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# Determinants of survival in patients on extracorporeal membrane oxygenation therapy due to severe covid-19

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## Abstract

*Background:* Severe acute respiratory distress syndrome (ARDS) due to Coronavirus Disease-19 (COVID-19) is associated with high mortality. Although survival on mechanical circulatory support has improved, determinants for better prognosis are still unclear. Here, we report on the outcome of our patient population with the need for mechanical circulatory support due to severe COVID-19 (sCOVID-19) induced ARDS.

*Methods:* All patients treated with extracorporeal membrane oxygenation (ECMO) for severe ARDS due to sCOVID-19 were analysed. Patients > 18 years of age at the time of initiation of ECMO were included. Pre-existing comorbidities, complications during ECMO implantation, and ECMO runtime were reviewed. The latency to intubation, proning, tracheotomy, and ECMO implantation was analysed. Furthermore, the survival and non-survival population were compared to determine factors in favour of a better outcome.

*Results:* In total, 85 patients were treated with veno-venous membrane oxygenation (vv-ECMO) for severe ARDS in our medical centre. The patient population was predominantly male (83.5%) with a mean patient age of 54.9 years. A history of cardiovascular disease ($p = .01$), smoking ($p < .05$), need for vasopressor- ($p < .05$), and renal replacement therapy ($p < .001$) was associated with a worse prognosis. Overall survival was 50%. The survival population was significantly younger ($p = .004$), had a significantly higher body weight ($p = .02$) and body mass index (BMI) ($p = .01$). Furthermore, survival was significantly better when vv-ECMO was initiated within 48 h after admission ($p < .001$).

*Conclusions:* Pre-existing cardiovascular disease, higher age, history of nicotine abuse, and development of renal failure are associated with poor outcome. Early start of vv-ECMO therapy may lead to better survival in sCOVID-19 patients, although complications during ECMO therapy are associated with a worse prognosis.

## Keywords

extracorporeal membrane oxygenation, coronavirus disease-19, acute respiratory distress syndrome, respiratory failure, determinants

## Introduction

The rapid development of the coronavirus disease 2019 (COVID-19) pandemic has led to an exponential increase in the hospitalization of patients due to respiratory disease. Mild forms of COVID-19 with symptoms including dyspnoea, dry cough, and fever can be treated ambulatory. In some cases, however, severe pulmonary involvement can lead to respiratory failure with the need for invasive mechanical ventilatory support.[1] Pathogenesis of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) includes infection of the

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bronchial and alveolar epithelial cells leading to an inflammatory response. Furthermore, the release of pro-inflammatory cytokines leads to an inflammatory response, thickening of the pulmonary interstitium, oedema, and microthrombus formation.[2] Previous research has shown a beneficial role for mechanical circulatory support in patients non-responsive to conventional mechanical ventilatory therapy. Furthermore, the use of veno-venous membrane oxygenation (vv-ECMO) in patients with respiratory failure due to severe acute respiratory distress syndrome (ARDS) was associated with improved survival and was implemented in the Extracorporeal Life Support Organisation (ELSO) guidelines for adult respiratory failure.[3] In sCOVID-19 patients, vv-ECMO has been proven to be a relatively safe therapy, it furthermore enables lung-protective ventilation and survival was comparable to patients on vv-ECMO due to severe ARDS from other causes.[4] Although survival on vv-ECMO has improved since its initial use in sCOVID-19 patients, clear determinants for improved survival are still unclear. In this paper, we discuss the determinants for survival in our patient population.

## Patients and methods

*Patients*. This study was done retrospectively using medical records of patients treated with vv-ECMO for severe COVID-19 at our medical center. All patients > 18 years were included. Coronavirus disease 2019 was confirmed using polymerase chain reaction (PCR) analysis of tracheal swabs. All patients were sedated using propofol/sufentanil; inhalation anaesthetics (isoflurane) were delivered as per house standard. Implementation of vv-ECMO was considered when patients met the criteria outlined in the Extracorporeal Life Support Organization guidelines [10]. In brief, patients were evaluated for vv-ECMO when Horowitz index <80mmHg for > 6 h or <50mmHg >3 h due to severe respiratory failure under lung-protective ventilation. The Horowitz index was determined as $\text{PaO2/FiO2 ratio (mmHg)} = \frac{\text{Partial pressure of oxygen PaO2 (mmHg)}}{\text{Fraction of inspired oxygen FiO2 (\%)}}$. Furthermore, prolonged hypercapnic acidosis (pH< 7.25 due to PaCO2 > 60 mmHg for >6 h) was also considered an inclusion criterion for vv-ECMO evaluation. Myocardial pump function was monitored using transthoracic echocardiography throughout the patient's stay in the ICU.

