. Ultimately, the decision to use scarce resources to support individual patients in crisis can only be guided by the collection and publication of data.

## Methods

Experts from Germany, Italy, Spain, and United Kingdom held a webinar organized by the German Heart Centre Berlin in collaboration with the Department of Anaesthesiology and Intensive Care Medicine, Charité - University of Medicine Berlin on April 17, 2020, where the local experience with the treatment of COVID-19 patients with severe acute respiratory failure requiring VV-ECMO support was shared and discussed. Following this, a retrospective anonymous review of contemporaneous non-ECMO COVID-19 patients requiring ventilation (but not requiring VV-ECMO) in these centers was conducted.

## Results

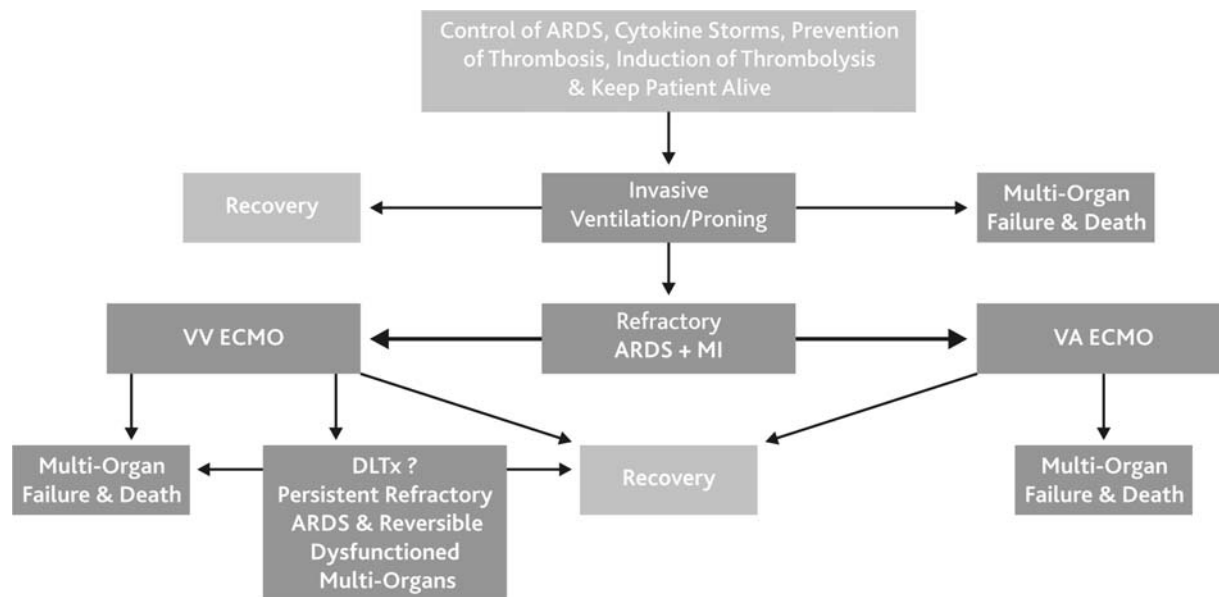
Until April 17, 2020, a total of 140 patients (43 females and 97 males; average age: 59 years) with COVID-19 requiring mechanical ventilation were admitted to the three participating centers (► **Table 1**). The immune response was characterized by the following laboratory median values: lymphocytopenia (0.87 [normal: 1,000–4,800 in 1  $\mu$ L]), high levels of C-reactive protein (CRP) (21.75 mg/L [normal: <5–10 mg/L]), interleukin-6 (IL-6) (213 [normal: 0–16.4 pg/mL]), and D-dimer (2.5 [normal: 0.4  $\mu$ g/mL]). Some of the patients supported with VV-ECMO received immune-modulatory therapy with, anti-IL receptor antibody, tocilizumab. All patients were systemically anticoagulated unless contra-indicated.