## Extracorporeal mechanical circulatory support

Patients were evaluated for vv-ECMO therapy multidisciplinary and the decision to implement vv-ECMO was taken in case inclusion criteria were met. At the bedside in the ICU, sonographic confirmation of the patency of the jugular- and the femoral vein was established. Successively, guidewires were placed percutaneously and a bolus of 5000 IE unfractionated heparin was given intravenously. Venous blood was drained via Seldingers technique into the femoral vein using a 55-cm long HLS cannula with BIOLINE coating (Getinge, Rastatt, Germany), size 21, 23, or 25 Fr, depending on the patient's weight and size. The optimal position for the outflow cannula was the entrance of the inferior vena cava to the right atrium. The position of the cannula was optimized using an ultrasound examination. A similar technique was used for the inflow cannula, a 15-cm long HLS cannula coated with BIOLINE, size 13, 15, or 17 Fr, which was placed in the jugular vein. In one patient, the inflow cannula was placed in the contralateral femoral vein. After successful cannulation, the cannulas were connected to our mobile ECMO system, the CardioHelp pump (Getinge, Rastatt, Germany), and to an HLS Set Advanced oxygenator (Getinge, Rastatt, Germany). The anticoagulation regime in our hospital included a continuous intravenous heparin infusion, the infusion rate was adjusted according to the activated clotting time. The activated clotting time goal was set at 160–180s according to the ECMO standard at our medical center. The patient was weaned from vv-ECMO as soon as pulmonary function was restored. Ventilation parameters such as FiO2, peak pressure, PEEP, and driving pressure were used to determine the possibility of vv-ECMO support reduction. Extracorporeal membrane oxygenation removal was done after the pulmonary gas exchange was sufficiently restored: spontaneous breathing, Horowitz index ≥ 150 mmHg, PEEP ≤ 15 mbar, and tidal volumes ≥ 4–6 ml/kg of predicted body weight. After weaning, the percutaneously placed cannulas were extracted using 0/0 skin sutures.

## Statistical analysis

Summary statistics were presented as medians with ranges. Categorical variables are presented as counts and percentages. Group comparisons were done using the Student t-test for continuous variables. For categorical analysis, both Fisher's exact test and Pearson's $\chi^2$ test were used depending on the sample size. A $p$-value < .05 was considered significant in all tests. SPSS version 27 (SPSS Inc., Chicago, IL, USA) software was used to analyze the data. Significant differences were indicated as follows: * $p < .05$, ** $p < .01$, *** $p < .001$.

# Results

Between January 2020 and August 2021, 85 patients (71 male (83.5%)) were presented to our tertiary centre with sCOVID-19 in need of ECMO support. A total of 30

patients (35.3%) were presented to us for ECMO therapy after the primary presentation in external medical centres. These patients were cannulated on-site and transferred to our medical centre either by land or air. The patient's mean age was 54.9 (range 19–71) years. Mean patient weight and body mass index (BMI) were 98.2 (range 60–170) kg and 31.2 (range 20.5–55.1) respectively. Patient characteristics are presented in Table 1. To exclude cardiac causes for respiratory failure, each patient was examined using transthoracic echocardiography, no significant myocardial dysfunction or valvular defects were noted in our patient population. The mean time from admission to intubation was 4.5 (range 0–21) days. The long time to intubation can be explained due to long non-invasive ventilation either by mask ventilation or high flow oxygen therapy. The majority of our patients (77 patients (90.6%)) were treated with proning therapy before vv-ECMO initiation. The mean time to initiation of proning from admission was 5.4 (range 0–27) days. The proning regime at our centre involves 3 times proning for 12 h, this was repeated when needed. In 61 (71.7%) patients a tracheostomy was performed during their stay at our intensive care unit. All patients were treated with vv-ECMO for respiratory support. The mean time to vv-ECMO initiation was 10.1 (range <24h–39) days. The mean time on ECMO support was 15.3 (range 1–51) days. Due to the development of COVID-associated pulmonary embolisms, 3 (3.5%) patients needed an upgrade to veno-arterial-venous (vav)-EVMO to manage hemodynamic instability, there was no need for surgical removal of the pulmonary thrombus.

**Table 1.** Patient characteristics of all patients treated with vv-ECMO for ARDS due to sCOVID-19.

| Patient characteristics | *n* = 85 (100%) |
|---|---|
| Male | 71 (83.5%) |
| Age in years (mean ± SEM) | 54.9 ± 1.3 |
| Weight in kg (mean ± SEM) | 98.2 ± 2.5 |
| Height in cm (mean ± SEM) | 177 ± 1 |
| BMI in kg/m$^2$ (mean ± SEM) | 31.2 ± 0.7 |
| COPD | 14 (16.5%) |
| DM II | 20 (23.5%) |
| Cardiovascular disease | 13 (15.3%) |
| Renal insufficiency | 9 (10.6%) |
| Arterial hypertension | 40 (47.1%) |
| Smoking | 11 (12.9%) |
| Obesity | 69 (81.2%) |

BMI: body mass index, COPD: chronic obstructive pulmonary disease, DM II: diabetes mellitus type II, SEM: standard error of the mean.

### *Extracorporeal membrane oxygenation, complications, and survival*

Patients receiving prone positioning continued to do so after the initiation of ECMO. Extracorporeal membrane oxygenation management was done according to clinical presentation, the fluid balance was kept at mild negative during ECMO therapy, vv-ECMO blood flow was kept between 4 – 5 L/min. Sweep gas flow was adjusted to need. No ECMO-associated complications due to prone positioning in patients on vv-ECMO treatment were seen. All patients received heparin as an anticoagulation regiment.

The most common complication during ECMO therapy was impaired kidney function, this was seen in a total of 45 (52.95%) patients. Renal replacement therapy was needed in 41 (48.2%) patients. Neurological complications due to bleeding were seen in 3 (3.5%) patients. Gastrointestinal complications due to bleeding or ischemia were seen in 6 (7.1%) patients and pulmonary bleeding was seen in 12 (14.1%) patients. Cumulative, bleeding was seen in 21 (24.7%) patients, this is comparable to our non-COVID-19 population on vv-ECMO.[5] Bleeding was seen in the brain (3 patients; 3.5%), in the lungs (12 patients; 14.1%) and the gastrointestinal tract (6 patients; 7.1%). There was no significant bleeding from the cannulation site.

In the total population, weaning from ECMO was possible in 44 (51.8%) patients. Criteria for vv-ECMO weaning included improved pulmonary gas exchange function. After ECMO removal all patients were breathing spontaneously with PEEP <15mmHg, Horowitz >150mmHg, and tidal volumes >4–6 ml/kg predicted body weight. Patients were transferred to a respiratory weaning centre for further recovery after weaning from mechanical support. No patients were readmitted due to respiratory failure. Overall survival was 49.4%. The cause of death was a multi-organ failure (27 patients; 31.8%), and septic shock (13 patients; 15.3%). In two (2.4%) patients therapy was terminated due to severe brain haemorrhage.To determine variables supporting better survival, the patient population was divided into survival and non-survival groups. The survival population was significantly younger ($p < .001$). Stratification of patient age showed a significantly poorer survival in patients >40 years old at the time of admission ($p = .03$). Interestingly, the survival population had significantly higher body weight ($p = .02$) and BMI ($p = .01$). When compared, significantly worse survival was seen in patients with pre-existing cardiovascular disease ($p = .01$) and history of nicotine abuse ($p = .026$). Medical treatment during vv-ECMO therapy was further analysed, here a significantly worse survival was seen in patients with a continued need for