The mean duration of mechanical ventilation was 16.5 days and that of VV-ECMO support was 10.6 days. Gender distribution of ECMO patients was as follows – female/male: 12/30

**Table 1** Summarized data from three European Specialist ECMO Centers, Barcelona, London, Wurzburg, until the webinar on April 17, 2020

ECMO center	On ventilation (COVID-19. Total & F/M n	On ventilation Average age F/M Range (years)	ECMO COVID-19 Total & F/M n	ECMO Average age F/M Range (years)	ECMO weaned by April 17, 2020	ECMO duration (days)	30-D survival ECMO to April 17, 2020
Hospital Clinic, University Barcelona (Spain)	21: 5/16	64/86 25–79	5: 1/4	73/51.4 25–73	4	8	80%
Royal Brompton Hospital London (UK)	93: 27/66	51/54 21–85	29: 7/22	46/46 29–64	9	10.6	93.1%
University Hospital Wurzburg (Germany)	26: 11/15	63.6 36–83	8: 4/4	55.8/53.5 36–69	4	13.1	50%
Total	140: 43/97	59.2: 21–85	42: 12/30	58.3/50.3: 25–73	17	10.6	74.4%

Abbreviations: COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation.



**Fig. 1** Goals of cardiorespiratory support in COVID-19 patients with ARDS. ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; DLTx, double lung transplantation; ECMO, extracorporeal membrane oxygenation; MI, myocardial infarction; VA, veno-arterial; VV, venovenous.

(*n* = 42) and the age distribution was 58/50 years (→ **Table 1**). At the time of the webinar, 17 patients had been decannulated from ECMO, and 7 (25.6%) had died with multiorgan failure. Eighteen patients remained on ECMO, with their final outcomes unknown at the time of the webinar. Thirty-day patient survival (as of April 17, 2020) was 74.4% (→ **Table 1**).

## Discussion

The unprecedented global COVID-19 pandemic with propensity to cause ARDS and high rate of death on invasive ventilation has demanded rescue VV-ECMO therapy in moderate- to high-risk patients. Depending on the individual patient pathophysiology, vascular status, cardiac function, local expertise, and local resources, the optimal ECMO strategy needs to be considered.<sup>11–13</sup>

Mortality in critically ill COVID-19 patients ranges between 24 and 68%.<sup>14,15</sup> The clinical course and outcome of COVID-19 patients were influenced by age, gender, body mass index, and coexisting pathology. Comorbidities were important predictors of increased mortality and were found in 74% of critically ill COVID-19 patients.<sup>16,17</sup> The high mortality rate in critically ill COVID-19 patients should prompt early evaluation of at-risk patients, including early measurement of biomarkers of pulmonary injury and cardiothoracic imaging.<sup>1,3,4,10,18</sup> The pathology of the associated pulmonary injury described includes alveolar damage, hypersecretion and plugging, vasculitis, and extensive systemic microthrombosis. The immune response is often characterized by lymphocytopenia, high levels of CRP, cytokines, IL-6, and D-dimer.<sup>8–10,18</sup> Elevated D-dimer levels (>1 g/L), IL-6, and troponin are associated with in-hospital death.<sup>10,19</sup> Cytokine storms activate the coagulation pathway and vascular endothelial cells, which also inhibit myocardial cell function.<sup>10</sup> IL-6 blocking therapy with anti-IL-6 receptor (tocilizumab) may be a novel therapeutic strategy for controlling

cytokine storm and prevention of multiorgan failure in COVID-19 infection.<sup>20</sup> Selective filtration of macrophages using the “CytoSorb technique” is also under investigation but requires validation.<sup>21</sup>

Where conventional critical care interventions, including lung-protective ventilatory strategies and proning, are insufficient, preliminary data suggest that VV-ECMO may improve survival rates.<sup>17</sup> Participating experts from the three<sup>3</sup> centers reported their local experience with a cumulatively low in-hospital mortality rate (30 days) of 25.6% (as of April 17, 2020).

These promising results from expert centers and the algorithm in → **Fig. 1** may offer some additional guidance for those considering the role of VV-ECMO in the ongoing pandemic, including its potential role in any future pandemic surges.<sup>22</sup>

It is well recognized that higher volume ECMO centers have superior outcomes when compared with intermittent/low-volume providers. The excellent outcomes discussed in this webinar further underscore the role of the “expert center.” Any wider expansion considered in future should focus on developing additional capacity in those centers with existing programs and expertise. Indeed, the ELSO recommends against starting new ECMO centers for the sole purpose of treating patients with COVID-19.<sup>7</sup> Finally, the international collaboration and rapid sharing of expertise through the expanded use of technology and case-based discussion should be considered as a model for the future.

### Conflict of Interest

None declared.

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