vasopressor therapy ($p$ = .03) while on ECMO. Furthermore, the need for dialysis ($p$ < .001) was associated with a poor prognosis. The use of plasmapheresis was not associated with improved survival. To determine the effect of therapy delay, time from admission to intubation, proning, and ECMO therapy was analysed. The delay of ECMO implantation from admission was significantly lower in the survival population ($p$ = .023). Further analysis showed significantly better survival in patients when ECMO therapy was initiated within 48 h after hospital admission ($p$ < .001). This confirms the importance of ECMO implantation without delay in patients with severe respiratory failure. The delay between admission and intubation and prone therapy did not show significant benefit. All values are shown in Table 2. In the analysis of the ECMO-related complications and survival, there was no significant benefit in survival for patients presented primarily in our tertiary centre in comparison to patients transferred on ECMO to our hospital. In our opinion, this is furthermore an argument for the avoidance of ECMO therapy delay. Although the development of complications in general ($p$ = .024) was considered a significant determinant for poor prognosis, individually, neurological, gastrointestinal, and pulmonary bleeding was not associated with poor outcome. The development of renal failure ($p$ <.001) during ECMO therapy did however show a significantly poorer prognosis, as well as the need for dialysis ($p$ < .001) (Table 3).

## Discussion

In this manuscript, we analysed determinants associated with survival in patients on vv-ECMO support due to sCOVID-19-induced ARDS. Our results showed improved survival in patients younger than 40 years at the time of presentation. Furthermore, no prior history of cardiovascular disease or smoking was associated with a better outcome. The time of intubation and time of initiation of proning was not associated with better survival. However, patients treated with vv-ECMO within 48 h after admission showed significantly better survival.

Prognostic factors for mortality and disease progression in the sCOVID-19 patient population have previously been determined, similar to our findings age and absence of previous cardiovascular disease were associated with survival.[4] Although this study compared both non-ECMO and ECMO patients and thus may not be suitable for comparison, other research showed

**Table 2.** Comparison in determinants between survival and non-survival population. All times are calculated from the time of admission.

| Comorbidities and survival | Survival $n$ = 43 (51%) | Non-survival $n$ = 42 (49%) | $p$-value |
|---|---|---|---|
| Age in years (mean ± SEM) | 52.1 ± 1.9 | 59.2 ± 1.4 | ***.004*** |
| Weight in kg (mean ± SEM) | 103.7 ± 3.7 | 92.5 ± 2.8 | ***.019*** |
| Height in cm (mean ± SEM) | 177.9 ± 1.6 | 176.3 ± 1.2 | n.s. |
| Male | 33 | 38 | n.s. |
| BMI in kg/m$^2$ (mean ± SEM) | 33.1 ± 1.4 | 29.5 ± 0.8 | ***.028*** |
| COPD | 7 | 7 | n.s. |
| DM II | 9 | 11 | n.s. |
| Cardiovascular disease | 2 | 11 | ***.013*** |
| Renal insufficiency | 4 | 6 | n.s. |
| Arterial hypertension | 19 | 21 | n.s. |
| Smoking | 2 | 9 | ***.026*** |
| Obesity | 39 | 30 | ***.047*** |
| Time to intubation in days (mean ± SEM) | 4.2 ± 0.9 | 4.8 ± 0.5 | n.s. |
| Time to tracheotomy in days (mean ± SEM) | 13.7 ± 1.5 | 15.4 ± 1.3 | n.s. |
| Time to proning in days (mean ± SEM) | 4.5 ± 1.1 | 6.3 ± 0.8 | n.s. |
| Time to ECMO implantation in days (mean ± SEM) | 8.1 ± 1.3 | 12.1 ± 1.2 | ***.024*** |
| ECMO <48 h after admission | 16 | 2 | ***<.001*** |
| ECMO runtime in days (mean ± SEM) | 12.4 ± 1.5 | 18.2 ± 1.9 | ***.022*** |
| Administration of antibiotics | 41 | 41 | n.s. |
| Administration of antivirals | 9 | 11 | n.s. |
| Need for inotropes | 0 | 1 | n.s. |
| Need for vasopressors | 27 | 36 | ***.025*** |
| Proning | 37 | 40 | n.s. |

BMI: body mass index, COPD: chronic obstructive pulmonary disease, DM II: diabetes mellitus type II, ECMO: extracorporeal membrane oxygenation, SEM: standard error of the mean.

**Table 3.** ECMO-related complications and rate of interhospital patient transfer on ECMO. Significantly more complications were seen in the non-survival population. Development of renal failure and the need for dialysis was seen significantly more in the non-survival population.

| ECMO related survival | Survival $n$ = 43 (51%) | Non-survival $n$ = 42 (49%) | $p$-value |
|---|---|---|---|
| Interhospital transfer | 16 | 14 | n.s. |
| Plasmapheresis | 6 | 11 | n.s. |
| General complications on ECMO | 10 | 20 | ***.024*** |
| Renal failure | 14 | 31 | ***<.001*** |
| Dialysis | 12 | 29 | ***<.001*** |
| Cerebral bleeding | 1 | 2 | n.s. |
| Gastrointestinal complications | 1 | 5 | n.s. |
| Pulmonary bleeding | 4 | 8 | n.s. |

similar associations between age and survival in solely ECMO patients.[6] These findings suggest that age can be considered in the decision of whether to initiate vv-ECMO therapy or not. This opinion is supported by the ELSO guidelines.[7] Furthermore, although not supported in our population, pre-existing comorbidities such as renal failure and chronic respiratory insufficiency were associated with poor outcome.[6]

Brain haemorrhage during ECMO therapy is a common complication, however, compared to data provided by others (5%–41.7%) our population showed a relatively low incidence.[6,8,9] Gastrointestinal and pulmonary complications during vv-ECMO are similar to data provided in the literature.[10–12]

To date, no data on body weight and survival in ECMO patients is available. However, in the general COVID-19 population, an increased percentage of visceral fat was associated with the severity of the disease.[13,14] Our patient population, however, showed significantly better survival in patients with higher body weight and BMI. This may be due to the protective role of increased expression levels of angiotensin-converting enzyme-2 (ACE-2) in visceral fat.[15,16] The use of vasopressor therapy after implementation of vv-ECMO may be multifactorial and the effect of vasopressor therapy on renal function has been described extensively. Deterioration in renal function has been associated with poor outcome in our population. Renal congestion due to right ventricular overload and renal endothelial damage due to mitochondrial dysfunction and acute tubular necrosis have been suggested as causes for impaired renal function in COVID-19.[17]

Our previous work discussed the role of early implementation of vv-ECMO on patient outcome. However, due to a relatively small number of patients, we could not establish significant results.[18] In this study, we were able to provide proof that vv-ECMO implantation <48 h after admission was associated with improved survival. To our knowledge, this is the first time that a clear correlation between the time of vv-ECMO implantation and survival has been described. Although previous literature suggests that early vv-ECMO implantation is associated with improved survival, to date this is the largest patient population to confirm this hypothesis.[19,20] Furthermore, interhospital patient transfer on ECMO can be done safely and reduces delay in initiation of ECMO therapy.[21] Our results confirm that there is no reduction in survival in the patient population transferred on ECMO to our centre, provided it is done by experienced staff.

## Conclusion

Our work provides determinants for survival in vv-ECMO patients with sCOVID-19 induced ARDS. Patient age, pre-existing cardiovascular disease, history of nicotine abuse, and the continued need for vasopressor therapy on vv-ECMO therapy were associated with poor outcome. Veno-venous membrane oxygenation implantation within 48 h after admission was associated with better survival. We suggest early vv-ECMO evaluation and implementation in patients with deteriorating sCOVID-19 disease.

### Declaration of conflicting interests

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### Ethics approval and consent

This retrospective study was performed in our tertiary medical facility. The ethics committee at our institution (Hannover Medical School, Hannover, Germany) waived the need for

patient consent for this study. All data were retrieved by retrospective review of patient records.

## Availability of data and materials

The dataset used and/or analysed during the current study is available from the corresponding author on reasonable request.

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